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Clinical Outcomes Improvement and Perioperative Management of Surgical Patients

2nd Edition

Edited by
Dimitrios E. Magouliotis and Dimitris Zacharoulis

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Guest Editors

Dimitrios E. Magouliotis
Dimitris Zacharoulis

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Guest Editors

Dimitrios E. Magouliotis
Department of Cardiac Surgery Research
Lankenau Institute of Medical Research
Wynnewood
USA

Dimitris Zacharoulis
Department of Surgery
University of Thessaly
Larissa
Greece

Editorial Office
MDPI AG
Grosspeteranlage 5
4052 Basel, Switzerland

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About the Editors

Dimitrios E. Magouliotis

Dimitrios E. Magouliotis is a Research Assistant Professor at the Department of Cardiac Surgery Research at the Lankenau Institute of Medical Research in Wynnewood, USA. His work focuses on clinical outcomes research, aortic surgery, artificial intelligence in cardiothoracic surgery, and quality-improvement science. He has authored more than 150 peer-reviewed publications and contributes to several international collaborative projects involving advanced analytics, perioperative optimization, and translational cardiovascular research. His current efforts center on developing predictive tools, enhancing perioperative pathways for high-risk cardiac patients, and integrating machine learning approaches into surgical decision-making. He also serves as a Guest Editor and reviewer for multiple journals and actively participates in academic societies dedicated to aortic disease, surgical quality, and innovation in perioperative care.

Dimitris Zacharoulis

Dimitris Zacharoulis is a Professor of Surgery at the Department of Surgery at the University of Thessaly in Larissa, Greece. His academic and clinical work focuses on gastrointestinal, oncologic, and general surgery, with a strong interest in perioperative management and surgical outcomes. He has contributed to numerous national and international research efforts aimed at improving surgical safety, enhancing recovery pathways, and strengthening evidence-based perioperative protocols. His commitment to surgical education and clinical quality improvement is reflected in his involvement with multidisciplinary initiatives addressing patient-centered care and postoperative morbidity. Through his editorial work, he supports the dissemination of high-quality scientific research that advances the standards of surgical practice.

Preface

The Reprint, "Clinical Outcomes Improvement and Perioperative Management of Surgical Patients (2nd Edition)", reflects our shared commitment to advancing safe, evidence-based, and patient-centered surgical care. Surgical patients today present with increasing complexity, requiring thoughtful perioperative planning, multidisciplinary collaboration, and the integration of novel technologies and clinical insights. Our motivation in assembling this Reprint was to bring together high-quality scientific work that addresses these realities and highlights pathways to improved outcomes.

This Reprint is intended for surgeons, anesthesiologists, intensivists, perioperative physicians, and all healthcare professionals engaged in the care of surgical patients. We hope that the articles included will stimulate critical thinking, support clinical decision-making, and inspire further innovation in perioperative practice. It has been a privilege to collaborate with authors and reviewers who share the goal of improving surgical outcomes globally.

Dimitrios E. Magouliotis and Dimitris Zacharoulis
Guest Editors

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Editorial

He Lives and He Reigns

Dimitrios E. Magouliotis [1,*], Vasiliki Androutsopoulou [2] and Dimitrios Zacharoulis [3]

[1] Department of Cardiac Surgery Research, Lankenau Institute for Medical Research, Main Line Health, Wynnewood, PA 19096, USA
[2] Department of Cardiothoracic Surgery, University of Thessaly, Biopolis, 41110 Larissa, Greece; androutsopoulouvasiliki@uth.gr
[3] Department of Surgery, University of Thessaly, Biopolis, 41110 Larissa, Greece; zacharoulis@uth.gr
* Correspondence: magouliotisd@mlhs.org

Among the most enduring legends of the Greek seas is that of Thessalonike, the sister of Alexander the Great. After her brother's death, she was said to have been transformed into a mermaid who wandered across the Aegean, halting ships to ask a single question: "Does King Alexander live?" The sailors' answer determined their fate. If they replied, "He lives and reigns and rules the world," the sea remained calm, and their voyage continued in peace; but if they said he was dead, the waves rose in fury to destroy them. Beneath this tale lies a timeless truth: it is not enough merely to live; one must live and reign [1].

This allegory captures the evolution of modern surgery and the science of quality improvement. For decades, surgical success was defined by a single, binary measure: survival. Did the patient live? Yet survival alone is only the beginning of the story. True quality demands a deeper, more demanding question, one that echoes Thessalonike's cry across centuries and seas: Does the patient live and reign? Does the operation restore vitality, independence, and dignity? Does it return the patient not simply to life but to the sovereignty of living?

The contemporary movement for surgical quality improvement reflects this shift. Recent evidence shows that implementing patient-reported outcome measures (PROMs) at a national scale is feasible and crucial to capturing the full patient journey [2]. Surgical QI collaboratives, particularly in the UK, have not only demonstrated effectiveness but also underscored the need for improved methodology and design [3]. Frameworks for scaling surgical quality across global contexts have emerged, offering structured pathways to reduce morbidity and mortality through systems innovation [4]. Principles tailored for frontline surgical QI emphasize feasibility, resource optimization, and sustainable implementation in small-scale settings [5]. Continuous learning models in cardiothoracic surgery have shown how data transparency and shared responsibility can transform outcomes across regions [6–9].

Quality improvement in surgery thus represents far more than the refinement of processes or the pursuit of lower mortality; it is a cultural transformation—a collective reimagining of what it means to heal. Each iterative audit, protocol, and multidisciplinary discussion seeks to calm the turbulent waters that follow an operation and ensure that our patients not only survive the storm but also emerge whole, empowered, and reigning once more over their own lives.

The articles presented in this Special Issue of the *Journal of Clinical Medicine* embody this evolution. They move beyond technical success to explore how incremental refinements (e.g., in anesthetic strategy, infection control, or system design) translate into meaningful outcomes for surgical patients.

In the realm of perioperative optimization, Kim et al. demonstrate that dexmedetomidine-based opioid-sparing anesthesia in minimally invasive pectus excavatum repair significantly reduces opioid consumption and pain without compromising hemodynamic stability [10]. Similarly, Tsaousi et al. synthesize global evidence on prophylactic antiepileptic drugs after craniotomy, offering a network-meta-analytic framework that refines decision-making in neurosurgical practice [11]. Both studies remind us that perioperative care is not ancillary; instead, it is integral to recovery and quality.

At the interface of surgical craftsmanship and outcomes, Magouliotis et al. compare transthoracic clamping and endoaortic balloon occlusion in minimally invasive mitral valve surgery, revealing equivalent safety and highlighting evidence over convention as the foundation of progress [12]. In the same context, Burysz et al. expanded this philosophy to aortic interventions, demonstrating that thoracic endovascular repair can be safely performed even in medium-volume centers by experienced cardiac surgeons, affirming that quality is not the privilege of size but of structure and commitment [13].

The domain of infection control and surgical sterility is illuminated by Duffy et al., who reveal that skin-dwelling bacteria survive standard preoperative antisepsis, reminding us that even when protocols seem perfect, unseen margins of risk persist [14]. Weiss et al. and Elgabsi et al. explore procedural refinements in biliary and appendiceal surgery, demonstrating how stent dwell time, morphology, and timing influence readmissions and recurrent events [15,16].

Quality, however, transcends the operating room. Xanthopoulos et al. showed that the initiation of sodium–glucose co-transporter 2 inhibitors at discharge improved outcomes in hospitalized heart failure patients, illustrating the continuity between surgical and medical optimization [17]. Likewise, Huh and Hwang's review on anesthetic influences in lung cancer recurrence reframes the perioperative period as a biological opportunity for improving long-term oncologic control [18].

Together, these contributions reaffirm a unifying message: quality improvement is not a static checklist but a living dialogue between science, systems, and humanity. Each dataset, each analysis, each reflection contributes a verse to the same enduring question—Does the patient live and reign?

As editors, clinicians, and scientists, we are entrusted with ensuring that our collective answer, grounded in data and empathy, remains steadfast:

Yes—he lives, and he reigns.

Author Contributions: Conceptualization, D.E.M., V.A. and D.Z.; methodology, D.E.M., V.A. and D.Z.; software, D.E.M., V.A. and D.Z.; validation, D.E.M., V.A. and D.Z.; formal analysis, D.E.M., V.A. and D.Z.; investigation, D.E.M., V.A. and D.Z.; resources, D.E.M., V.A. and D.Z.; data curation, D.E.M., V.A. and D.Z.; writing—original draft preparation, D.E.M., V.A. and D.Z.; writing—review and editing, D.E.M., V.A. and D.Z.; visualization, D.E.M., V.A. and D.Z.; supervision, D.E.M., V.A. and D.Z.; project administration, D.E.M., V.A. and D.Z.; funding acquisition, D.E.M., V.A. and D.Z. All authors have read and agreed to the published version of the manuscript.

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Article

Outcomes of Prolonged Biliary Plastic Stent Dwell Time in Patients with Choledocholithiasis Undergoing ERCP Followed by Cholecystectomy

Tal Weiss [1,2,*], Oren Gal [3,†], Miri Elgabsi [1], Neev Tchernin [1,4], Veacheslav Zilbermints [1,4] and Boris Kessel [1,4,*]

[1] Department of General Surgery, Hillel Yaffe Medical Center, The Rapaport School of Medicine, Technion, Haifa 3525433, Israel
[2] Faculty of Medicine and Public Health, Tel Aviv University, Tel Aviv-Yafo 6997801, Israel
[3] Department of Gastroenterology, Hillel Yaffe Medical Center, The Rapaport School of Medicine, Technion, Haifa 3525433, Israel
[4] Rappaport Medical School, Technion, Haifa 3525433, Israel
* Correspondence: magertal@gmail.com (T.W.); bkkessel01@gmail.com (B.K.)
† This author contributed equally to this work.

Abstract

Introduction: ERCP with temporary biliary stenting followed by elective cholecystectomy and postoperative ERCP is commonly used to treat choledocholithiasis. While early stent removal (within 3–6 months) is generally recommended, some studies suggest that longer dwell time may not increase morbidity. This study aims to evaluate outcomes associated with prolonged stent dwell time of more than six months. **Methods:** We conducted a retrospective study of all patients who underwent ERCP with plastic biliary stent insertion, followed by elective cholecystectomy and postoperative ERCP at a single tertiary center between 2018–2024. Patients were divided into early-ERCP ($\leq$6 months) and late-ERCP (>6 months) groups. The primary outcome was the rate of recurrent biliary episodes. Secondary outcomes included urgent postoperative ERCP, stent reinsertion, and the need for additional ERCP's. **Results:** A total of 203 patients were included (mean age 58.3 $\pm$ 19.8 years). Thirty-one patients (15%) had a stent dwell time of more than six months. Demographic and presenting characteristics were comparable between groups, except for acute cholecystitis, which was more frequent in the early-ERCP group (18% vs. 3.2%, p = 0.034). Recurrent biliary episodes were significantly more frequent in the late-ERCP group (19.4% vs. 5.8%, p = 0.021), as were urgent postoperative ERCP (16.1% vs. 5.2%, p = 0.044), stent reinsertion (35.5% vs. 14.5%, p = 0.008), and additional ERCPs (38.7% vs. 15.7%, p = 0.006). **Conclusions:** Prolonged biliary stent dwell time beyond six months is associated with significantly higher rates of recurrent biliary episodes, urgent postoperative ERCP, postoperative stent reinsertion, and additional ERCP's.

Keywords: endoscopic retrograde cholangiopancreatography (ERCP); biliary stent; choledocholithiasis; cholecystectomy; recurrent biliary episodes

1. Introduction

Choledocholithiasis (bile duct stones) occurs in approximately 10–20% of patients with gallstones [1]. When untreated, it may result in obstructive jaundice, acute cholangitis, or gallstone pancreatitis, each carrying significant morbidity and mortality [2].

The recommended management of choledocholithiasis is guided by risk stratification and institutional expertise. The American Society for Gastrointestinal Endoscopy (ASGE) recommends that patients at high risk for choledocholithiasis—defined by the presence of a common bile duct (CBD) stone on imaging, ascending cholangitis, or both total bilirubin > 4 mg/dL and CBD dilation—should undergo endoscopic retrograde cholangiopancreatography (ERCP) as the preferred first-line diagnostic and therapeutic intervention for bile duct clearance. This should be followed by cholecystectomy to prevent recurrent biliary events, unless contraindicated by comorbidities or patient preference [2].

For patients with intermediate risk, further evaluation with endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP), or intraoperative cholangiography is recommended before proceeding to ERCP or surgery [2].

Surgical alternatives, such as laparoscopic common bile duct exploration (LC-BDE), can be performed as a single-stage procedure during cholecystectomy and have demonstrated comparable rates of stone clearance and adverse events to two-step strategies involving ERCP and cholecystectomy [3]. Randomized trials indicate that, although overall outcomes are similar, the two-step approach is often associated with longer hospital stays, particularly when ERCP is performed preoperatively [3]. In younger patients, single-stage LCBDE is frequently preferred because it avoids papillotomy and enables definitive treatment in one session [4]. Other two-step strategies, such as laparoscopic cholecystectomy with intraoperative cholangiography followed by postoperative ERCP for positive findings, show similar efficacy; however, choledochotomy carries a notable risk of bile leak. More recently, selective strategies guided by intraoperative cholangiography have been associated with shorter hospitalizations by avoiding unnecessary procedures in patients with a low prevalence of choledocholithiasis [2].

When ERCP is employed for the treatment of choledocholithiasis, an endoscopic sphincterotomy is routinely performed as an inherent part of the procedure. The ASGE specifically recommends sphincterotomy as the standard technique for bile duct stone removal, since it provides reliable access to the common bile duct and significantly improves the likelihood of successful and complete stone extraction. Furthermore, sphincterotomy has been shown to decrease the risk of recurrent biliary events when it is followed by a definitive cholecystectomy [2]. However, it should not be regarded as a substitute for surgical removal of the gallbladder and is generally reserved as a sole therapy only for patients who are considered poor surgical candidates or medically unfit for operative intervention [5].

A plastic biliary stent is often placed during the index ERCP, particularly in patients with acute cholangitis or significant obstructive jaundice, as it provides immediate biliary drainage and decompression, and may also facilitate delayed stone extraction when initial clearance is unsuccessful [6,7]. A plastic biliary stent is also considered beneficial when the interval to subsequent cholecystectomy cannot be definitively assured at the time of the index ERCP, due to either patient- or system-related limitations. Less frequently, stent placement may be indicated in the context of anesthesiological constraints requiring urgent termination of the procedure, or in patients whose clinical condition necessitates minimizing procedure duration.

Current guidelines issued by both the European Society of Gastrointestinal Endoscopy (ESGE) and the American Society for Gastrointestinal Endoscopy (ASGE) recommend that plastic biliary stents should be exchanged at regular intervals, ideally every three months, in order to minimize the risks of stent occlusion, cholangitis, and other procedure-related complications [2,6]. In line with these recommendations, the majority of institutions worldwide schedule a follow-up ERCP for stent retrieval within approximately three to

six months after the index procedure [8]. Primary ERCPs performed urgently for biliary drainage in cases of acute cholangitis, hemodynamic instability or severe inflammation during the acute phase may occasionally be limited in their ability to achieve complete ductal clearance at the initial intervention. In such cases, post-cholecystectomy ERCP also serves to confirm biliary clearance and manage any residual stones or sludge [9,10].

Several articles demonstrate that adherence to the recommended timelines for biliary stent exchange in real-world practice is often variable and influenced by multiple factors. This issue became particularly evident during the COVID-19 pandemic, which disrupted the scheduling of endoscopic procedures, including timely removal of plastic biliary stents [8,11,12]. Despite this, data on the outcomes of prolonged stent dwell time beyond six months remain limited. While a number of studies have reported an increased risk of complications—most notably acute cholangitis, stent occlusion, and recurrent biliary obstruction [13]—others have not demonstrated a clear association between extended stent dwell time and increased morbidity [12,14,15]. One study suggested that although maintaining a biliary stent in place for more than 12 months may increase the likelihood of developing cholangitis, this strategy can still be considered an acceptable management option in carefully selected high-risk patients who are not suitable for more definitive interventions [16]. However, this study specifically evaluated a cohort of patients who were not eligible for repeated sessions of endoscopic lithotripsy or for surgical procedures, thereby limiting the application of its findings to the broader population of patients with choledocholithiasis.

Other studies have referred to these long-dwelling biliary stents, which were not intentionally left in place for delayed retrieval, as "forgotten biliary stents." These are often defined as stents retained for longer than 12 months [17–19]. Forgotten biliary stents have been associated with adverse outcomes, including stent occlusion, stent migration, and cholangitis. While these complications have also been reported to occur earlier after stent placement, they are generally observed at lower rates during the initial months. [12,20]. The extent and timing of these complications remain incompletely understood, and an optimal time frame for safe stent removal has yet to be clearly defined.

One potential mechanism for these complications is the development of a stent–stone complex, wherein the stent acts as a nidus for stone formation regardless of the presence of choledocholithiasis at the time of the initial ERCP [21,22]. Over time, these stones may encase or adhere to the stent, complicating retrieval and increasing the risk of infection or obstruction. This phenomenon has been particularly associated with stenting durations exceeding 301 days [21].

Given the clinical implications of prolonged stent dwell time, this study aimed to evaluate the outcomes associated with plastic biliary stent dwell times exceeding six months in patients undergoing ERCP followed by elective cholecystectomy for the management of bile duct stones.

2. Materials and Methods

This retrospective study was designed to evaluate the clinical outcomes associated with prolonged biliary stent dwell time beyond six months in patients undergoing ERCP followed by elective cholecystectomy for the treatment of bile duct stones.

2.1. Patients' Selection

The study population included all patients who underwent ERCP with plastic biliary stent insertion followed by cholecystectomy and postoperative ERCP at Hillel Yaffe Medical Center between January 2018 and November 2024. Patients were excluded if they had

pancreaticobiliary malignancies, benign biliary strictures, or a non-naïve major papilla, as well as those who did not ultimately undergo cholecystectomy.

2.2. Ethical Aspects

The study protocol was reviewed and approved on 24 November 2024 by the Institutional Review Board of Hillel Yaffe Medical Center (HYMC-0076-22).

2.3. Study Outcomes

The primary aim of the study was to evaluate and compare the risk of recurrent biliary episodes after stent insertion between patients whose stent dwell time was less than six months and those in whom the dwell time exceeded six months. Recurrent biliary episodes were defined as the occurrence of symptomatic biliary obstruction, acute cholangitis, or stent migration, each supported by corresponding laboratory abnormalities and imaging findings, and requiring either hospitalization or therapeutic intervention. These recurrent events were systematically assessed across three distinct time intervals: the preoperative period, the postoperative period, and the post-stent extraction period.

The secondary aims of the study were to compare, between the two groups, the incidence of urgent postoperative ERCP, the frequency of restenting during postoperative ERCP, and the overall requirement for additional ERCP procedures. In order to minimize bias related to variability in follow-up duration, the maximum follow-up period for all patients was standardized and set according to the longest stent dwell time observed within the cohort.

2.4. Study Design and Definition

Data for the analysis were retrieved from the hospital's electronic medical records. Collected variables included demographic characteristics, such as age and gender as well as clinical parameters at presentation, including laboratory and imaging findings.

The diagnosis at first admission was defined as the primary indication for further biliary evaluation and included choledocholithiasis, acute cholangitis, biliary pancreatitis, or acute cholecystitis. Choledocholithiasis was considered the diagnosis at first admission when patients were assigned relevant ICD-9 codes (574.21, 574.51, or 574.91), regardless of subsequent diagnostic confirmation by additional imaging or endoscopic evaluation. Complicated disease was defined as a primary diagnosis of choledocholithiasis, biliary pancreatitis, or cholangitis at the time of initial presentation. The decision to pursue further biliary evaluation with endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP), or endoscopic retrograde cholangiopancreatography (ERCP) was made primarily in accordance with contemporary guideline recommendations. Patients presenting with clear indications for ERCP—such as ascending cholangitis, the presence of visible bile duct stones on primary imaging, or persistent jaundice with a bilirubin level exceeding 4 mg/dL in the context of a dilated common bile duct (CBD > 6 mm)—were directed to undergo ERCP as the initial diagnostic and therapeutic step. In contrast, patients with borderline or less definitive features underwent further evaluation with EUS or MRCP, and ERCP was subsequently performed only when choledocholithiasis was confirmed. An additional indication for ERCP was the demonstration of CBD filling defects on cholangiography, which was performed through a previously placed cholecystostomy tube. In our institution, patients treated with a cholecystostomy for acute cholecystitis routinely undergo cholangiography prior to tube clamping or removal, as well as before definitive cholecystectomy.

At our institution, the target is to schedule the postoperative ERCP for stent removal within 3 months of the index ERCP and no later than 6 months whenever feasible. There were no protocolized criteria to intentionally maintain stents beyond 6 months; dwell times >6 months reflected real-world constraints (intercurrent illness or exacerbation of existing chronic health conditions, social/logistic barriers and adherence, endoscopy capacity limits, and COVID-19-related postponement of elective activity). Stent dwell time was defined as the interval from the index ERCP (stent placement) to the postoperative ERCP (stent removal). Patients were categorized as early-ERCP (dwell time $\leq$ 6 months) or late-ERCP (dwell time > 6 months).

2.5. ERCP Procedure

The biliary stent routinely used in our institution is the Boston Scientific Flexima biliary stent (Amsterdam type), which measures 7 cm in length and 10 Fr in diameter. During the index ERCP, the standard strategy in our institution is to perform an endoscopic sphincterotomy in all cases to facilitate bile duct access and effective stone clearance, in accordance with published ASGE recommendations. In cases where prophylaxis for post-ERCP pancreatitis was indicated, a pancreatic stent measuring 5 cm in length and 5 Fr in diameter, without a leading barb, was inserted. This particular type of pancreatic stent was selected for its self-migrating properties, which allow for spontaneous passage and minimize the need for subsequent retrieval.

2.6. Postoperative Management and Follow-Up

For elective laparoscopic cholecystectomy, patients received a single prophylactic antibiotic dose within 60 min before skin incision to prevent surgical-site infection; postoperative antibiotics were not routinely continued unless there was documented cholangitis or intraoperative contamination requiring targeted therapy. Multimodal analgesia was used (paracetamol $\pm$ non-steroidal anti-inflammatory drugs, with short-course opioid rescue if needed). Oral intake was initiated on the day of surgery and advanced as tolerated, with early ambulation encouraged. Discharge was typically planned for postoperative day 1 if the patient was afebrile, hemodynamically stable, tolerating diet, mobilizing independently, and had adequate pain control with oral medications, with no concern for bile leak or other complications. Outpatient follow-up was scheduled at ~4 weeks, and the postoperative ERCP for stent removal was arranged at discharge.

2.7. Statistical Analysis

Statistical analysis was carried out using R software, version 4.3.1 (The R Foundation for Statistical Computing, Vienna, Austria) in conjunction with RStudio 2024.12.1+563. Categorical variables were summarized and reported as frequencies with corresponding percentages, while continuous variables were expressed either as means with standard deviations or as medians with interquartile ranges (IQR, 25th–75th percentiles), depending on the distribution of the data. Normality of continuous variables was evaluated using the Shapiro–Wilk test and inspection of Q–Q plots. Nominal data were compared using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were analyzed with the Mann–Whitney U test. A p-value of $\leq$0.05 was considered to indicate statistical significance. Multivariate regression analysis was performed to identify predictors of recurrent biliary episodes, and the results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Kaplan–Meier analysis was used to estimate the cumulative incidence of recurrent biliary episodes over time. Time zero was the date of the index ERCP (stent placement). The event was the first recurrent biliary episode (symptomatic biliary

obstruction, acute cholangitis, or stent migration) requiring hospitalization or therapeutic intervention. Patients were censored at the earliest of: (i) the date of postoperative ERCP + 7 days (to capture immediate post-extraction events), (ii) last clinical contact documented in the EHR, or (iii) the standardized maximum follow-up of 966 days. Cholecystectomy itself did not constitute a censoring event.

3. Results

A total of 203 patients underwent ERCP with plastic biliary stent insertion followed by subsequent cholecystectomy and postoperative ERCP at a single medical center between 2018 and 2024 (Table 1). The mean age was 58.3 ± 19.8 years. The distribution of sex within the cohort was relatively balanced, with females accounting for 52.7% of the study population. The majority of patients underwent laparoscopic surgery, which was successfully completed in 192 cases (94.6%). Open surgery was performed in 5 patients (2.5%), while laparoscopic procedures required conversion to open surgery in 6 cases (2.9%).

The most common indication for ERCP was choledocholithiasis, observed in 87 patients (42.9%), followed by acute cholangitis in 53 patients (26.1%), acute cholecystitis in 32 patients (15.8%), and biliary pancreatitis in 31 patients (15.3%).

The primary imaging modality at presentation was ultrasound (US), used in 58% of the patients, followed by computed tomography (CT) in 24.4%, and both modalities in 17.6%. Based on initial laboratory and imaging findings, upfront ERCP was performed on 65% of the patients. Ten patients (4.9%) underwent MRCP, 56 patients (27.6%) underwent EUS, and 5 patients (2.5%) were diagnosed with choledocholithiasis by means of cholangiography performed through a cholecystostomy tube.

At presentation, 71 patients (31.0%) had CBD stones on primary imaging, 131 patients (64.5%) demonstrated a dilated CBD, and 82 patients (40.4%) showed elevated bilirubin levels.

The median interval between the initial and postoperative ERCP was 113 days (IQR 93–161). The median time from the index ERCP to surgery was 38 days (IQR 14–57), while the median time from surgery to postoperative ERCP was 78 days (IQR 52.5–107). Eight patients had an ERCP-to-ERCP interval longer than 12 months, with the maximum interval reaching 966 days. This duration served as the reference for the total follow-up period for all patients.

In the Late-ERCP group (n = 31), 22 patients had delays attributed to compliance/social factors or COVID-19–related disruptions. Three patients had surgical issues contributing to the delay before the second ERCP (one cholecystoduodenal fistula that was diagnosed during cholecystectomy; two postoperative collections), and six experienced exacerbations of comorbid conditions that postponed ERCP.

Overall, 16 patients (7.9%) had a recurrent biliary episode during the follow-up period. Of these, 9 events occurred in the interval between surgery and the postoperative ERCP, 5 episodes were recorded within one week of stent retrieval, and 2 episodes developed later during follow-up. Fourteen patients (6.9%) required an urgent postoperative ERCP instead of a scheduled ambulatory procedure. Thirty-six patients (17.7%) underwent biliary stent insertion during the postoperative ERCP due to incomplete biliary clearance, and 39 patients (19.2%) required additional ERCP.

Of the total cohort, 172 patients had a stent dwell time of less than six months (Early-ERCP group), while 31 patients had a stent dwell time exceeding six months (Late-ERCP group) (Table 2). There were no significant demographic differences between the groups. However, acute cholecystitis as the initial diagnosis was significantly more common in the Early-ERCP group (18% vs. 3.2%, p = 0.034), whereas complicated presentations such as

cholangitis, biliary pancreatitis, and choledocholithiasis were more frequent in the Late-ERCP group. Despite these clinical differences, imaging and laboratory findings—including dilated common bile duct, presence of CBD stones, and elevated bilirubin—were similar between the groups.

The rate of recurrent biliary episodes was significantly higher in the late-ERCP group compared to the early-ERCP group. (19.4% vs. 5.8%, $p = 0.021$). Similarly, the incidence of urgent postoperative ERCP, postoperative biliary stent insertion, and the requirement for additional ERCP procedures were all significantly more frequent in the late-ERCP group than in the early-ERCP group (16.1% vs. 5.2%, $p = 0.044$; 35.5% vs. 14.5%, $p = 0.008$; and 38.7% vs. 15.7%, $p = 0.006$, respectively). Notably, when the late-ERCP group was further stratified into two subgroups according to stent dwell time—those with dwell times of less than 12 months and those with dwell times exceeding 12 months—the corresponding rates of recurrent biliary episodes were 13.0% and 37.0%, respectively.

Table 1. Demographic/clinical characteristics and outcomes of patients who underwent ERCP with temporary biliary stenting followed by elective cholecystectomy and postoperative ERCP ($N = 203$).

Median Age in Years (± SD)	58.3 ± 19.8
Female gender	107 (52.7%)
Diagnosis at first admission	
Acute cholecystitis	32 (15.8%)
Cholangitis	53 (26.1%)
Biliary pancreatitis	31 (15.3%)
Choledocholithiasis	87 (42.9%)
Primary imaging modality	
US	112 (58%)
CT	47 (24.4%)
Both	34 (17.6%)
Further evaluation	
MRCP	10 (4.9%)
EUS	56 (27.6%)
Cholangiography through a cholecystostomy tube	5 (2.5%)
Surgical approach	
Laparoscopic surgery	192 (94.6%)
Open surgery	5 (0.2%)
Laparoscopic surgery converted to open surgery	6 (0.6%)
CBD stones on primary imaging	71 (35%)
Wide CBD on primary imaging	131 (64.5%)
Elevated bilirubin on first admission	82 (40.4%)
Median Time between ERCPs in days (IQR)	113 [93–161]
Median Time from ERCP to surgery in days (IQR)	38 [14–57]
Median Time from surgery to post-op ERCP in days (IQR)	78 [52.5–107]
Recurrent biliary episode	16 (7.9%)
Urgent postoperative ERCP	14 (6.9%)
Stent reinsertion during post-op ERCP	36 (17.7%)
Third ERCP	39 (19.2%)

SD, standard deviation; ERCP, endoscopic retrograde cholangiopancreatography; US, ultrasound; CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasound; CBD, common bile duct; IQR, interquartile range.

Table 2. Comparison between Early-ERCP group (stenting period less than 6 months) and Late-ERCP group (stenting period more than 6 months).

	Early-ERCP Group (*N* = 172)	Late-ERCP Group (*N* = 31)	*p* Value
Age (±SD)	58.1 ± 19.4	59.3 ± 22.5	$p = 0.791$
Female gender	93 (54.1%)	14 (45.2%)	$p = 0.436$
Diagnosis at first admission			
Acute cholecystitis	31 (18%)	1 (3.2%)	$p = 0.034$
Cholangitis	44 (25.6%)	9 (29%)	$p = 0.663$
Choledocholithiasis	72 (41.9%)	15 (48.4%)	$p = 0.557$
Biliary pancreatitis	25 (14.5%)	6 (19.4%)	$p = 0.586$
Wide CBD on primary imaging	107 (63.3%)	24 (77.4%)	$p = 0.153$
Bile duct stones on primary imaging	58 (34.3%)	13 (41.9%)	$p = 0.421$
Elevated bilirubin on first admission	71 (43%)	11 (35.5%)	$p = 0.552$
Recurrent biliary episode	10 (5.8%)	6 (19.4%)	$p = 0.021$
Urgent postoperative ERCP	9 (5.2%)	5 (16.1%)	$p = 0.044$
Stent reinsertion during post-op ERCP	25 (14.5%)	11 (35.5%)	$p = 0.008$
Additional ERCP	27 (15.7%)	12 (38.7%)	$p = 0.006$

SD, standard deviation; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct.

Multivariate regression analysis was performed to identify predictors of recurrent biliary episodes (Table 3). Demographic characteristics, the presence of complicated primary diagnoses, and undergoing open surgery were not significantly associated with the occurrence of these events. In contrast, a stent dwell time longer than six months was found to be independently associated with a higher risk of recurrent biliary episodes, with an odds ratio (OR) of 4.42 and a 95% confidence interval (CI) of 1.30–14.52

Table 3. Multivariate Logistic Regression: Predictors of Recurrent Biliary Episodes.

Variable	OR (95% CI)	*p*-Value
Age (per year)	0.99 (0.96–1.02)	$p = 0.4502$
Female gender	0.67 (0.22–1.94)	$p = 0.4567$
Complicated diagnosis	0.53 (0.14–2.54)	$p = 0.3707$
Prolonged stenting	4.42 (1.3–14.52)	$p = 0.0141$
Open surgery	0.73 (0.03–5.11)	$p = 0.7865$

Kaplan–Meier survival analysis was used to depict the cumulative risk of recurrent biliary episode based on the duration of biliary stent retention, as shown in Figure 1.

The probability of remaining free of a recurrent biliary episode was 98.5% at 3 months (95% CI 96.8–100), 87.0% at 6 months (95% CI 78.2–96.7), and 79.6% at 12 months (95% CI 67.6–93.6), corresponding to cumulative incidences of 1.5%, 13.0%, and 20.4%, respectively. Median follow-up by reverse Kaplan–Meier was 3.75 months (≈114 days).

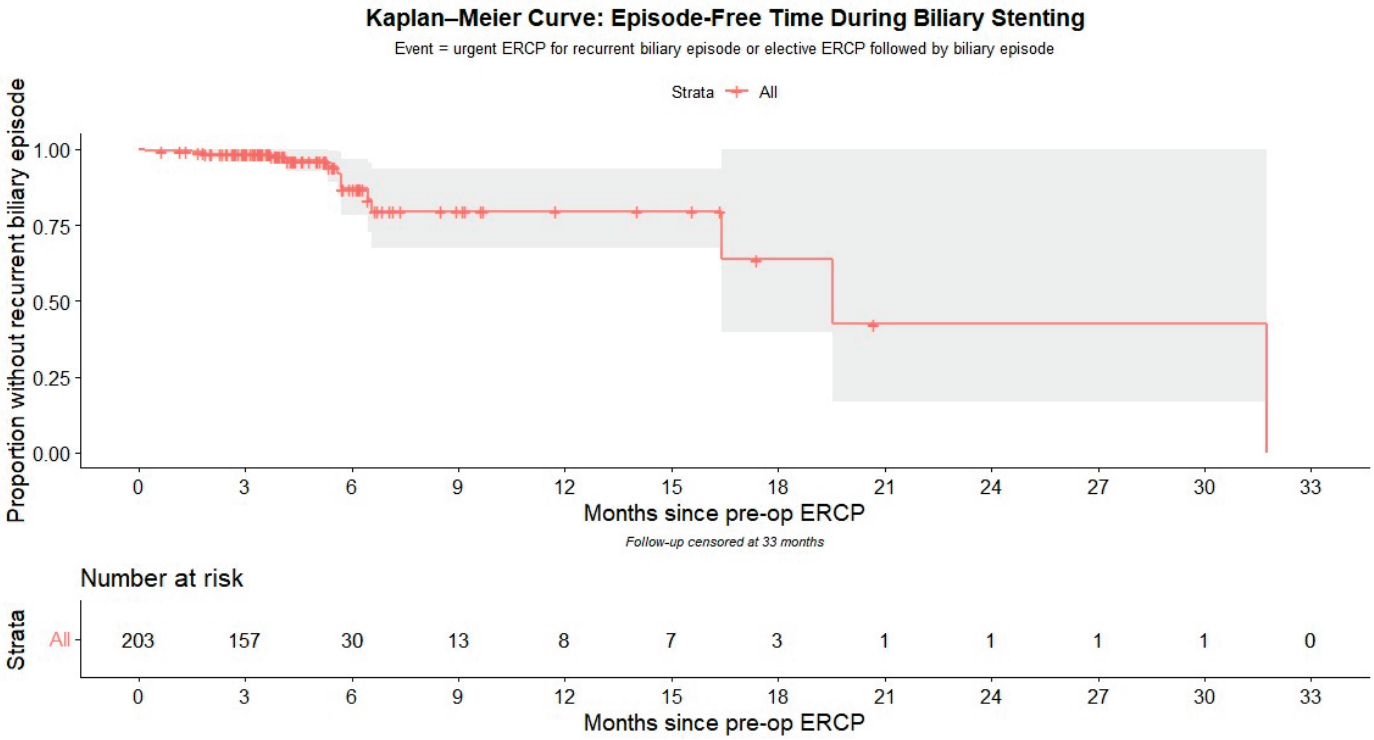

Figure 1. Kaplan—Meier Curve: Episode-Free Time During Biliary Stenting.

4. Discussion

ERCP followed by subsequent cholecystectomy is a widely adopted approach for the management of bile duct stones and their associated complications [3]. During the index ERCP, biliary stents are frequently inserted to ensure adequate drainage and to facilitate further biliary clearance at a later stage [2,6]. In such cases, a postoperative ERCP is generally required for stent removal. This second, post-cholecystectomy ERCP also provides an additional opportunity to achieve complete bile duct clearance in situations where this was not fully accomplished during the initial intervention [9,10].

The reported incidence of recurrent CBD stones after cholecystectomy with initial duct clearance varies considerably across the literature, ranging from 2% to 21%, depending on the study series [23–28]. The most severe manifestation of this complication is acute suppurative cholangitis, which may progress to sepsis and, if untreated, result in death. Early post-cholecystectomy choledocholithiasis (typically within two years) is generally attributed to retained stones—either undetected preoperatively or spilled from the gallbladder during surgery [29]. In contrast, late recurrences are more often considered to be de novo stones formed within the bile ducts [30].

The wide variability in CBD stones recurrence rates is thought to reflect the influence of multiple patient-related, anatomical, and procedural factors. Patient factors associated with higher recurrence include advanced age (particularly >65–70 years). Anatomical risk factors include a markedly dilated CBD ($\geq$15 mm), the presence of multiple or large stones ($\geq$2 stones or $\geq$10 mm in size), cholesterol stone composition, sharp bile duct angulation (<120–145°), and the presence of a periampullary diverticulum. Procedural contributors to recurrence include repeated ERCP sessions and the use of endoscopic mechanical lithotripsy [25,26,28,31–34].

Importantly, the presence of biliary stents has been implicated as a meaningful contributing factor in the development and recurrence of bile duct stone formation. Emerging evidence suggests that biliary stents may promote stone formation via a process known

as the "stent–stone complex". Prolonged stent retention is thought to contribute to biliary stasis, bacterial colonization, and precipitation of bile components, resulting in stones that encase or adhere to the stent [21]. Recent studies have reported that the recurrence rate of common bile duct stones after ERCP may be higher than after surgical common bile duct exploration—ranging from 6–21% versus 2–14%, respectively [23,24]. These findings further support the hypothesis that biliary stents may increase the risk of de novo stone formation.

In our cohort, 16 patients (7.9%) experienced a recurrent biliary episode, defined as the occurrence of symptomatic biliary obstruction, acute cholangitis, or stent migration that necessitated hospitalization or therapeutic intervention. Notably, while other studies often classify these events separately—such as distinguishing cholangitis, stent occlusion, and stent migration—we elected to analyze them collectively as a single entity, as they all essentially represent stent-related morbidity. Furthermore, in clinical practice, it can be challenging to clearly differentiate between these entities. For example, patients with clinically significant stent obstruction or migration are frequently managed as presumed cholangitis, even when they do not strictly meet the diagnostic criteria outlined in the Tokyo guidelines. A larger cohort would likely be required to allow for sufficient statistical power to identify specific risk factors for each individual complication.

No patient experienced a recurrent biliary episode during the interval between ERCP and cholecystectomy, a finding that can likely be attributed to the relatively short waiting period between procedures, with a median of 38 days (IQR 14–57). A total of nine recurrent biliary events were documented in the interval between surgery and the postoperative ERCP. An additional five episodes occurred within one week of stent retrieval, and it is not unlikely that these were related to the recent endoscopic intervention, possibly reflecting a technically difficult procedure. Finally, two biliary episodes occurred later during follow-up, which likely coincides with the well-known phenomena of biliary episodes occurring in post cholecystectomy patients after ERCP. This phenomenon remains a significant clinical concern, mostly during the first few years with recurrence rate as high as 4–24% [35].

A longer stenting duration was significantly associated with these events, supporting the hypothesis that de novo stone formation may partly explain post-cholecystectomy cholangitis or obstructive jaundice in patients with biliary stents. Notably, the multivariate regression analysis did not demonstrate any statistically significant association between the occurrence of recurrent biliary episodes and initial presentation with complicated disease, defined as choledocholithiasis, cholangitis, or biliary pancreatitis. This finding further supports the assumption that the primary cause of biliary events in these cases is stent related recurrent stone formation, rather than residual or retained stones resulting from inadequate biliary clearance at the time of the initial procedure.

In a prospective study that included 78 patients who were treated with plastic biliary stents for common bile duct stones, performing regular stent exchanges at fixed intervals of every three months was shown to significantly reduce the incidence of cholangitis when compared with an on-demand exchange strategy [13]. In accordance with these findings, the European Society of Gastrointestinal Endoscopy (ESGE) recommended in 2019 that plastic stents be exchanged within three to six months in order to minimize the risk of stent-related complications [6]. However, more recent studies—mostly conducted during the COVID-19 pandemic—have reported that stent retrieval after longer dwell durations can be performed safely, without a marked increase in adverse outcomes [12,14]. In our cohort, approximately one in five patients (19.4%) with stents retained beyond six months had a recurrent biliary episode, whereas only 5.8% of patients in the early-ERCP group developed such an event. Notably, previous studies included heterogeneous patient

populations, comprising both benign and malignant etiologies, as well as patients eligible for cholecystectomy and those managed with repeated ERCP and stenting alone. In contrast, our study focused exclusively on patients undergoing ERCP followed by cholecystectomy as definitive treatment for choledocholithiasis.

Currently, an increasing number of ERCPs are performed in patients without a naïve major papilla, primarily for stent exchange or removal. A recent study from a tertiary care center reported that only 25% of ERCPs were index procedures, with the remaining 75% performed as follow-ups [27]. In our study, we demonstrated that a stenting duration exceeding six months was significantly associated with a higher rate of restenting during the second ERCP, as well as an increased likelihood of requiring additional ERCP. This may reflect persistent biliary stones or technical challenges that necessitate placement of a new protective stent, thereby leading to the need for further sessions to achieve definitive bile duct clearance.

This study adds to the literature suggesting that prolonged plastic stent dwell time (>6 months) is associated with increased complications. Given the higher event rates observed with dwell times >6 months, it is reasonable for centers to aim for stent removal within approximately 3 months and to generally avoid retention beyond 6 months when feasible.

This study has several limitations. First, we lack definitive documentation of bile duct clearance prior to cholecystectomy. At our institution, the goal is to achieve complete biliary clearance during the index ERCP whenever feasible. However, even under optimal conditions, ERCP has inherent diagnostic limitations due to its reliance on two-dimensional imaging, which may fail to detect small or residual stones. As already mentioned, even when clearance appears to be complete, a plastic biliary stent is sometimes placed to maintain bile duct patency when the timing of the subsequent cholecystectomy cannot be definitively assured at the index ERCP due to patient- or system-related limitations, or based on the indication for ERCP. A second post-cholecystectomy ERCP is then performed to retrieve the stent and confirm bile duct clearance. Given that 26% of the patients in our cohort presented with cholangitis, it is plausible that some underwent cholecystectomy without complete bile duct clearance. Nonetheless, the comparable baseline characteristics and cholangitis rates between the Early- and Late-ERCP groups suggest that incomplete initial clearance is unlikely to fully account for the observed differences in outcomes.

Second, the Early-ERCP (n = 172) and Late-ERCP (n = 31) groups were uneven, reflecting our institutional practice to remove stents within $\leq$6 months whenever feasible. The small Late-ERCP group may limit statistical power and increase the risk that observed associations reflect chance or unmeasured confounding. We therefore emphasize effect sizes with 95% confidence intervals rather than significance alone. Larger prospective studies with standardized event adjudication are needed to confirm our findings and refine risk estimates.

Third, ERCP-related adverse events (e.g., post-ERCP pancreatitis, bleeding, perforation, cholangitis) and intra-procedural difficulties at stent removal (e.g., fragmentation, occlusion, unplanned repeat ERCP) were not systematically captured in the source records and therefore could not be quantified by group. As a proxy, we counted biliary events within 7 days after stent removal as stent-related, which may under- or over-estimate true procedure-related complications. Future prospective studies should include standardized complication reporting.

Finally, we lacked comprehensive data on patients' comorbidities and socioeconomic status. At our institution, the target is to schedule the postoperative ERCP for stent removal within 3 months of the index ERCP and, when feasible, no later than 6 months. There

were no protocolized criteria to intentionally maintain a stent beyond 6 months; prolonged dwell time reflected real-world constraints—including intercurrent illness, exacerbation of existing chronic health conditions, social or logistical barriers and adherence, limited endoscopy capacity, and COVID-19–related delays of elective services. It is plausible that patients with prolonged biliary stenting represented a sicker population or had more complex social and medical circumstances than those who underwent timely follow-up; this, in turn, could confound outcomes by introducing selection bias. Nevertheless, the approximately 20% rate of recurrent biliary episodes observed in the Late-ERCP group represents a clinically significant adverse outcome, with potential for major morbidity and even mortality—particularly in medically vulnerable patients. Further research into the predictors of delayed follow-up ERCP could help identify at-risk patients and guide targeted interventions. In selected cases—such as patients with a prolonged interval between initial ERCP and cholecystectomy, or those with barriers to follow-up—it may even be reasonable to consider performing the postoperative ERCP during the same hospital admission to reduce the risk of complications associated with delayed stent removal.

5. Conclusions

Prolonged biliary stent dwell time beyond six months is associated with significantly higher rates of recurrent biliary episodes, urgent postoperative ERCP, postoperative stent reinsertion, and the need for additional ERCP procedures. Our findings support targeting plastic stent removal within 3 months and avoiding dwell times >6 months whenever feasible.

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Informed Consent Statement: Patient consent was waived due to the retrospective design and use of fully anonymized data, as approved by the Institutional Review Board of Hillel Yaffe Medical Center (Project ID: HYMC-0076-22).

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ASGE	American Society for Gastrointestinal Endoscopy
CBD	Common bile duct
CI	Confidence interval
CT	Computed tomography
EUS	Endoscopic ultrasound
ERCP	Endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy

IQR	Interquartile range
LCBDE	Laparoscopic common bile duct exploration
MRCP	Magnetic resonance cholangiopancreatography
OR	Odds ratio
US	Ultrasound

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Clinical Impact of Appendiceal Morphology on Surgical Outcomes and Readmissions: Does Size Matter?

Miri Elgabsi [1], Gal Malkiely [1,*], Tal Weiss [1], Neev Tchernin [1], Boris Kessel [1,2,*] and Veacheslav Zilbermints [1,2]

[1] Division of Surgery, Hillel Yaffe Medical Center, Hadera 3820302, Israel; miriv42@gmail.com (M.E.); magertal@gmail.com (T.W.); neevtch@gmail.com (N.T.); veacheslavz@hymc.gov.il (V.Z.)
[2] Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa 3200003, Israel
* Correspondence: galmalki@gmail.com (G.M.); bkkessel01@gmail.com (B.K.)

Abstract

Background: While the severity of acute appendicitis is routinely evaluated, the significance of its morphological characteristics remains underexplored. This study aimed to evaluate the clinical impacts of appendiceal dimensions. **Methods:** This retrospective study included patients who underwent appendectomy. Data on demographics, appendiceal morphology, time from admission to surgery, postoperative complications, and readmission rates were analyzed. Statistical tests, including correlation analysis and multivariate regression, were used. p-value ≤ 0.05 was considered statistically significant. **Results:** Appendix diameter demonstrated positive correlations with age, complicated appendicitis, and surgery duration. Multivariate analysis showed that appendix diameter was found to be a significant predictor of readmission rates, regardless of clinical factors, and has a significant positive association with age in both univariate/multivariate analyses. **Conclusions:** Our findings demonstrate the significance of appendicular morphology in the prediction of readmission rates and the importance of age-specific diagnostic thresholds. The observed age-related changes may warrant re-evaluation of recent diagnostic criteria.

Keywords: appendicitis; morphology; appendix diameter; appendix length; appendectomy; surgical outcome

1. Introduction

Acute appendicitis (AA) is the most common cause of acute abdominal surgical emergencies requiring surgical intervention [1]. Appendicular morphology varies significantly, with lengths ranging from 0.5 to 23 and an average between 5.3 and 11.7 cm. The normal appendiceal diameter is generally accepted as 3–10 mm, and its enlargement usually indicates pathology [2,3].

The primary pathophysiological mechanism of AA is luminal obstruction, often caused by fecaliths, lymphoid hyperplasia, or other blockages [4]. This obstruction results in bacterial overgrowth and increased mucus secretion, causing elevated intraluminal pressure, ischemia, and, if untreated, eventual necrosis or perforation [5].

The diagnosis often relies on a combination of patient anamnesis, physical examination, laboratory tests, and advanced imaging modalities such as ultrasound and abdominal computed tomography (CT), particularly for atypical presentations [6].

CT imaging has established an average appendiceal diameter of 6.6 mm $\pm$ 1.5 mm, with wall thickness rarely exceeding 6 mm [7]. These thresholds are essential for identifying

appendicitis, as age-related changes in normal appendix dimensions are minimal. This consistency underscores the utility of fixed diagnostic thresholds. Currently, despite the development of multiple clinical scores and diagnostic techniques, the morphological features of the appendix (length/diameter) remain under-evaluated as markers for both diagnosis and outcomes. While the appendiceal diameter typically increases during inflammation, its length remains relatively constant. Consequently, the length-to-diameter ratio has been proposed as a potential indicator of disease severity [8]. There are multiple factors that may have an influence on appendix diameter, such as anatomical position, timing from the debut of the inflammatory process, and the speed of its progression. However, at the time of the diagnosis, larger diameters and thicker walls are associated with an increased risk of perforation, regardless of its topography [9]. Additionally, a length-to-diameter ratio below 10 has been proposed as an early diagnostic marker for perforation [10].

This study aims to evaluate the role of appendiceal morphology, specifically its length and diameter, in diagnosis, surgical outcomes, and clinical management.

2. Patients and Methods

This retrospective, single-center study was conducted at Hillel Yaffe Medical Center, Israel. The study included patients aged 18 years and older who underwent appendectomy due to acute appendicitis between 1 August 2020 and 30 October 2021. Inclusion criteria required documented morphological measurements of the appendix (length and diameter) obtained through pathological examination. Patients with incomplete clinical or pathological data were excluded from the final analysis. The severity of the inflammation, classified as either acute simple or complicated appendicitis, was validated based on the final pathological report.

The study was approved by the local ethics committee (protocol number 0118-23-HYMC).

2.1. Data Collection

The data was retrieved retrospectively from hospital electronic medical records. Data collection included patient demographics (age and gender), the time from emergency department admission to surgery, and surgical details: type of procedure (laparoscopic or open), and the method of appendix stump closure (Endoloop, Stapler, or Suturing). Additional clinical data included the duration of the operation (in minutes), the length of hospitalization (in days), and readmission rates, which were defined as hospitalization within one year following appendectomy due to surgery-related complaints. Surgical site infections were classified as superficial (involving only the skin and subcutaneous tissue) or deep (involving the fascial and muscle layers). Morphological measurements, including appendiceal length and diameter, along with pathological diagnoses, were obtained from pathology reports. Pathologists measured the appendix length from the base to the tip using a calibrated ruler. While the appendiceal diameter measured in pathology provides valuable insights into postoperative outcomes, its utility for real-time clinical decision-making is limited as it becomes available only after surgery. To address this limitation, we evaluated preoperative imaging measurements (CT or ultrasound) of appendiceal diameter to assess their correlation with pathological findings. In cases where two radiologic modalities were performed, the diameter of the appendix was confirmed by CT. All radiologic measurements were extracted from electronic reports.

2.2. Statistical Analysis

Continuous variables were assessed for normality using the Shapiro–Wilk test. Relationships between appendiceal morphology (length and diameter) and quantitative

variables were evaluated using Spearman's correlation coefficients, appropriate for non-parametric data. Group comparisons of continuous variables were conducted using the Mann–Whitney U test for two groups or the Kruskal–Wallis test for multiple groups. Categorical variables were analyzed using the Pearson χ^2 test or Fisher's exact test, as appropriate. Univariate analyses identified potential predictors of surgical outcomes, including operation duration, length of hospitalization, and readmission rates. Significant variables from the univariate analysis were included in multivariate regression models to evaluate their independent effects. All analyses were performed in Python using Pandas and statistical libraries, with statistical significance defined as $p \leq 0.05$.

3. Results

A total of 6 patients were excluded from the study due to incomplete data, resulting in a final cohort of 248 patients, including 123 males (51.7%) and 115 females (48.3%), with a mean age of 38.8 years (range: 18–87 years). The mean appendiceal diameter was 0.99 cm (range: 0.4–2.5 cm).

Imaging was performed using either CT (n = 196, 79.0%) or abdominal ultrasound (US). The mean diameter measured on CT was 1.01 cm (median: 1.00 cm; range: 0.40–2.50 cm), while US imaging showed a mean diameter of 0.96 cm (median: 1.00 cm; range: 0.50–1.50 cm). The mean appendiceal length was 6.57 cm (range: 3–14 cm). The mean time since admission to surgery was 742.04 min (range: 210.12–3512.07 min). Operation duration had a mean of 54.42 min (range: 17–214 min). Most procedures were performed laparoscopically (97.5%), while open surgeries accounted for only 2.52% of cases. Closure methods for the appendix stump were predominantly Endoloop (87.4%), followed by Suturing (6.7%) and Stapler (5.9%).

Pathological diagnosis reported that Acute Simple Appendicitis comprised 81.1% of cases, with a mean diameter of 0.98 cm. Complicated Appendicitis, including gangrenous and perforated appendicitis with or without peritonitis, accounted for 18.5% of cases and had a mean diameter of 1.09 cm. Appendix Tumor was observed in 0.4% of cases and had a mean diameter of 0.80 cm.

Readmission occurred in 4.2% of cases, with a mean interval to readmission of 52 days (range: 3–292 days). The most common reason for readmission was deep site surgical infection (four cases), all of them treated with antibiotics alone. One patient was readmitted due to a superficial surgical site infection. Three others presented with abdominal pain and vomiting without signs of bowel obstruction. One patient experienced abdominal pain accompanied by postoperative changes observed on imaging without collection. One patient was hospitalized for surgical repair of an incisional port-site hernia, who had the longest interval to readmission, occurring 292 days post-surgery.

Appendix diameter was positively correlated with age (r = 0.132, $p = 0.042$) and operation duration (r = 0.215, $p = 0.001$).

Additionally, the appendix diameter showed a significant negative correlation with time to surgery (r = −0.196, $p = 0.002$). Appendix length demonstrated limited associations, with only a weak but significant positive correlation with operation duration (r = 0.159, $p = 0.014$) (Table 1).

Male patients had a significantly longer appendix length compared to females ($p = 0.007$), with a mean length of 6.9 cm in males versus 6.3 cm in females. There was no difference in diameter found between both genders ($p = 0.849$). A significant association was identified between appendiceal diameter and readmission rates ($p = 0.004$), with larger diameters observed in patients who experienced readmissions. No significant associations

were observed between appendiceal length and readmission rates ($p = 0.129$) or between appendiceal morphology and type of surgical procedure (laparoscopic vs. open) (Table 2).

Table 1. Spearman correlations of appendix length and diameter with clinical variables.

Appendix Morphology	Variable	Correlation (r)	*p*-Value
Length (cm)	length of hospitalization (days)	0.033	0.610
	Age (years)	0.042	0.515
	Admission to operation (minutes)	−0.056	0.388
	Operation Duration (minutes)	0.159	0.014
Diameter (cm)	length of hospitalization (days)	−0.021	0.745
	Age (years)	0.132	0.042
	Admission to operation (minutes)	−0.196	0.002
	Operation duration (minutes)	0.215	0.001

Table 2. Group Comparisons of Appendix Length and Diameter Among Clinical Variables.

Variable	Comparison Group	U/H *-Value	*p*-Value
Length (cm)	Gender	5645.500	0.007
	Readmission	1461.500	0.129
	Procedure type	571.000	0.451
	Closure methods for appendix stump	1.762	0.414
	Pathology diagnosis group	9.769	0.008
	Age category	2.501	0.286
Diameter (cm)	Gender	6974.000	0.849
	Readmission	1736.000	0.004
	Procedure type	494.500	0.212
	Closure methods for appendix stump	14.805	0.001
	Pathology diagnosis group	21.587	0.000
	Age category	9.498	0.009

* U-Value: Mann–Whitney U test; H-Value: Kruskal–Wallis test, applied as appropriate.

A significant relationship was identified between closure methods of appendicular stump and appendix diameter ($H = 14.805$, $p = 0.001$). The Stapler group exhibited the largest mean diameter (1.22 cm), followed by the Suturing group (0.98 cm) and the Endoloop group (0.98 cm). Post-hoc analysis revealed significant differences in diameter between the Stapler and Endoloop groups ($p = 0.000$) and between the Stapler and Suturing groups ($p = 0.011$).

In terms of operation duration, Stapler used was associated with longer durations ($p = 0.001$) (Table 2).

Significant differences in appendiceal length were observed between cases of acute simple appendicitis and complicated appendicitis (H = 9.769, $p = 0.008$). The mean length of the appendix was 7.38 cm in cases of acute simple appendicitis, compared to 6.51 cm in cases of complicated appendicitis ($p = 0.005$). No significant differences were found involving the tumor group.

For appendiceal diameter, even stronger differences were identified (H = 21.587, $p < 0.001$). Complicated Appendicitis exhibited a significantly larger mean diameter (1.09 cm) compared to Acute Simple Appendicitis (0.98 cm), $p < 0.001$. The tumor group had a mean diameter of 0.80 cm, though no significant differences were observed between this group and the others, likely due to the small sample size.

Multivariate Analysis

Multivariate regression analysis revealed that appendix diameter was significantly associated with readmission rates ($p = 0.001$), despite the limited number of readmission cases (n = 10), indicating that a wider appendix diameter increases the probability of readmissions (Table 3).

Table 3. Multivariate Regression Analysis of Readmission Rates.

Variable	Coefficient	Standard Error	*t*-Statistic	*p*-Value
const	−0.1937	0.085	−2.276	0.024
Appendix Diameter (cm)	0.1699	0.048	3.524	0.001
Appendix Length (cm)	0.0067	0.009	0.754	0.452
Age	−0.0002	0.001	−0.241	0.81
Operation Duration (min)	0.0005	0.001	0.974	0.331
Length Of Hospitalization (Days)	0.008	0.012	0.684	0.495
Admission to Operation (min)	-1×10^{-5}	3.18×10^{-5}	−0.319	0.75
Procedure Type (Open/Laparoscopic)	0.1415	0.084	1.682	0.094
Gender (Male/Female)	−0.0044	0.026	−0.168	0.867
Pathology Diagnosis Group	−0.0304	0.034	−0.897	0.37

However, neither appendix diameter ($p = 0.184$) nor appendix length ($p = 0.161$) was found to be statistically associated with operation duration. Similarly, neither diameter ($p = 0.383$) nor length ($p = 0.735$) was significantly associated with length of hospitalization.

Notably, in contrast to the univariate model and clinical expectations, pathology diagnosis (acute vs. complicated appendicitis) was not significantly associated with readmissions. Similarly, the time interval between admission to the emergency department and surgery was not a significant predictor of readmissions. Furthermore, no significant associations were observed between these variables and operation duration or length of hospitalization, emphasizing the need to explore appendix diameter and other clinical variables beyond pathology diagnosis and time to surgery.

Age emerged as the most consistent and significant predictor in the multivariate model. Age was strongly associated with operation duration ($p < 0.001$) and length of hospitalization ($p = 0.027$). Additionally, operation duration itself was significantly associated with length of hospitalization ($p = 0.002$).

A significant positive association was observed between appendix diameter and patient age (r = 0.132, $p = 0.042$). This association remained significant in the multivariate model after adjusting for confounding factors such as operation duration, time to surgery, and pathological diagnosis ($p = 0.044$).

In order to evaluate the relationship between age and appendix diameter, the patients were divided into three age groups: under 40 years, 40–70 years, and over 70 years. The

mean diameter increased across groups, from 0.96 cm (range: 0.4–2.5 cm) in patients under 40, to 1.06 cm (range: 0.7–2.0 cm) in the 40–70 age group, and 1.08 cm (range: 0.8–1.5 cm) in those over 70. Significant differences in diameter were observed ($H = 9.50$, $p = 0.01$), particularly between patients under 40 and those aged 40–70 ($p = 0.033$). No significant difference was observed between the 40–70 and over 70 groups ($p = 0.086$), suggesting a plateau effect in older populations (Figure 1).

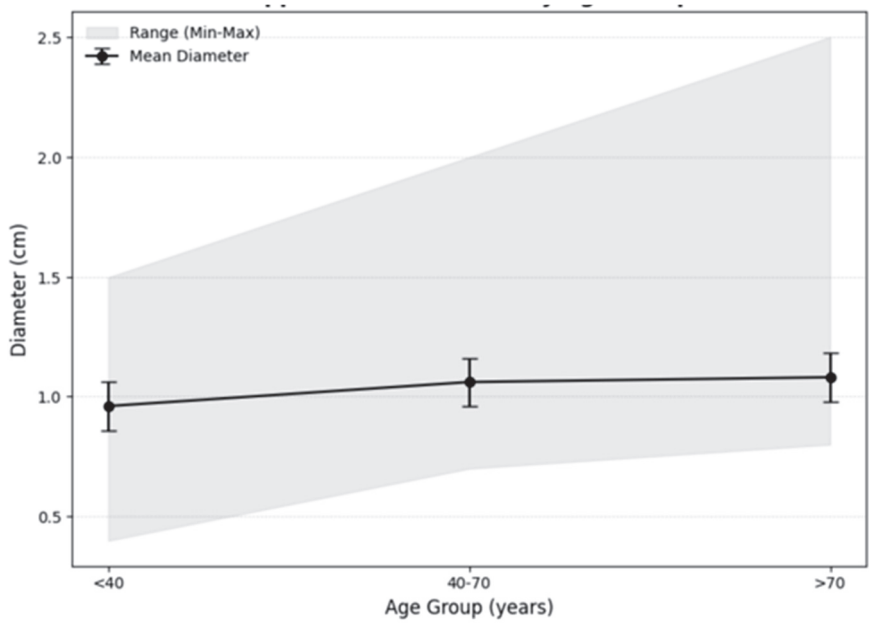

Figure 1. Appendiceal diameter by age groups.

4. Discussion

This study aimed to examine the relationship between appendix morphology (length and diameter) and clinical variables, as well as operative and postoperative outcomes.

In univariate analysis, significant relationships were observed between appendiceal diameter and clinical variables, including age, operation duration—potentially reflecting greater surgical complexity—and time from admission to surgery. Appendix diameter was also significantly associated with complicated appendicitis pathology. In contrast, appendix length showed limited associations, with a weak but significant correlation to operation duration and gender, with males exhibiting significantly longer appendices than females. These findings are consistent with previous studies that noted minimal impact of gender on diagnostic thresholds in adult populations [11]. Length in our study did not show a significant correlation with perforation risk, aligning with findings from Dibekoğlu, who similarly reported no association between appendiceal length and perforation [12].

Pathological diagnoses demonstrated significant differences in appendiceal diameter and length, with larger diameters and longer operations favoring the complicated appendicitis group. This supports the hypothesis that appendiceal diameter reflects pathological progression, with larger diameters marking advanced inflammatory states.

Additionally, appendix stump closure methods were associated with larger diameters and longer operation durations in the Stapler group.

Multivariate regression analysis revealed that appendix diameter was significantly associated with readmission rates ($p = 0.001$), with wider diameters linked to an increased probability of readmissions. Most readmissions were due to infections, aligning with findings from Liang et al. [13], who demonstrated that a larger appendiceal diameter

predicts an increased risk of wound infections following laparoscopic appendectomy. Importantly, this association was independent of other factors, including appendiceal pathology (acute vs. complicated appendicitis) or the time from admission to surgery, highlighting the unique role of diameter in predicting postoperative outcomes.

Age also played a significant role in appendiceal diameter variation. A positive correlation was observed between age and appendiceal diameter in univariate analysis ($\rho = 0.132$, $p = 0.042$), which remained significant in the multivariate model after adjusting for confounding factors ($p = 0.044$). When age was analyzed categorically, patients aged 40–70 exhibited larger diameters compared to those under 40 ($p = 0.033$), while no significant difference was observed between patients aged 40–70 and those over 70 ($p = 0.086$). The mean appendix diameter increased consistently with age (0.96, 1.06, and 1.08 cm), as did the minimum diameter (0.4, 0.7, and 0.8 cm, respectively), across the age groups under 40, 40–70, and over 70. The observed increase in appendix diameter with age has important diagnostic implications, particularly for older populations. Measurements that might indicate pathology in younger adults (e.g., a diameter of 1.0 cm) could represent normal findings in individuals over 70 years. This trend aligns with changes observed in other tubular anatomical structures, such as the common bile duct (CBD), where diameter increases by approximately 1 mm per decade, reflecting age-related adaptations [14,15]. These findings emphasize the diagnostic importance of accounting for age-related changes in appendiceal diameter.

Contrary to our findings, which identified a relationship between age and appendiceal diameter, several studies have reported no such association. A sonographic study spanning pediatric and adult populations demonstrated that an appendiceal diameter > 6 mm remains a reliable marker for diagnosing appendicitis, independent of age [16]. Similarly, sonographic studies in pediatric populations have shown minimal correlation between age and appendiceal diameter, instead identifying body weight as a more significant predictor of diameter [17]. Neal et al. found that an appendiceal diameter greater than 7 mm was more predictive of appendicitis than the traditional 6 mm threshold, particularly in younger children [18]. Notably, this aligns with our suggestion that the diagnostic threshold for appendiceal diameter should increase in adults, particularly in older patients, to account for physiological changes and reduce the risk of overdiagnosis. Additionally, a study conducted in Bangladeshi adults observed a significant reduction in appendiceal diameter with age, with measurements taken at the base, middle, and tip showing a decrease from 6.50 mm in individuals under 20 years to 5.51 mm in those over 60 years [19].

In recent years, there has been a growing interest in the conservative management of uncomplicated appendicitis. Studies have demonstrated that larger appendiceal diameters are often predictive of treatment failure in nonoperative approaches [20,21]. Given that older patients face increased risks of surgical complications, including infections, prolonged recovery periods, and higher mortality rates [22], tailoring treatment strategies based on appendiceal diameter could provide significant clinical benefits. However, the risk of missed appendiceal cancers in nonoperative management should also be considered, as highlighted by Meier et al., who estimated an incidence of 1.7–3.9% in patients aged 65 years and older [23]. This underscores the need for further research into the relationship between appendiceal diameter and the risk of malignancies [24].

The economic burden of appendectomy, particularly in older patients, is considerable, with costs escalating in cases involving perforation or sepsis [25].

Importantly, a positive correlation was observed between both CT and US measurements and pathology findings ($r = 0.573$) and ($r = 0.148$), respectively; ($p < 0.001$), underscoring their utility as surrogates for postoperative pathological evaluations.

Strengths and Limitations

This study has some limitations, mostly resulting from a retrospective design, the relatively small study population, and being performed in a single center. While multivariate analysis showed a significant association between appendix diameter and readmission rates, the small number of readmission cases (n = 10, 4.2%) necessitates cautious interpretation of these findings. Another limitation is the relatively short period of time of the study—1 year. An additional limitation is potential bias due to variations in experience of medical staff performing the procedures, which were not standardized or controlled. In addition, the database did not capture the time elapsed from the onset of symptoms to hospital arrival.

However, despite these limitations, the present research is among the few studies evaluating the clinical significance of appendicular morphology. Our data incorporated the final diagnosis based on pathology results, which ensures its accuracy.

5. Conclusions

Our findings demonstrate that the diameter of the inflamed appendix is significantly associated with key clinical outcomes, including operative duration, surgical complexity, and postoperative infections. Furthermore, a wider appendiceal diameter was found to be significantly correlated with higher readmission rates, whereas no association was observed between appendiceal length and clinical outcomes evaluated in this study. Our results also demonstrated that the diameter of the inflamed appendix increases with age. We believe these findings provide valuable insights into existing knowledge and may warrant further prospective research to establish better age-specific thresholds for acute appendicitis diagnosis accuracy, particularly in older populations.

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Skin-Dwelling Bacteria Survive Preoperative Skin Preparation in Reconstruction Surgery

Hannah R. Duffy [1,2], Nicholas N. Ashton [1], Porter Stulce [1,2], Abbey Blair [1], Ryan Farnsworth [1,2], Laurel Ormiston [3], Alvin C. Kwok [3,†] and Dustin L. Williams [1,2,4,5,*,†]

[1] Department of Orthopaedics, University of Utah, Salt Lake City, UT 84112, USA; hannah.duffy@utah.edu (H.R.D.); n.ashton@utah.edu (N.N.A.); u1270386@utah.edu (P.S.); abbey.blair@hci.utah.edu (A.B.); u1190395@utah.edu (R.F.)
[2] Department of Biomedical Engineering, University of Utah, Salt Lake City, UT 84112, USA
[3] Department of Surgery, Division of Plastic Surgery, University of Utah Health, Salt Lake City, UT 84112, USA; alvin.kwok@hsc.utah.edu (A.C.K.)
[4] Department of Pathology, University of Utah, Salt Lake City, UT 84112, USA
[5] Department of Physical Medicine and Rehabilitation, Uniformed Services University of the Health Sciences, Bethesda, MD 20814, USA
* Correspondence: dustin.williams@utah.edu
† Co-senior authors: These authors contributed equally to this work.

Abstract

Background/Objectives: Accurately determining the bacterial bioburden that survives preoperative skin preparation (PSP) is critical in understanding PSP efficacy and its limitations. Clinical PSP approval relies on a bacterial sampling method described in the American Society for Testing and Materials (ASTM) standard E1173-15. Though common, this technique may overlook deep-dwelling skin bacteria. The objective of this study was to test the hypothesis that deep-dwelling skin flora would survive PSP, and more growth would be detected using a destructive sampling method compared with ASTM E1173-15. **Methods:** Twelve female participants with a scheduled deep inferior epigastric perforator (DIEP) artery flap procedure at the Huntsman Cancer Institute in Salt Lake City, UT, were enrolled between January and August 2024. PSP was performed using three 26 mL ChloraPrep applicators (2% CHG), and excess tissue was collected. Bacteria in the skin were quantified using a destructive sampling method and ASTM E1173-15, and bioburden outcomes were compared. Two participants were excluded from the quantitative analysis. **Results**: Bacteria survived PSP in every participant. A greater diversity and more bacteria were quantified with destructive sampling than ASTM E1173-15 ($p < 0.01$). Generally, anaerobic bioburden values were higher than aerobic bioburden values. Higher bioburden correlated with processing more skin from a participant. Genotypic identification of select isolates identified *Staphylococcus epidermidis* and *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*) as surviving bacteria, among others. Immunofluorescence revealed bacteria in all skin layers. No participant exhibited clinical signs of infection in the abdominal region. Human data corroborated previous porcine data collected using destructive skin sampling after PSP. **Conclusions**: Clinical PSP application does not create a sterile field. Destructive skin sampling techniques may be more effective than ASTM E1173-15 at resolving bacterial PSP survivors contributing to SSI risk.

Keywords: preoperative skin preparation; surgical site infection; skin microbiome; bacterial sampling

1. Introduction

Since the adoption of preoperative skin preparation (PSP) and modern surgical techniques, infection rates have plummeted to single digits, yet the efficacy of clinical PSP may be overstated [1–3]. PSP-surviving microorganisms colonize surgical sites, leaving 55–90% of surgical wounds contaminated upon closure [4,5]. Bacterial colonizers principally originate from deeper skin layers, out of antiseptic reach, and may replicate in the surgical site. Surviving bacteria account for 70–95% of surgical site infections (SSIs) [6]. Thus, endogenous microflora is the most significant contributor to SSIs, exceeding contaminants from room air, instruments, or surgical personnel [6–9]. Consequences of SSIs are severe: SSIs increase patient morbidity and mortality and cost the United States (US) healthcare system up to 10 billion USD annually [1,7]. Tissue quantification techniques that thoroughly detect microbial survival following PSP are critical in determining PSP efficacy and addressing SSIs.

Histological and quantification evidence indicates that bacteria survive PSP. Gram staining, scanning electron microscopy, and fluorescence imaging have shown that bacteria live throughout the skin's layers, concentrated along hair follicle tracts and pilosebaceous glands [10–13]. Since 1949, operating room contamination has been deemed largely preventable except for bacteria originating from the patient microbiota; chemical skin sterilization was considered "impossible" [14,15]. In the operating room, surgical instruments carry up to 4.4×10^3 colony forming units (CFU) after use [16], most patients have positive cultures from at least one swabbed location before wound closure [17], and pedicle screws handled in the sterile field culture 10^5 to 10^7 CFU per screw [18]. Notwithstanding PSP and aseptic techniques, more than 70 years of data show viable bacteria living deep in skin layers.

Resolving deeper-dwelling microbes using today's test methods is challenging. The industry relies on the American Society for Testing Materials (ASTM) standard E1173-15, *Standard Test Method for Evaluation of Preoperative, Precatheterization, or Preinjection Skin Preparations*, for testing chemical antiseptics [19]. In 1994, 59 Federal Register 31402 was released by the Food and Drug Administration (FDA), promoting ASTM E1173-15. This standard is referred to as the cup scrub method as it comprises the following steps: (1) filling a sterile cylinder (the cup) on the skin with solution, (2) suspending skin bacteria into the liquid by scrubbing with a rubber spatula, (3) culturing the suspension. While the cup scrub method is common, it fails to resolve deep-dwelling microbes. Researchers estimate that scrubbing accounts for 4–85% of the total microflora [11,20–22]. For example, skin scrubbing produced an average bioburden of 5.1×10^3 CFU/cm^2 compared with 3.0×10^4 CFU/cm^2 from a small excision [11]. Similarly, the calculated total skin bioburden was 5×10^4 CFU/cm^2 for skin scraping, but 10^6 CFU/cm^2 for a biopsy [21]. These investigations indicate that scrubbing methods may not detect bacterial PSP survivors from deeper skin layers [21,22].

In contrast to scrubbing methods like the cup scrub method, destructive methods excise and destroy the skin where PSP is applied and account for deeper-dwelling organisms. Previously, we used full-thickness tissue homogenization—the tissue blend method—in a Yorkshire/Landrace hybrid pig model to test the effectiveness of common clinical PSP [23,24]. Neither povidone-iodine nor chlorhexidine gluconate (CHG) produced the required 2–3 $\log_{10}$ reduction proposed by the FDA [23]. When we compared the cup scrub method with the tissue blend method following a 4% CHG PSP, the tissue blend method resolved more than 100× the bacteria than the cup scrub method/cm^2 of pig skin [24]. The tissue blend method is advantageous because it uses large surface areas, and PSP can be rapidly screened for effectiveness. In clinical practice, destructive methods are

usually limited to a biopsy punch. However, extra tissue may be available in reconstructive surgeries, such as deep inferior epigastric perforator (DIEP) artery flap procedures.

Previous studies quantifying the bacterial survivors after PSP focused on the bacteria present on surgical tools or have insufficiently addressed deep-dwelling microorganisms [4,16–18]. In this study, we applied the cup scrub and tissue blend methods to discarded skin from DIEP surgeries. The primary objective was to quantify PSP-surviving microbes across a large surface area and depth of human skin. We hypothesized that skin flora would survive PSP, and more growth would be detected using the tissue blend method than the cup scrub method. The secondary objective was to determine if the post-PSP bacterial profiles in human skin paralleled those in pig skin. We hypothesized that human skin would have similar quantities and types of bacterial survivors following PSP as in pigs.

2. Materials and Methods

2.1. Recruitment

Following approved Institutional Review Board protocol 00161032 (approved on 11 October 2023) at the University of Utah, 12 participants from the Huntsman Cancer Institute in Salt Lake City, UT, were recruited between January and August 2024 (2 were excluded from quantitative and statistical analysis based on using an alternate PSP or systemic antibiotic use disclosed after collection, see Section 2.2 below). Participants were English-speaking adults (18+) with a scheduled DIEP procedure at the Huntsman Cancer Institute. Patients in a vulnerable population including pregnant patients, prisoners, children, or disabled individuals were excluded from participation.

All subjects provided written informed consent to participate in this observational study. Gender was participant-identified. Individuals who were in vulnerable populations, taking systemic antibiotics at the time, or undergoing cancer treatments were excluded. Treatment that occurred >14 days before surgery was allowed. No compensation was provided.

For sample size determination, we assumed the same effect size as a previous animal study comparing the tissue method with the cup scrub method [24]. We reported means of 3.24 and 1.05 $\log_{10}$ CFU/cm^2 for the tissue blend and cup scrub methods, respectively. Standard deviations (disregarding data clustering) were 1.10 and 1.11 $\log_{10}$ CFU/cm^2 for the tissue blend and cup scrub methods, respectively [24]. We required 6 participants per group to detect this effect size with 80% power using a two-sided comparison (alpha = 0.05). We recruited more than 6 participants per group to allow flexibility in our sample size assumptions. When possible, we further increased the sample size by collecting data from multiple sites using each method type (tissue blend and cup scrub) per participant. This additional data collection increased the statistical power to greater than 80%.

2.2. Surgery and Skin Collection

PSP was performed using three 26 mL BD ChloraPrep Hi-Lite applicators (2% CHG in a solution of 70% isopropyl alcohol) (Figure 1A). Cefazolin (~2 g) was prophylactically administered intravenously within 30 min of incision. Antimicrobial washes or wipes were not prohibited.

Excess abdominal skin tissue was collected aseptically, concurrent with surgery. Specimen(s) were placed in 1 or 2 sterile containers and transported to the Bone and Biofilm Research Lab (BBRL) for immediate processing (a 10-min walk).

Samples were collected from two individuals who were excluded from the quantitative and statistical analysis. The first exclusion occurred after the participant received a

povidone-iodine PSP instead of a CHG PSP. As the regular surgical protocol at the Huntsman Cancer Institute consists of a CHG PSP, except in the case of allergy or sensitization, we excluded the numerical data for this individual to maintain PSP consistency across the participant pool. For the second exclusion, it was only after tissue collection was performed that we learned the participant had received systemic antibiotic treatment. This participant was not taking systemic antibiotics upon consent and, thus, was enrolled. We excluded this participant's data because systemic antibiotics could have influenced bioburden outcomes and, thus, data analysis. We reported the outcomes of these participants only generally.

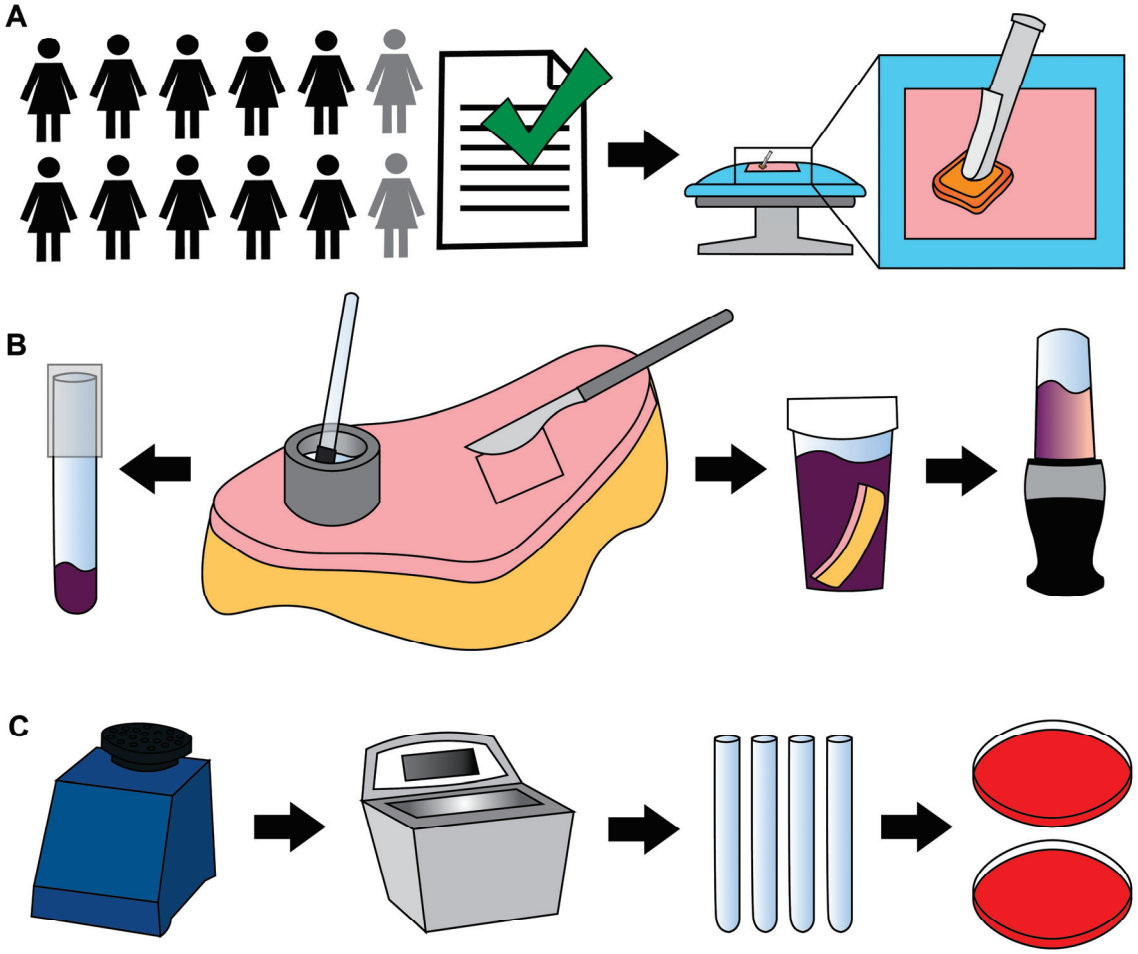

Figure 1. Methods schematic. (**A**) Informed consent of 12 female participants. Ten were included in the quantitative analysis. Before surgery, each participant's skin was treated with PSP. (**B**) Participant tissue was processed using the cup scrub method using a stainless-steel cylinder (the cup), a small rubber spatula, and a glass tube (left arrow). The tissue blend method involved using a scalpel to cut full-thickness skin and a blender to homogenize the tissue (right arrows). CHG was neutralized using D/E broth. (**C**) Each sample was vortexed, sonicated, serially diluted, and plated on Columbia blood agar in duplicate, then incubated under aerobic or anaerobic conditions.

2.3. Processing

The skin was aseptically transferred to a sterile surface. Areas were designated for cup scrub and tissue blend samples. The cup scrub method was performed using up to 5 sterile, custom-made stainless-steel cylindrical cups (1 ½ in. outer diameter × ¼ in. wall thickness × 1 in.) as previously described [24]. Cup scrub sampling solution was mixed following ASTM E1173-15 by dissolving 0.4 g KH_2PO_4 (1048711000, MilliporeSigma, Burlington, MA, USA), 10.1 g Na_2HPO_4 (ACM7558794, Alfa Chemistry Materials, Holbrook, NY, USA), and

1.0 g of Triton X-100 (108643, MilliporeSigma) in 1 L of distilled water, then autoclaved [19]. With a cup held in place on the skin's surface, 3 mL of prepared solution were pipetted into the cup (Figure 1B). A sterile rubber spatula (Cole-Parmer, Vernon Hills, IL, USA) was used to scrub the skin within the cup (~1 min). One mL of solution from the cup was pipetted into a sterile tube containing 1 mL of Dey–Engley (D/E) neutralizing broth (D3435, MilliporeSigma). Tubes were vortexed (1 min) and sonicated (10 min) (Figure 1C).

The tissue blend method was performed by cutting 4 cm × 4 cm full-thickness samples, leaving ~1–2 cm of subcutaneous fat. Tissue pieces were placed individually into sterile sample containers (2767M1, Medicus Health, Kentwood, MI, USA) containing 50 mL of D/E broth. When the skin's geometry did not allow a 4 cm × 4 cm shape, images of the pieces were collected, and the surface area was determined using ImageJ (version 1.54g, National Institutes of Health). Where possible, sections were cut to areas approaching 16 cm^2. Tissue sections used to collect cup scrub data were not used to collect tissue blend data, and vice versa.

Blender cups and blades (Ninja QB3001SS Fit Compact, SharkNinja, Needham, MA, USA) were cold sterilized using 200-proof ethanol as described previously [23,24]. Blenders were run with ethanol (~15 s), then rinsed and blended with sterile deionized water (~15 s).

Full-thickness tissue samples and D/E broth were transferred to a sterile blender cup and blended (45 s), vortexed (1 min), and sonicated (10 min) as previously described [24]. Blending was performed without tissue to confirm that the processing technique was contamination free [23,24].

Four hundred µL of each sample mixture were plated on Columbia blood agar (A16, Hardy Diagnostics, Sandy, UT, USA) to make a 0-dilution plate. Bioburden was quantified as previously described [23]. Plates were incubated under aerobic and anaerobic conditions using Anaerogen packs (AN25US/AN35US, Hardy Diagnostics) for 48 ± 4 h and 72 h to 5 days, respectively, at 37 °C in a jacketed incubator. Colony counts constituted bioburden (CFU/cm^2).

A representative colony of each distinct morphology from the individual study groups was isolated with a sterile loop, cultured on agar, cataloged, and cryopreserved (−80 °C) as previously described [23]. Isolates were classified by morphology, color, and Gram stain to determine biodiversity. Nelson Labs genotyped ten unique species using Organism ID: Genotypic, MicroSeq w/Gram stain.

2.4. Additional Analyses: Clinical Outcome, Surface Area and Time

A retrospective chart review was performed to record surgical outcomes (including infection) at least 90 days after surgery. We also analyzed the number of samples processed per participant (correlated to increased surface area) compared with bioburden. Finally, we investigated the impact of surgical and processing (collection to incubation) times (to the nearest half hour) on bioburden.

2.5. Statistical Analysis

Up to five samples of the same method type (cup scrub or tissue blend) from the same participant introduced data clustering across our participant population. Therefore, we analyzed the data using a mixed-effects linear regression, also known as a multilevel model, using a restricted maximum likelihood (REML). This process accounted for multiple samples within a single participant's tissue. We used an REML fitting algorithm in order to obtain p values based on the t distribution, rather than base significance tests on the z distribution used by other fitting algorithms. This makes the REML model more correct for small sample sizes.

In our model, the experimental condition (cup scrub or tissue blend) was a fixed effect, and the participant was a random effect. Average bioburden values were reported as the mean ± the standard error. All statistical results were obtained using Stata statistical software (version 18.0, StataCorp LLC, College Stata, TX, USA). All reported p values are from a two-sided comparison, where statistical significance was set at $p < 0.05$.

2.6. Histology

ARUP Laboratories performed Hematoxylin and Eosin (H&E) staining. Four participant skin samples were selected for immunofluorescence (IF) analysis based on features present on the H&E stains. IF staining was performed using a Gram-Positive Bacteria Lipoteichoic acid (LTA) Monoclonal Mouse Antibody (primary, G43J, ThermoFisher Scientific) and a Goat Anti-Mouse IgG Alexa Fluor 488 Polyclonal antibody (secondary, SouthernBiotech, Birmingham, AL, USA). The blocking buffer consisted of 1% Bovine albumin (Millipore Sigma), 0.1% Tween 20 (Sigma-Aldrich, St. Louis, MO, USA), and 0.1% Triton-X 100 (Sigma-Aldrich) diluted in phosphate-buffered saline. Visualization occurred using inverted microscopes: a Nikon Eclipse E600 (Nikon, Minato City, Tokyo, Japan) for H&E and Leica DMi8 (Leica, Wetzlar, Germany) for IF.

2.7. Comparison to Previous Work

We compared the bioburden outcomes of this study to those of previous animal work [23,24].

3. Results

Participants were females aged 35 to 65 (mean = 48.6 ± 8.1 years). No participant exhibited clinical signs of infection in the abdominal region. Antibiotics were administered to two participants prophylactically after surgery for issues unrelated to the flap removal.

Bacteria were detected in the PSP-prepared skin of every participant. Bioburden quantification values ranged from below detectable limits (noted with 0 $\log_{10}$ CFU/cm^2 in Figure 2) to 5.36 $\log_{10}$ CFU/cm^2. The detection limits for the cup scrub and tissue blend methods were 0.47 and 0.89 $\log_{10}$ CFU/cm^2, respectively. Variability was observed across participants and sampling methods. Eight out of ten participants had aerobic growth using the cup scrub method. Eight out of ten participants had aerobic growth using the tissue blend method, although these participants differed from those with positive cultures using the cup scrub method. A negative culture result using one method was not predictive of the other. Some samples with negative aerobic cultures exhibited growth on the anaerobically cultured plates. Infrequently, a cup scrub sample exhibited substantial growth, while the tissue blend sample taken from the skin immediately adjacent had little to no detectable growth. Yet, tissue blend samples generally exhibited more growth than cup scrub samples.

Higher bioburden was observed in tissue blend samples compared with cup scrub samples (Figure 2A). Cup scrub samples had 1.18 ± 0.25 (mean ± standard error) and 1.41 ± 0.33 $\log_{10}$ CFU/cm^2 for aerobically and anaerobically grown cultures, respectively (p = 0.474). Tissue blend samples had 1.97 ± 0.36 and 2.61 ± 0.47 $\log_{10}$ CFU/cm^2 for aerobically and anaerobically grown cultures, respectively (p = 0.007). Data point clusters increased from the cup scrub aerobic bioburden to the tissue blend anaerobic bioburden. On average, there were 0.79 $\log_{10}$ more CFU/cm^2 cultured aerobically from tissue blend samples than from cup scrub samples (p = 0.006). Similarly, 1.20 $\log_{10}$ more CFU/cm^2 cultured anaerobically from tissue-blended samples than cup scrub samples ($p < 0.001$).

Similar trends were observed when considering biodiversity (Figure 2B). Per 400 µL of plated solution, all samples had between 0 and 5 different bacterial types. The cup

scrub method resulted in 1.00 ± 0.20 (mean ± standard error) and 1.43 ± 0.39 bacterial types for aerobic and anaerobic samples, respectively. The tissue blend method resulted in 1.49 ± 0.27 and 1.78 ± 0.33 bacterial types for aerobic and anaerobic samples, respectively. The difference between the cup scrub and the tissue blend methods was significant ($p = 0.021$ for aerobic and $p = 0.042$ for anaerobic).

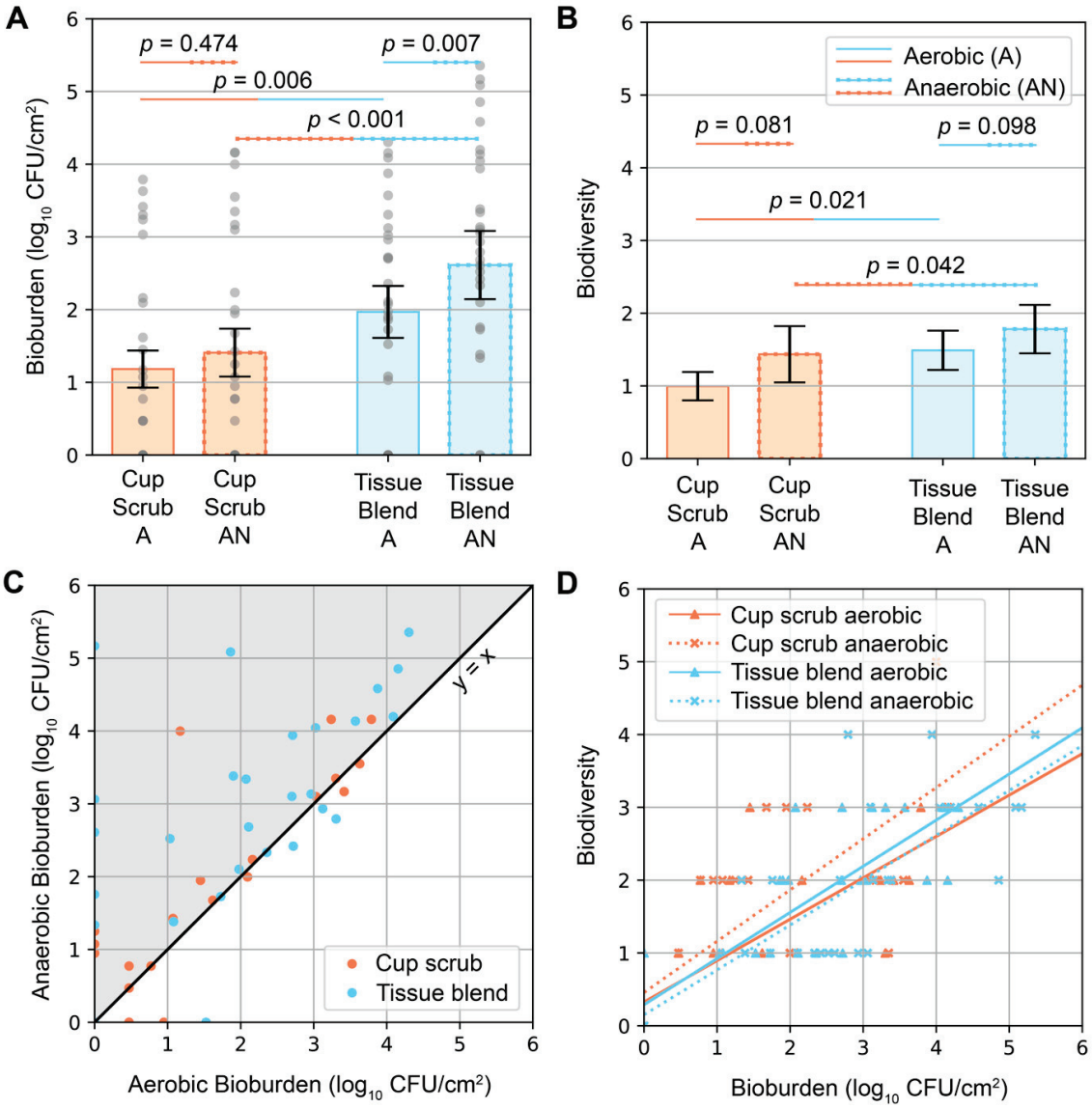

Figure 2. Aerobic and anaerobic bioburden quantities and biodiversity following the cup scrub and tissue blend methods. "A" = aerobic conditions. "AN" = anaerobic conditions. (**A**) Bioburden (log_{10} CFU/cm^2) differentiated by processing method and incubation environment. Orange bars represent the cup scrub method. Blue bars represent the tissue blend method. Gray circles represent pooled data points across all participants. Error bars show the standard error. (**B**) Biodiversity as determined by colony types using morphology and Gram stain. Orange bars represent the cup scrub method. Blue bars represent the tissue blend method. Error bars show the standard error. (**C**) Anaerobic and aerobic bioburden for each sample were plotted against each other as (aerobic bioburden, anaerobic bioburden). The black line is x = y. Most samples had higher anaerobic bioburden than aerobic bioburden (gray area). (**D**) Biodiversity correlated positively with bioburden across all sample groups. The linear regression trendlines were y = 0.57x + 0.33 (cup scrub aerobic), y = 0.70x + 0.46 (cup scrub anaerobic), y = 0.63x + 0.29 (tissue blend aerobic), and y = 0.62x + 0.15 (tissue blend anerobic).

Anaerobic bioburden values were higher than aerobic bioburden values for the same sample (Figure 2C). Biodiversity correlated positively with bioburden (Figure 2D); the more bacteria we observed, the more likely we were to observe different bacterial types.

Samples cultured from a participant who received a PSP containing povidone-iodine resulted in bioburden values similar to those who received a CHG PSP. In contrast, the individual who received systemic antibiotics had calculated bioburdens that approached 0 CFU/cm^2 or were below detectable limits. Most plates from this individual had no growth. This result prompted the investigation into the clinical case which exposed the antibiotic dosage.

Secondary investigations of surface area and time produced varying results. In general, the more skin samples we obtained from a participant, the greater the average bioburden (Figure 3A). This pattern was most notable in samples that were tissue-blended and cultured anaerobically. The time from surgery start to tissue removal, and from removal to completion of sample processing varied from participant to participant (Figure 3B). These differences depended on the type of surgery (unilateral or bilateral), surgical complications, the number of samples collected, and varying processing duration. From start to finish, the surgical and sample processing times ranged from 7 to 15 h (mean = 9.5 $\pm$ 2.2 h). The average surgical time and processing times were 5.5 $\pm$ 1.9 h (mean $\pm$ standard deviation) and 4.0 $\pm$ 2.2 h, respectively. Plotting the total surgical and processing times against bioburden did not elucidate a distinguishable pattern; bioburden levels of all types were found across varying times (Figure 3C).

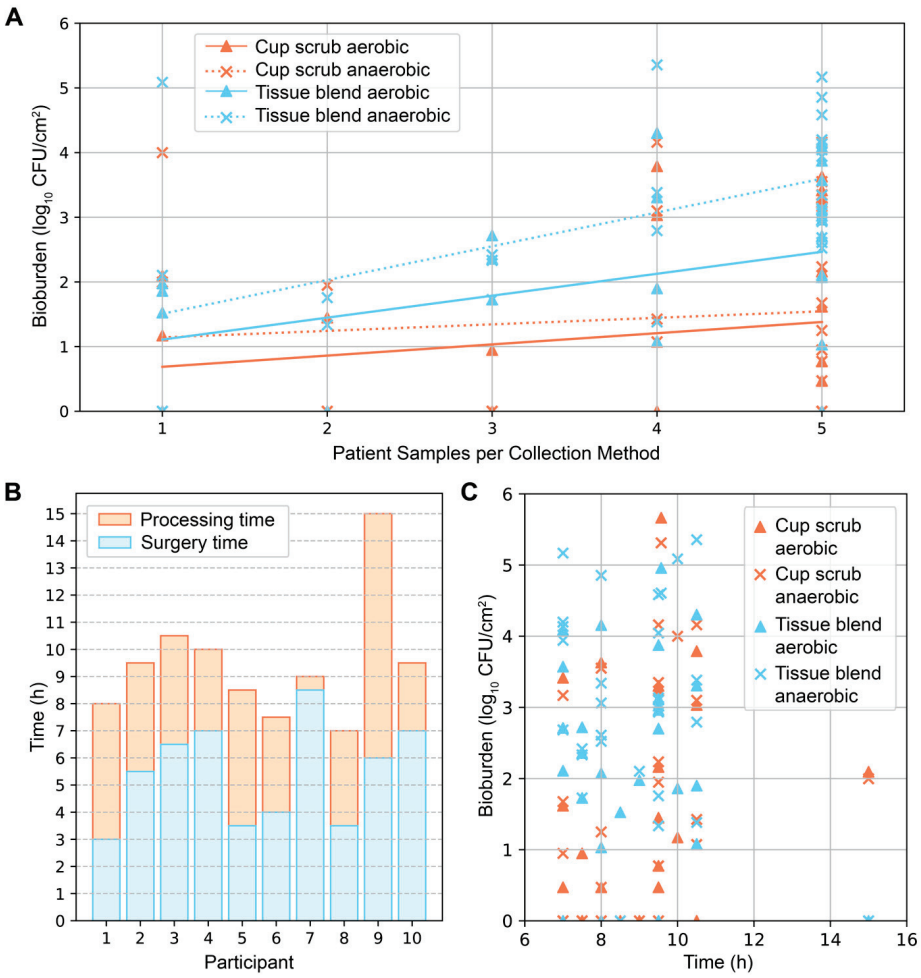

Figure 3. Additional analyses of surface area and time. (**A**) Bioburden ($\log_{10}$ CFU/cm^2) plotted

against the number of skin samples collected per patient differentiated by sampling technique and incubation environment. The number of skin samples (1–5) correlated with increased surface area for each sampling technique by approximately 5 cm^2 for cup scrub samples and 16 cm^2 for tissue blend samples. Positive trendlines were observed: y = 0.17x + 0.51 (cup scrub aerobic), y = 0.10x + 1.04 (cup scrub anaerobic), y = 0.34x + 0.77 (tissue blend aerobic), and y = 0.52x + 0.98 (tissue blend anerobic). (**B**) Time from surgery start to processing end for each participant. Surgery time was calculated from surgery start until estimated tissue removal. Processing time was calculated using the estimated tissue removal time to incubation time. Transport and laboratory processing time varied. (**C**) No correlation was observed between the total time from surgery start to processing end and bioburden.

Of the 116 representative isolates analyzed, nearly all (96.6%) were Gram-positive, with 57.8% cocci and 42.2% rods. Most species grew aerobically and anaerobically. We identified the following unique species (not representative): *Staphylococcus epidermidis*, *Cutibacterium acnes*, *Bacillus toyonensis*, *Staphylococcus lugdunensis*, *Lysinibacillus xylanilyticus*, *Cupriavidus pauculus*, *Chryseobacterium massiliae*, *Enterococcus casseliflavus*, *Staphylococcus lugdunensis*, and *Stenotrophomonas pavanii*.

H&E stains showed characteristic skin samples of the abdominal region (Figure 4). One sebaceous gland was observed in the skin of participant 1. Hair follicles were only observed in participant 4. IF corresponding to LTA, a characteristic component of Gram-positive bacterial cell walls, was observed in pockets scattered throughout all layers throughout the epidermis and dermis (Figure 4A–G). Fluorescence intensity varied across patients, sections, and locations, but was present in every slide stained. The signal was especially concentrated around features such as sebaceous glands and hair follicle shafts when present. Positive and negative controls were used to confirm the presence of bacteria.

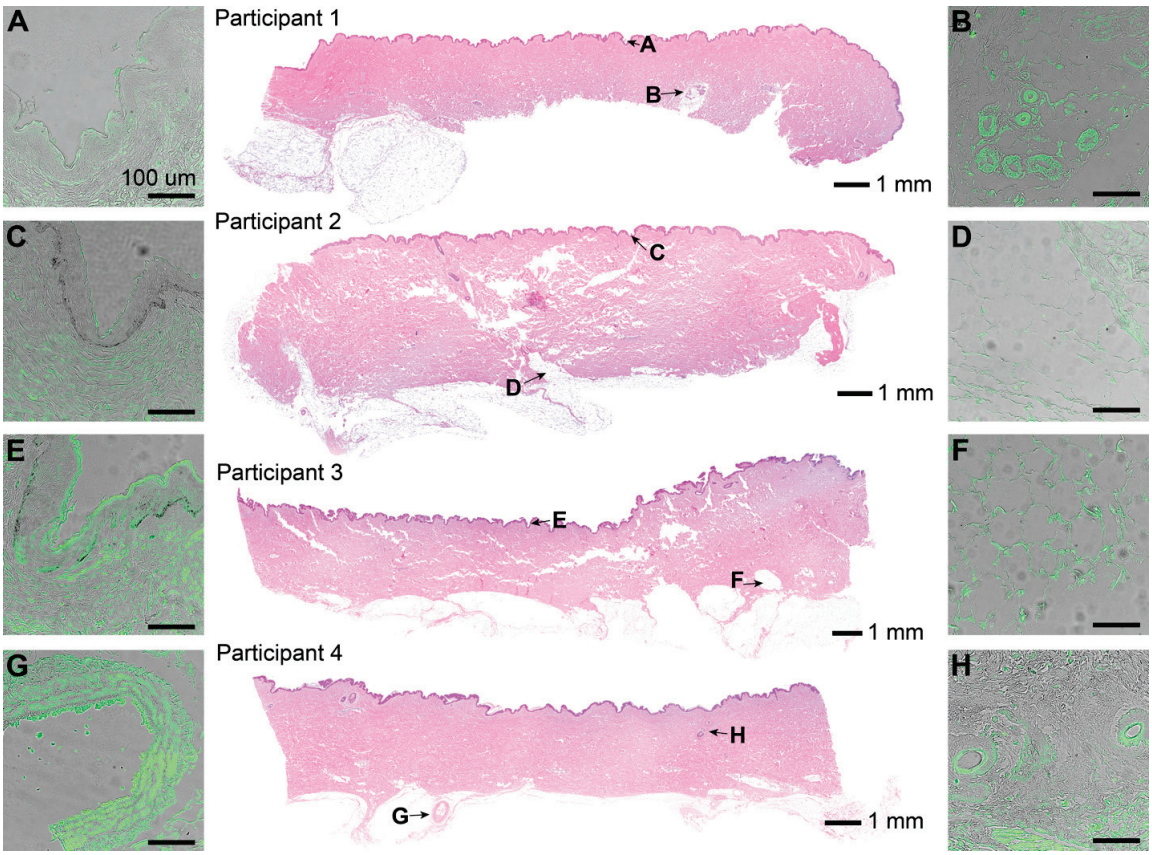

Figure 4. Representative histological sections from the skin of 4 participants treated with PSP (CHG

or povidone-iodine). The central column shows skin sections stained with H&E (4× magnification, processed using Adobe Lightroom, version 4.3), letters corresponding to areas of the skin cross-section, and individual scale bars. The left and right columns show 20× magnified raw images of the skin sections stained with IF targeting LTA as an antigen using 250 ms of exposure, a gain of 4, and 55% light intensity. IF was overlayed with the background image of the same slide using 10 ms exposure and 90% light intensity. Each scale bar for (**A**–**G**) represents 100 µm. (**A**) Stratum corneum from participant 1. (**B**) Sebaceous gland from participant 1. (**C**) Stratum corneum from participant 2. (**D**) Subcutaneous tissue from participant 2. (**E**) Stratum corneum from participant 3. (**F**) Subcutaneous tissue from participant 3. (**G**) Larger hair follicle (partially broken) from participant 4. (**H**) Two small hair follicles from participant 4.

Data were consistent with our previous animal findings of CHG PSP efficacy [23,24]. An overlay of pig data correlated with the human skin outcomes (Figure 5). The difference between the cup scrub and tissue blend methods was significant in both pigs ($p < 0.001$, aerobic) and humans ($p = 0.006$, aerobic)

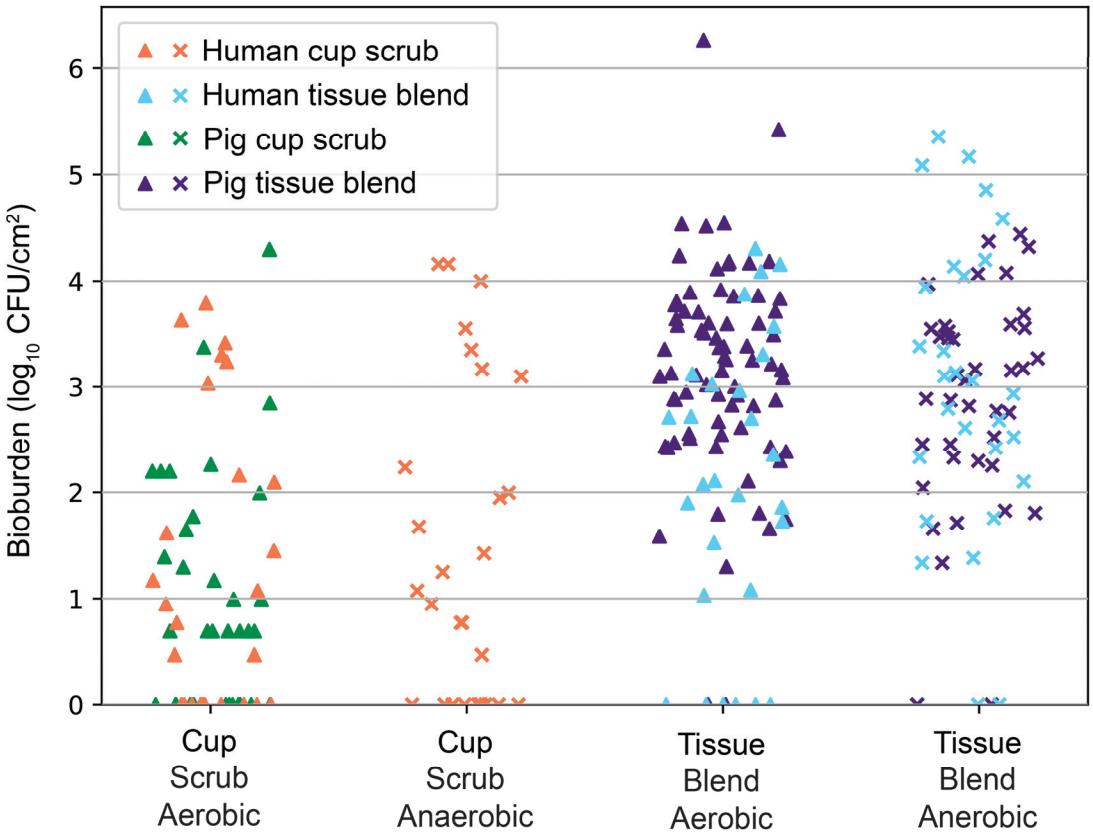

Figure 5. Overlay of human cup scrub and tissue blend bioburden following a CHG PSP with previously collected pig cup scrub and tissue blend bioburden ($\log_{10}$ CFU/cm^2) from 2021 and 2022 [23,24]. Each point represents a unique sample collected from either a participant or an animal. Human cup scrub data are indicated in orange. Human tissue blend data are shown in blue. Pig cup scrub data are recorded in green. Pig tissue blend data are marked in indigo.

4. Discussion

PSP is a critical disinfection step before surgery, but quantification and histological data show that viable bacteria remain post PSP. Our hypothesis that skin flora would survive PSP and more bacteria would be detected with the tissue blend method was supported. Samples quantified using the tissue blend method consistently cultured more bacteria from all skin regions compared with the cup scrub method, underpinning the

potential benefit of using a destructive skin sampling method to test PSP. Our secondary hypothesis was also supported as post-PSP bacterial profiles in human skin were similar to what we previously identified in pig skin [23].

The cup scrub method primarily considered surface-dwelling bacteria, while the tissue blend method considered all skin layers using full-thickness excisions. At most, the cup scrub rubber spatula could dislodge bacteria from a few cell layers deep. Thus, more than 10x the quantity of bioburden was detected using the tissue blend method compared with the cup scrub method for anaerobic cultures. Biodiversity results showed a less drastic difference between the two methods than bioburden. In positive cultures, only one or two species usually dominated, even if more types of bacteria were present. This finding suggested that bacterial communities are often found in pockets and not evenly distributed.

The presence of *C. acnes*, a common skin commensal and frequent SSI culprit of shoulder, breast, and spine surgery, may explain why anaerobic cultures were more plentiful and diverse than aerobic ones [25–27]. Because *C. acnes* grow best in a low-oxygen environment and were not visible in aerobic colony counts, we allowed the anaerobic plates to incubate for up to 5 days [28]. In the skin, anaerobic environments can be found in the hair follicles and glands, deep enough to be suspended in sebum. In contrast, some participants had matching aerobic and anaerobic counts, indicating that *C. acnes* were not necessarily colonizing all participants. These findings are supported by previous work [20,29].

The data correlating higher bioburden with more surface area suggest that operations with large surgical incisions introduce more bacteria into the surgical site than smaller incisions. Across a bacterial population that is randomly distributed, the likelihood of a direct hit with a surgical instrument to a highly colonized follicle increases with greater surface area transected. Additionally, surgeries with larger incisions often incorporate more biomaterials, e.g., sutures, that may become a nidus for bacterial replication. Biomaterials may reduce the infectious dose of bacteria by 10^3 CFU/g [30]. While previous work has shown that biomaterials with antimicrobial coatings may be useful in minimizing this effect, infections persist [31]. These scenarios warrant future work to assess the benefits of antimicrobial biomaterials and minimally invasive laparoscopic or robotic surgery to decrease bioburden.

The culture results using the tissue blend method addresses the weaknesses of previous work by quantifying skin bioburden using large surface areas and full-thickness depths. In a comparison of abdominal colonization using a modified cup scrub method and a 1 cm^2 excision, the cup scrub method produced 5.1×10^3 ($3.7 \log_{10}$) CFU/cm^2 compared to 3.0×10^4 ($4.5 \log_{10}$) CFU/cm^2 from the excision [11]. While these values are higher than what we detected from the individuals in this study, no PSP type or processing method was specified for the excisions. In a different group of patients, 14.5% of the skin biopsies cultured bacteria immediately following PSP preparation. This percentage is lower than our 100% positive detection rate; however, the study did not list surface area size or depth and, therefore, is not a true comparator [5]. The positive culture rate for the same group of patients rose to 55% using a cotton swab on the skin's surface after wound closure, suggesting that bacteria may have initially survived below detectable limits and replicated in the surgical wound [5]. Similarly, 71% of open-heart surgery patients were culture-positive from a tissue swab [17]. Others have suggested that ~90% of implantation sites may be immediately colonized [4]. While swab or selective cultures produce valuable data, they may underreport bacterial survival [11]. The design of this study fully assesses PSP-surviving microbes by using large surface areas and accounting for microbes in all skin layers.

Patterns of fluorescence confirmed microbiological outcomes showing bacteria in all skin layers. The lack of skin features was likely due to the anatomical region we investigated (abdomen) and the participant population we recruited. This area is relatively hairless in females, and glands are sparser than regions with more hair and moisture. Despite fewer features, fluorescence pockets of varying intensity were observable across all slides and skin layers. Thus, the bioburden we reported may be a low-end estimate compared with areas with dense skin appendages. The nature of this study provides a basis for future work investigating the bioburden of various anatomical locations following PSP.

This small cohort study was principally designed as an observational investigation for hypothesis testing and, therefore, had limitations. Due to the nature of the DIEP flap surgery as a breast reconstruction procedure following mastectomy, we recruited from a female-identifying population. There are some variations between males and females stemming from physiological and anatomical differences between the sexes. Sweat, sebum, and hormone production levels in males and females as well as hair density and pH play a large role in the skin microbiome [32,33]. Though significant, sex is one of many factors including age, ethnicity, and location of residence that significantly impact our microbial communities [33]. Although we did not collect specific data on patient location of residence, participants were all receiving care in Salt Lake City, UT, further increasing participant similarity. Finally, immediate microbiological analysis of fresh tissue and the DIEP procedure scheduling at the Huntsman Cancer Institute implicated a maximum recruiting cap of two participants per week. Our minimum recruiting threshold was ten participants who received the same PSP application. As the main outcome of this study was detecting surviving bioburden, some homogeneity within a small participant cohort is acceptable, even if the bioburden numbers may not be broadly applicable to all patients.

While modern surgeries exhibit far fewer infections than in the past, PSP-surviving skin flora remains an SSI risk. As bioburden was present in the tissue of every patient sampled, additional skin disinfection practices that can be utilized before clinical PSP is performed merit future investigation. Antiseptic diffusion may be limited by the time frame of PSP, the available concentration, and the diffusion characteristics of clinical antiseptics today. Testing current and new PSP technology using full-thickness skin sampling to detect surviving skin flora may lead to improved antiseptic strategies to increase decolonization efficacy. Having observed that skin flora survives PSP similarly in human and pig skin, our previously established pig model may be an effective translational system to test current and develop future PSP technologies [23,24]. We encourage researchers to apply the tissue blend method during antiseptic product development to account for deep-dwelling bacteria and more thoroughly resolve organisms that increase SSI risk.

5. Conclusions

Current PSP approaches do not create a sterile field as they leave viable skin-dwelling bacteria on patient skin. Destructive skin testing techniques that incorporate large surface areas and full-thickness excisions may be more effective at resolving bacterial PSP survivors that contribute to SSI risk. New PSP approaches may be needed to overcome residual bioburden and should be tested using destructive sampling. Based on the clinical translatability observed from this study to our established porcine model, we propose that testing the efficacy of improved PSP technologies using the tissue blend method in our porcine model may lead to reduced infection risk for millions of patients.

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Abbreviations

The following abbreviations are used in this manuscript:

PSP	Preoperative Skin Preparation
SSI	Surgical Site Infection
US	United States
CFU	Colony Forming Units
ASTM	American Society for Testing and Materials
CHG	Chlorhexidine Gluconate
DIEP	Deep inferior epigastric perforator artery flap procedure
D/E	Dey–Engley Neutralizing Broth
H&E	Hematoxylin and Eosin
IF	Immunofluorescent
LTA	Lipoteichoic acid
REML	Restricted maximum likelihood

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Impact of Dexmedetomidine-Based Opioid-Sparing Anesthesia on Opioid Use After Minimally Invasive Repair of Pectus Excavatum: A Prospective Randomized Controlled Trial

Minju Kim, Jaewon Huh, Hoon Choi and Wonjung Hwang *

Department of Anesthesiology and Pain Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea; jkkpsk@gmail.com (M.K.); ether@catholic.ac.kr (J.H.); hoonie83@catholic.ac.kr (H.C.)
* Correspondence: amoeba79@catholic.ac.kr; Tel.: +82-2-2258-6162; Fax: +82-2-537-1951

Abstract: Background: Opioid-sparing anesthesia (OSA) using dexmedetomidine has gained attention as an alternative to opioid-based anesthesia (OBA) due to its potential to reduce opioid consumption and the associated side effects. This study aimed to investigate the effect of dexmedetomidine-based OSA on postoperative pain intensity, opioid consumption, and recovery outcomes in patients undergoing a minimally invasive repair of pectus excavatum. **Methods:** Eighty-four patients undergoing a minimally invasive repair of pectus excavatum were randomized to either the OSA group, receiving dexmedetomidine, or the OBA group, receiving remifentanil. The primary outcome was the total amount of analgesics administered within 24 h postoperatively. The secondary outcomes included pain intensity and analgesic consumption over 48 h, recovery outcomes, intraoperative hemodynamics, and opioid-related complications. **Results:** The OFA group reported a significantly reduced total morphine-equivalent dose within 24 h (55.4 ± 31.1 mg vs. 80.2 ± 26.7 mg, $p < 0.001$) and lower VAS scores at 24 h (3.9 ± 1.5 vs. 5.4 ± 2.1, $p < 0.001$). Pain intensity was lower, and analgesic consumption was reduced in the OSA group 1–6, 6–24, and 24–48 h after surgery. Recovery times and intraoperative hemodynamics were comparable between the groups, with no significant differences in opioid-related complications. **Conclusions:** Dexmedetomidine-based OSA effectively reduces postoperative pain and opioid use without compromising recovery or hemodynamic stability. These findings support its use as a viable alternative to OBA, particularly in the minimally invasive repair of the pectus excavatum.

Keywords: dexmedetomidine; opioid; opioid-free anesthesia; opioid-sparing anesthesia; pectus excavatum

1. Introduction

The minimally invasive repair of pectus excavatum (MIRPE) is widely performed in children to address progressive cardiopulmonary complications [1]. In pediatric patients, it relieves cardiopulmonary compression and enhances the long-term functional outcomes. However, in adults, pectus excavatum can still cause considerable physiological issues, including dyspnea, reduced exercise tolerance, and esthetic concerns [2]. Despite its benefits, MIRPE in adults is less common due to higher complication risks and significant postoperative pain.

Compared to pediatric patients, adults undergoing MIRPE encounter greater challenges [3]. A more rigid chest wall along with increased risks of bar displacement, bleeding, and extended recovery necessitate advanced pain management strategies. Effective postoperative pain control is essential to improving recovery quality, shortening hospital stays, and optimizing patient outcomes [4,5]. However, research on optimizing anesthetic techniques for adult MIRPE remains limited.

Opioids have long been the cornerstone of intraoperative and postoperative pain management, offering reliable analgesia and stable hemodynamics [6]. However, their use is frequently associated with a range of adverse effects, collectively termed opioid-related adverse drug events (ORADEs). Common complications include postoperative nausea and vomiting (PONV), constipation, urinary retention, pruritus, sedation, cognitive impairment, and respiratory depression, which, in severe cases, can lead to fatal outcomes [7,8]. These complications often result in prolonged hospital stays, higher healthcare costs, and decreased patient satisfaction [7,9].

Beyond these immediate risks, opioids carry significant long-term concerns, such as opioid-induced hyperalgesia, chronic pain syndromes, and dependency, even with appropriate use [10,11]. The widespread reliance on opioids in medical settings has also fueled a global health crisis, with opioid dependency and misuse now contributing significantly to morbidity and mortality worldwide [10,12]. These challenges underscore the urgent need for alternative pain management approaches that minimize opioid exposure while ensuring effective analgesia.

In response to the opioid crisis, opioid-sparing anesthesia (OSA) has garnered increasing interest [13,14]. OSA incorporates agents such as dexmedetomidine, lidocaine, ketamine, neuraxial blocks, and multimodal analgesia to minimize or eliminate opioid use while maintaining effective pain control. Among these, dexmedetomidine (DEX) has drawn particular attention for reducing opioid consumption and providing analgesia without the adverse effects typically associated with opioids [15].

DEX is a highly selective α-2 adrenergic agonist that inhibits norepinephrine release, thereby suppressing sympathetic activity in the central nervous system [16,17]. This mechanism provides dose-dependent and reversible sedation, analgesia, and sympatholytic effects. Unlike traditional sedatives, DEX induces a sedative state similar to natural sleep while preserving respiratory function, making it well-suited for light-to-moderate sedation [18,19]. Initially introduced for sedation in patients in intensive care units, DEX is widely used to manage patients who are being mechanically ventilated, offering advantages such as maintaining respiratory function, facilitating early extubation, and reducing the risk of delirium [20,21]. In anesthesiology, DEX is employed as an adjunct to primary anesthetics, neuraxial blocks, or patient-controlled analgesia (PCA) [22]. The perioperative use of DEX activates endogenous analgesic pathways and attenuates perioperative stress responses [23,24]. Through these mechanisms, it effectively lowers pain scores, reduces opioid use, and improves recovery quality [22,25,26].

Given these promising pharmacological and clinical properties, we hypothesize that implementing DEX-based OSA in MIRPE surgery will reduce opioid consumption, alleviate pain intensity, and lower opioid-related complications compared to conventional opioid-based balanced anesthesia. This study aims to compare opioid consumption between DEX-based OSA and opioid-based anesthesia (OBA) in patients undergoing MIRPE.

2. Materials and Methods

2.1. Study Population

This prospective, single-blind, randomized controlled trial was conducted following approval from the Institutional Review Board on 28 May 2019 (approval number: KC19MCSI0334) and registration on ClinicalTrials.gov on 2 September 2019 (NCT04073758). This study adhered to the ethical principles outlined in the Declaration of Helsinki, and written informed consent was obtained from all enrolled participants.

This study was conducted between September 2019 and December 2022. The inclusion criteria were as follows: age between 20 and 75 years; American Society of Anesthesiologists (ASA) physical status classification I–III; and scheduled for the elective minimally invasive repair of pectus excavatum (MIRPE). The exclusion criteria included the following: history of prior surgeries; chronic analgesic use or chronic pain; psychiatric or neurological disease; significant arrhythmia; severe cardiovascular, renal, or hepatic disorders; pregnancy or breastfeeding; known drug allergies; and refusal to participate.

2.2. Randomization and Blinding

Patients were randomly assigned to either the OBA group or the OFA group using a computer-generated randomization table. Due to differences in drug administration protocols, the attending anesthesiologists were aware of group assignments. However, the patients, the attending surgeons, and the medical caregiver responsible for perioperative care and outcome assessments remained blinded to group assignment throughout the study.

2.3. General Anesthesia and Surgical Procedure

Premedication was not administered before surgery. General anesthesia was initiated using intravenous propofol 1.5 mg/kg (Fresenius-Kabi, Bad Homburg, Germany) and rocuronium 0.8 mg/kg (Esmeron®, MSD Korea, Seoul, Republic of Korea), with standard monitoring which included electrocardiography, non-invasive blood pressure, pulse oximetry, oxygen saturation, end-tidal carbon dioxide ($EtCO_2$), and Bispectral Index™ (BIS; Aspect Medical Systems Inc., Newton, MA, USA). After tracheal intubation, mechanical ventilation was set with a fraction of inspired oxygen (FiO_2) of 0.5, a tidal volume of 6 mL/kg, and $EtCO_2$ maintained between 35 and 40 mmHg. Continuous arterial pressure was monitored via an arterial catheter inserted into the dorsalis pedis artery. Lactated Ringer's solution was infused at a maintenance rate of 4 mL/kg/h.

Anesthesia was sustained using 1.5–2.0 vol% sevoflurane (Sevorane®, AbbVie Korea, Seoul, Republic of Korea) and the assigned study medications. Adjustments to anesthetic drugs were guided by maintaining the systolic blood pressure and heart rate within 20% of the baseline values, with BIS between 40 and 60. In the OSA group, dexmedetomidine (Precedex®, Pfizer, New York, NY, USA) was administered as a loading dose of 0.6 μg/kg over 10 min before induction, followed by a continuous infusion at 0.5 μg/kg/h, titrated in increments of 0.1 μg/kg/h as needed. These doses were initially determined based on our institution's thoracic surgery protocols and further refined through an internally conducted pilot study. The infusion was discontinued once wound closure began. In the OBA group, remifentanil (Ultiva®, GlaxoSmithKline, Brentford, UK) was delivered via a target-controlled infusion system (Orchestra Base Primea®, Fresenius Vial, Brezins, France) with an effect-site concentration of 3.0–4.0 ng/mL during induction and adjusted to 2.0–5.0 ng/mL during the procedure. Hypotension (systolic blood pressure <90 mmHg) was treated with ephedrine (4 mg), and bradycardia (heart rate <50 bpm) was managed with atropine (0.25 mg). Sugammadex 2–4 mg/kg (Bridion®, Merk & Co., Rahway, NJ, USA) was administered at the end of the procedure based on the train-of-four (TOF) ratio, followed by extubation.

All surgeries were performed by a single surgeon following the same protocol [27]. Patients were positioned supine with arms suspended overhead to optimize the surgical field. The insertion points for the pectus bars were identified based on the depressed area and hinge points bilaterally. Each bar (Pectus Bar®, Biomet Microfixation, Jacksonville, FL, USA) was custom-shaped during surgery to match the patient's chest contour. Small incisions were made in the midaxillary region bilaterally, and the bars were inserted, passed under the sternum, and rotated 180° to elevate the chest wall. Stabilization was achieved using claw fixators or bridge plates, with drains placed only in cases of significant bleeding.

At the end of the procedure, intercostal nerve blocks were performed at the 4th to 9th intercostal spaces bilaterally using 2 mL of 0.5% ropivacaine per level in both groups. Additionally, a thoracic continuous wound infiltration system (CWIS; On-Q® Pain Relief System, Halyard, Alpharetta, GA, USA) was positioned subcutaneously to continuously deliver 0.25% ropivacaine (Naropin®, Aspen Pharmacare, Durban, South Africa) at a rate of 4 mL/h. Intravenous patient-controlled analgesia (PCA) was prepared with fentanyl (20 mcg/kg) diluted in saline to a total volume of 100 mL. PCA devices (AutoMed 3200®, ACE Medical Corp., Ltd., Seoul, Republic of Korea) were set to deliver a basal infusion of 1 mL/h and a bolus of 1 mL, with a lockout interval of 10 min. PCA was initiated in the postoperative anesthetic care unit (PACU). Pain was assessed using a visual analogue scale (VAS) at 10 min intervals in the PACU and every 4 h in the ward. If a patient's VAS score

exceeded 4 despite PCA, rescue fentanyl (1 μg/kg) was administered, and if pain persisted, intravenous tramadol (50 mg) was given. To prevent postoperative nausea and vomiting (PONV), palonosetron (75 mcg) was administered 30 min before surgery was completed. For cases of PONV, intravenous metoclopramide (10 mg) was administered as required.

2.4. Outcome Measurement

The primary outcome was the cumulative analgesic consumption within the first 24 h postoperatively. This included opioids delivered through PCA and any additional analgesics administered in the ward, such as tramadol and pethidine. All administered drugs were converted into morphine-equivalent doses (MEDs) using the Opioid Analgesic Conversion Table [28], and the total was calculated in MED.

The secondary outcomes included pain intensity assessed using VAS scores at the recovery unit, and at 1–6, 6–24, and 24–48 h postoperatively. Participants noted the highest pain intensity during each period using a 100 mm VAS ruler, reflecting the most severe pain experienced since the last assessment. Additionally, total analgesic consumption, converted into MED, was measured at these same time points.

Recovery outcomes, including the time from the discontinuation of volatile anesthetics to eye opening and extubation, were used to evaluate emergence speed. The time to first rescue analgesia was also documented. Hemodynamic variables such as blood pressure and heart rate were monitored at predefined intervals: before anesthesia induction, immediately post intubation, at the time of incision, 30 min after incision, and at the conclusion of surgery. The incidence of intraoperative hypotension (systolic blood pressure <90 mmHg) and bradycardia (heart rate <50 bpm) was recorded, along with the administration frequency of rescue medications (ephedrine and atropine).

Postoperative complications related to opioids—such as PONV, hypotension, constipation, urinary retention, dizziness, respiratory depression, and temporary PCA discontinuation—were documented. Blood samples for cortisol, epinephrine, and norepinephrine levels were collected at the baseline, at the time of incision, after the pectus bar flip, and immediately after surgery. Plasma samples were obtained by centrifuging at 3000 rpm for 10 min at a temperature of 4 °C, with all specimens processed within an hour and subsequently stored at −70 °C. Epinephrine and norepinephrine levels were quantified using high-performance liquid chromatography (Agilent 1200, Agilent Technologies, CA, USA), and cortisol levels were analyzed using an electrochemiluminescence immunoassay (Cat no. 06687733, Roche Diagnostics, Mannheim, Germany).

2.5. Sample Size and Statistical Analysis

The sample size was determined based on prior research [16], which indicated a 30% reduction in opioid consumption with an anticipated standard deviation of 10%. To ensure 80% statistical power at a significance level of 0.05, a minimum of 38 patients per group were required. Considering an estimated dropout rate of 10%, 42 participants were recruited for each group, totaling 84 subjects for this study.

Statistical analyses were conducted using the SPSS Statistics software (version 26.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and assessed using either independent *t*-tests or Mann–Whitney U tests, depending on the data distribution. Categorical variables were presented as frequencies (proportions) and analyzed using chi-square or Fisher's exact tests, as appropriate. Changes in pain intensity and opioid consumption over time were analyzed using repeated measures analysis of variance (ANOVA). For all statistical tests, significance was defined as a two-tailed *p*-value of less than 0.05.

3. Results

A total of 90 participants were recruited and randomly assigned to one of the two groups, with 84 individuals completing this study (Figure 1).

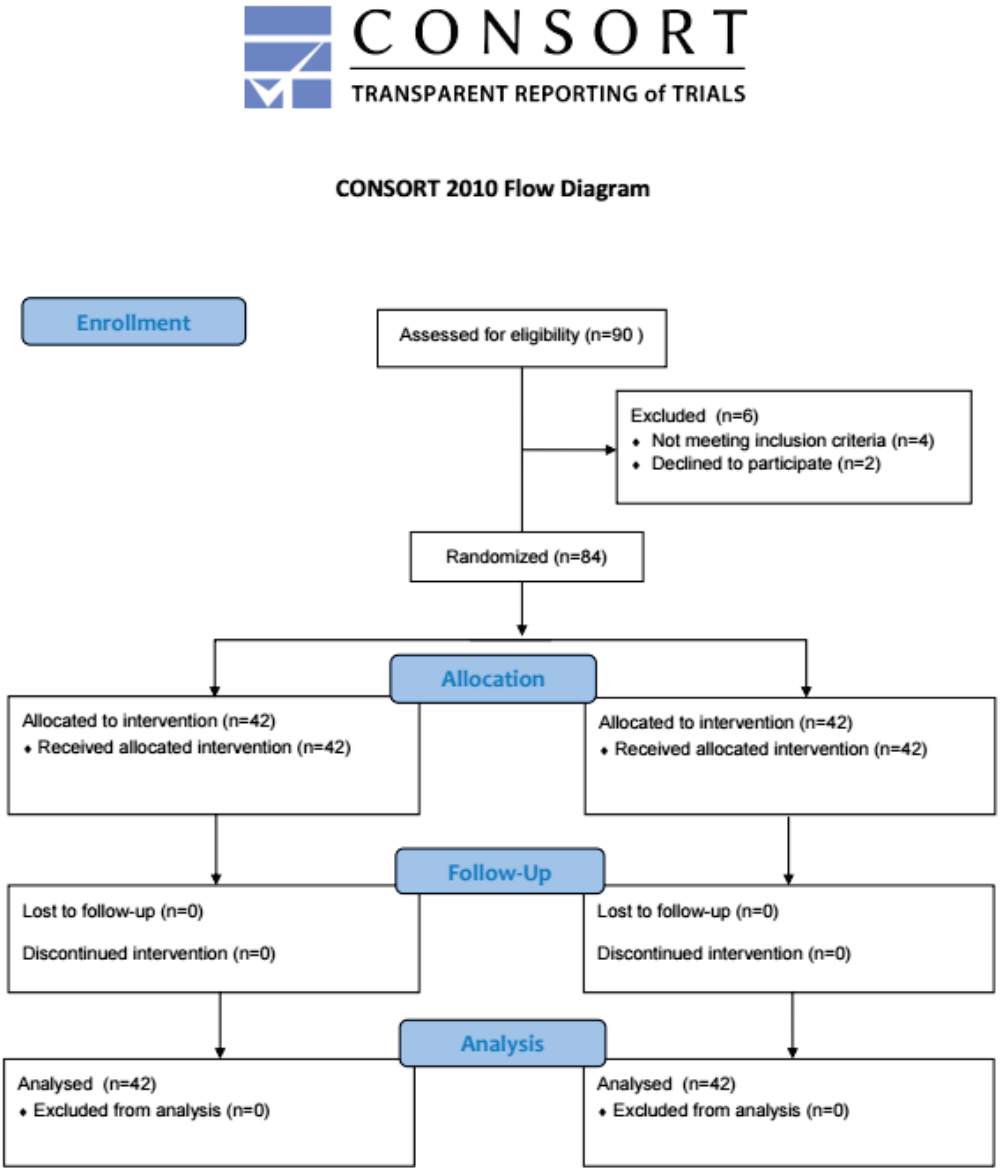

Figure 1. Consolidated standards of reporting trials (CONSORT) flowchart of this study.

No significant differences were observed between the two groups regarding the baseline characteristics, including age, sex, ASA classification, body measurements, and Haller index (Table 1). Similarly, intraoperative variables were found to be comparable across both groups (Table 1). The total amounts of remifentanil and dexmedetomidine administered in each group were 1117 ± 442 μg and 123 ± 33 μg, respectively, with mean infusion rates of 9.0 ± 4.5 μg/kg/hr for remifentanil and 0.9 ± 0.3 μg/kg/hr for dexmedetomidine. The concentration of fentanyl of IV PCA solution was comparable between the two groups, with 12.1 ± 2.0 μg/mL in the OBA group and 12.5 ± 3.2 μg/mL in the OSA group ($p = 0.513$).

Table 2 shows the postoperative pain intensity and analgesic consumption across several time intervals. The total MED administered within 24 h postoperatively, the primary outcome of this study, was considerably lower in the OSA group than in the OBA group. (55.4 ± 31.1 mg vs. 80.2 ± 26.7 mg, $p < 0.001$). The postoperative pain intensity, evaluated with the VAS, was consistently reduced in the OSA group across all measured time points. The OSA group also demonstrated significantly lower fentanyl consumption via intravenous PCA, and the total MED over 48 h was similarly reduced in the OSA group.

Additionally, fewer rescue analgesics were required in the OSA group, with a significant difference in the recovery unit ($p = 0.002$).

Table 1. Patient demographics and intraoperative variables.

	OBA Group (N = 42)	OSA Group (N = 42)	*p*
Age (yr)	23.8 ± 4.6	23.7 ± 2.7	0.954
Sex (male/female)	35/7	33/9	0.781
ASA class (1/2)	38/4	36/6	0.736
Height (cm)	172.5 ± 9.6	173.1 ± 7.2	0.763
Weight (kg)	61.2 ± 11.6	59.7 ± 12.3	0.585
Haller index	5.2 ± 1.1	5.0 ± 1.2	0.584
Number of pectus bars (2/3)	34/8	33/9	1.000
Operation time (min)	135.1 ± 40.9	136.4 ± 47.8	0.897
Anesthesia time (min)	174.3 ± 32.2	180.9 ± 39.1	0.407
Sevo (vol%)	1.8 ± 0.3	1.7 ± 0.3	0.257
Remifentanil infusion rate (μg/kg/h)	9.0 ± 4.5	N/A	
Dexmedetomidine infusion rate (μg/kg/h)	N/A	0.9 ± 0.3	

Values are expressed as a number or mean ± standard deviation, as appropriate. Sevo: intraoperative mean concentration of sevoflurane.

Table 2. Postoperative pain intensity and analgesic consumption.

	OBA Group (N = 42)	OSA Group (N = 42)	*p*
At recovery unit			
Highest VAS	8.0 ± 2.1	4.9 ± 1.5	<0.001
PCA consumption (mL)	6.2 ± 2.6	3.4 ± 1.5	<0.001
Rescue requirement (0/1/2)	2 / 36 / 4	14 / 25 / 3	0.002
Rescue opioid (μg)	65.0 ± 30.0	41.7 ± 34.8	0.001
MED (mg)	14.0 ± 4.4	10.8 ± 5.2	0.003
1–6 h after surgery			
Highest VAS	7.1 ± 1.9	5.3 ± 1.8	<0.001
PCA consumption (mL)	17.8 ± 7.7	12.9 ± 7.2	0.003
Rescue requirement (0/1/2)	16/19/7	24/15/3	0.178
Rescue opioid (μg)	16.9 ± 15.7	11.4 ± 13.4	0.089
MED (mg)	23.2 ± 10.1	17.6 ± 11.2	0.019
6–24 h after surgery			
Highest VAS	5.4 ± 2.1	3.9 ± 1.5	<0.001
PCA consumption (mL)	33.8 ± 18.8	20.3 ± 14.6	<0.001
Rescue requirement (0/1/2/3)	17/17/6/2	21/18/3/0	0.327
Rescue opioid (μg)	16.8 ± 15.0	12.9 ± 13.0	0.204
MED (mg)	43.0 ± 25.5	27.0 ± 22.8	0.003
24–48 h after surgery			
Highest VAS	4.6 ± 2.2	3.6 ± 1.7	0.018
PCA consumption (mL)	43.5 ± 15.5	33.1 ± 19.0	0.007
Rescue requirement (0/1/2)	17 / 21 / 4	27 / 9 / 6	0.027
Rescue opioid (μg)	21.2 ± 27.0	9.6 ± 13.2	0.001
MED (mg)	55.6 ± 22.1	41.1 ± 23.6	0.005

The values are expressed as numbers (proportions) or mean ± standard deviation, as appropriate. VAS: visual analogue scale; PCA: patient-controlled analgesia; and MED: morphine-equivalent dose.

Both groups maintained stable intraoperative hemodynamics, with no significant differences in blood pressure or heart rate at predefined time points (Figure 2). The incidence of hypotension was 54.8% in the OBA group and 42.9% in the OSA group ($p = 0.383$), while bradycardia occurred in 54.8% of the OBA group and 52.4% of the OSA

group (p = 1.000), showing comparable rates between the two groups. Rescue interventions, including ephedrine and atropine administration, were required with similar frequency in both groups (Table 3).

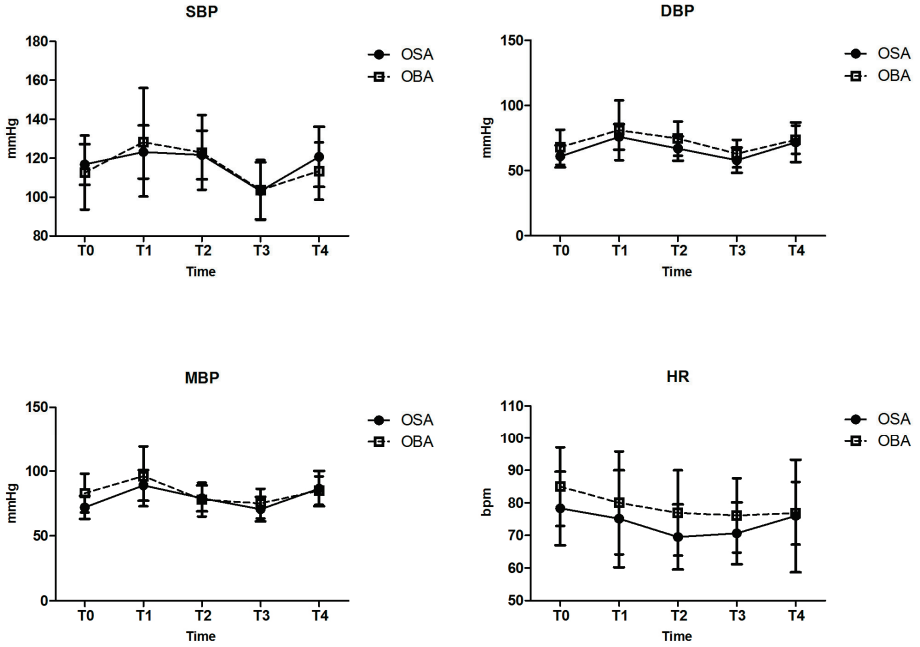

Figure 2. Intraoperative hemodynamic parameters. T0: before anesthesia induction; T1: immediately after tracheal intubation; T2: at the time of incision; T3: 30min after incision; T4: at the end of surgery; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; and HR: heart rate.

Table 3. Recovery characteristics and perioperative adverse events.

	OBA Group (N = 42)	**OSA Group (N = 42)**	p
At recovery unit			
Time to eye opening (min)	3.5 ± 1.3	4.1 ± 1.8	0.085
Time to extubation (min)	5.6 ± 2.0	6.5 ± 2.8	0.066
Time to first rescue (min)	12.3 ± 7.6	13.4 ± 14.3	0.663
Total recovery duration (min)	54.0 ± 14.6	57.7 ± 15.4	0.257
Intraoperative adverse events			
Hypotension (Y)	23 (54.8%)	18 (42.9%)	0.383
Rescue ephedrine (Y)	21 (50.0%)	15 (35.7%)	0.270
Ephedrine dose (mg)	0.5 ± 0.5	0.6 ± 0.5	0.190
Bradycardia (Y)	23 (54.8%)	22 (52.4%)	1.000
Rescue atropine (Y)	18 (42.9%)	19 (45.2%)	1.000
Atropine dose (mg)	0.6 ± 0.5	0.6 ± 0.5	0.829
Postoperative adverse events			
PONV	6 (14.3%)	5 (11.9%)	1.000
Constipation	1 (2.4%)	1 (2.4%)	1.000

Values are expressed as a number (proportion) or mean ± standard deviation. PONV: postoperative nausea and vomiting.

The postoperative recovery outcomes, including the time to eye opening, extubation, and first rescue analgesia, showed no significant differences between the groups (Table 3). The total recovery duration was also comparable, with no statistically significant differences.

Adverse events were rare in both groups. Six patients in the OBA group and five patients in the OSA group experienced PONV, without significant differences between the groups ($p = 1.000$). Constipation occurred in one patient from each group, and PCA was withdrawn in one patient from the OBA group due to PONV. No other opioid-related complications were reported.

Perioperative stress hormone levels, measured at the baseline, the time of incision, after the pectus bar flip, and immediately after surgery, showed that both groups experienced an increase in cortisol, epinephrine, and norepinephrine during surgery (Figure 3). However, the OSA group showed a smaller increase in epinephrine, with an insignificant decrease in norepinephrine, suggesting attenuated sympathetic activation. Notably, epinephrine levels peaked in both groups at the time of the pectus bar flip, although the OFA group showed a significantly lower peak compared to the OBA group. Cortisol secretion also increased continuously in both groups, but the OSA group demonstrated a more attenuated increase following DEX infusion, resulting in a significant difference between the two groups.

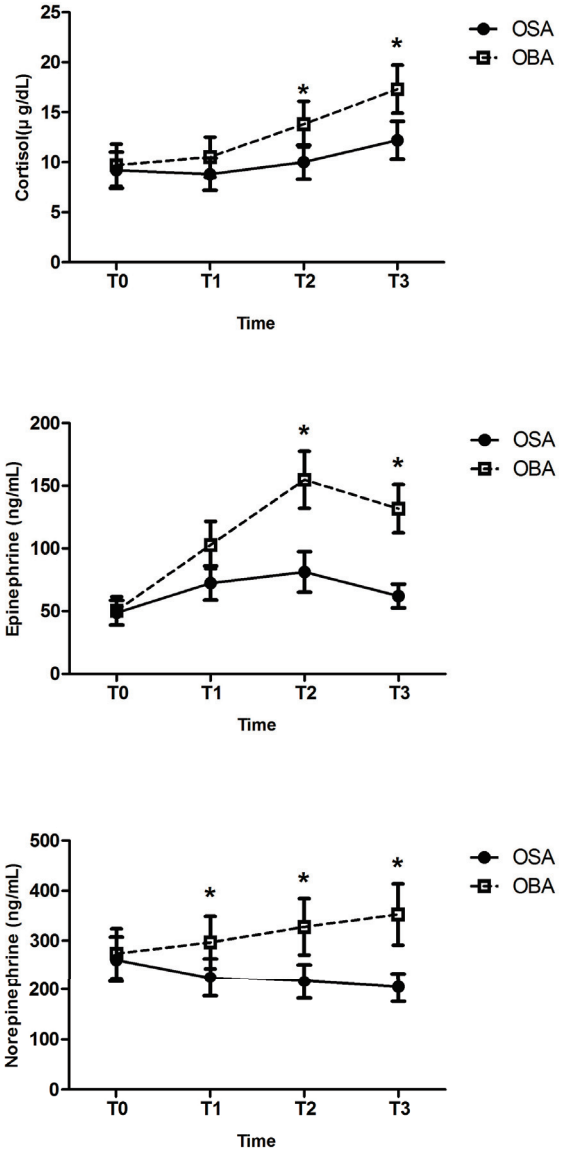

Figure 3. Perioperative stress hormone levels. T0: baseline; T1: at the time of incision; T2: after pectus bar flip; and T3: immediately after surgery. * $p < 0.05$ between two groups.

4. Discussion

This study aimed to investigate the influence of DEX-based OSA on postoperative opioid consumption in patients undergoing MIRPE. The findings demonstrated a significant reduction in both pain intensity and analgesic consumption within the first 48 h postoperatively in the OSA group. No significant differences were observed between the OSA and OBA groups concerning opioid-related complications, intraoperative hemodynamics, or recovery times.

Our findings are consistent with those of previous studies demonstrating the benefits of DEX-based OSA across various types of surgeries. In gynecological laparoscopy, DEX-based OSA was associated with reduced pain intensity, lower analgesic consumption, and fewer opioid-related side effects, with no significant differences in recovery times compared to traditional OBA [29]. Similarly, OSA protocols have been shown to improve quality of recovery (QoR) scores (QoR-40) and reduce pain scores, alongside decreased levels of stress hormones [30]. In laparoscopic cholecystectomy, DEX exhibited immunomodulatory effects by reducing IL-6 levels while simultaneously decreasing opioid consumption [31,32]. In bariatric surgery, the use of DEX was linked to reductions in PONV, pain scores, and analgesic requirements [33,34]. In major spine surgeries, intraoperative DEX effectively attenuated stress responses, maintained hemodynamic stability, and lowered the postoperative pain scores [35,36]. In video-assisted thoracic surgery (VATS), OSA protocols incorporating DEX significantly reduced morphine consumption and improved both QoR-40 scores and pain outcomes, while maintaining stable hemodynamics [37,38]. Collectively, these studies suggest that OSA protocols using DEX offer consistent benefits across various surgical settings, including reduced opioid use, enhanced recovery quality, and improved pain control, without compromising safety or hemodynamic stability. Beyond DEX-based protocols, recent studies have demonstrated the broader benefits of OSA across various surgical contexts. Several meta-analyses reported that OSA significantly reduced PONV and reduced postoperative opioid consumption while maintaining effective analgesia [39,40]. Similarly, Piccioni et al. found that OSA in thoracic surgeries resulted in lower opioid consumption, improved pain scores, and fewer complications at 48 h postoperatively [41]. These findings align with our study, emphasizing that OSA can optimize perioperative pain management, reduce opioid-related adverse effects, and improve overall recovery quality.

In contrast to our findings, several studies have reported no superior recovery outcomes in DEX-based OSA. In gynecological laparoscopy, Massoth et al. [42] found no significant reduction in PONV, pain scores, or opioid consumption when comparing DEX-based OSA with sufentanil-based OBA. Similarly, another study applying OSA within an ERAS protocol for gynecological surgery reported non-inferior pain outcomes but noted delayed emergence and reduced PONV with OSA [43]. In thoracic surgeries, propensity-matched studies involving intraoperative DEX infusions found no differences in pain scores or opioid use throughout the hospital stay [44,45]. These inconsistent findings suggest that the variability in DEX-based OSA outcomes may be attributed to differences in administration protocols, such as the use of adjunct medications, DEX dosage, timing of infusion, and patient populations. Future studies should aim to standardize OSA protocols and explore optimal dosing regimens to maximize the benefits of DEX while minimizing potential side effects.

While our study did not directly investigate the underlying mechanisms, we propose two potential explanations for the observed reduction in opioid consumption between the OBA and OSA groups. First, opioid-induced hyperalgesia (OIH) may have contributed to the higher opioid requirements in the OBA group due to the use of remifentanil. Previous studies have shown that remifentanil, a potent and short-acting opioid widely used in surgery, induces acute opioid tolerance and hyperalgesia by activating NMDA receptors and oxidative stress pathways [46,47]. These mechanisms can lead to heightened pain sensitivity, necessitating greater postoperative opioid consumption. Notably, even brief infusions of remifentanil (e.g., 90 min) can trigger acute tolerance, with higher doses

making patients more susceptible to OIH. By avoiding remifentanil in the OSA group, this effect may have been mitigated, contributing to the observed reduction in postoperative opioid use. Second, the intrinsic analgesic properties of DEX likely played a role. As a selective alpha-2 adrenergic receptor agonist, DEX reduces sympathetic outflow and suppresses norepinephrine release, leading to analgesic and stress-relieving effects [17]. This sympatholytic mechanism not only enhances multimodal analgesia but also aligns with the lower levels of stress hormones observed in the OSA group. By mitigating the physiological stress response, DEX likely contributed to reduced pain perception and opioid demand during the postoperative period. These findings highlight the clinical value of DEX-based OSA as a viable alternative to remifentanil, particularly in surgeries requiring prolonged opioid use, by reducing hyperalgesia, stress responses, and opioid-related side effects.

Contrary to expectations, our study found no difference in opioid-related complications, such as PONV, between the OSA and OBA groups. This contrasts with previous meta-analyses [48,49], which reported that intraoperative opioid avoidance significantly reduces PONV. A possible explanation for this discrepancy is the relatively low opioid consumption in both groups, driven by the multimodal analgesia protocol employed, including a CWIS, which reduced opioid use by nearly 60% in MIRPE surgeries at our institution. Additionally, the routine administration of prophylactic antiemetics before the end of surgery likely contributed to the low incidence of PONV. The lower proportion of female participants, who are more susceptible to PONV, may also have influenced the lack of difference in outcomes.

The prolonged analgesic effects of DEX observed in our study, extending up to 48 h postoperatively, raise important questions about its underlying mechanisms. While the elimination half-life of DEX is relatively short (2–2.5 h) [16,17], its analgesic effects appear to extend beyond its immediate pharmacokinetics. This discrepancy may be explained by two potential mechanisms. First, DEX exerts its analgesic effects primarily through alpha-2 adrenergic receptor activation, which modulates central and peripheral pain pathways [16,17]. Unlike its sedative effects, the analgesic action of DEX may involve distinct downstream signalling pathways with a prolonged duration. Second, DEX is known to enhance the efficacy of co-administered analgesics, including local anesthetics and opioids [50]. In our study, this effect likely potentiated the analgesic action of intercostal block- and CWIS-administered local anesthetics, as well as fentanyl delivered via intravenous PCA in the immediate postoperative period. Supporting evidence from previous studies further corroborates this hypothesis. In patients undergoing pulmonary resection, intraoperative DEX loading improved both the pain domain and overall QoR-40 scores up to postoperative day (POD) 2 [51]. Similarly, in colectomy patients, continuous intraoperative DEX infusion resulted in reduced VAS pain scores and opioid consumption at 24 h postoperatively, along with sustained improvements in QoR-40 scores up to PODs 3 and 7 [52]. These findings suggest that DEX may have a synergistic effect with other analgesic agents, contributing to prolonged postoperative pain relief. However, further studies are necessary to elucidate the exact mechanisms underlying these prolonged effects and explore the potential for optimizing multimodal analgesia protocols incorporating DEX.

Despite concerns that DEX may prolong recovery and cause hemodynamic instability [17,23], our study found no significant difference between the OSA and OBA groups in postoperative recovery time or intraoperative hemodynamic stability. DEX reduces sympathetic outflow from the locus ceruleus, decreasing norepinephrine release and activating parasympathetic pathways. While these effects can cause sedation and bradycardia, they appear to be dose-dependent, with higher doses linked to prolonged recovery and more profound hemodynamic changes. In our study, the use of a moderate loading dose followed by a controlled maintenance infusion (below 1 μg/kg/h) likely mitigated these effects, aligning with prior findings that lower DEX doses maintain stable hemodynamics without compromising recovery [33,37]. The absence of significant bradycardia or hypotension in our study reinforces the safety of this dosing regimen in procedures like MIRPE,

particularly in relatively healthy patients without cardiovascular comorbidities. Previous studies have reported severe bradycardia with higher DEX doses, leading to early trial termination in some cases [53]. The stable hemodynamics and comparable recovery times observed in our study suggest that this dosing protocol may represent an optimal approach for DEX-based OSA in minimally invasive thoracic surgeries.

This study has several limitations. First, the attending anesthesiologists were not blinded to the group allocation due to protocol differences between the two groups. This partial blinding may have introduced bias in intraoperative management, particularly in drug administration and monitoring. However, all other clinical staff involved in patient care, including surgeons and postoperative care teams, were blinded throughout the study to minimize potential bias. Second, the evaluation period was limited to 48 h postoperatively, during which the same multimodal analgesia protocol was applied to both groups. This short follow-up restricted our ability to assess longer-term outcomes. While no significant differences in short-term recovery were observed, previous studies on VATS suggest that DEX-based OSA may influence chronic pain syndromes rather than early recovery outcomes [45]. Therefore, future studies with extended follow-up durations are needed to explore the potential long-term benefits of OSA on postoperative pain and recovery. Third, the attending surgeon prioritized intercostal block combined with CWIS as the primary pain management strategy. Consequently, preoperative regional anesthesia techniques, such as erector spinae plane block or paravertebral block, were not utilized due to concerns about the cumulative dose of local anesthetics. Additionally, given the severity of postoperative pain, PCA with fentanyl was employed despite the use of non-opioid medications and CWIS. These factors limited our ability to fully evaluate a true opioid-free anesthesia protocol. Future studies should explore the combined use of preoperative regional anesthesia techniques and DEX to better assess the feasibility and efficacy of opioid-free anesthesia in surgeries associated with severe pain. Lastly, a limitation concerns the precise evaluation of DEX's mechanism in reducing OIH. DEX is believed to mitigate OIH by modulating reactive oxygen species production and NMDA receptor activity in the central nervous system. Although preclinical studies have shown that DEX suppresses oxidative stress pathways and NMDA receptor activation, these findings are based on spinal cord samples from animal models [54,55]. In our study, ethical and practical constraints precluded the collection of spinal samples, limiting our ability to directly confirm these central mechanisms.

5. Conclusions

In conclusion, our study demonstrated that DEX-based OSA significantly reduced postoperative pain intensity and opioid consumption within 48 h after MIRPE. Despite concerns about hemodynamic instability and delayed recovery with DEX, our results showed comparable recovery times and stable intraoperative hemodynamics between the OSA and OBA groups. These findings support the use of DEX-based OSA as a safe and effective alternative to OBA, ensuring effective pain management while reducing opioid consumption and the associated adverse effects. Further studies are necessary to corroborate these findings and investigate the potential long-term benefits of OSA across different surgical environments.

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Data Availability Statement: The data generated in this study can be shared upon reasonable request to the corresponding author.

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Aortic Stent Graft Treatment in a Medium-Size Aortic Center Performed by a Cardiac Surgeon Only—The 9 Years Experience in Poland

Marian Burysz [1,2], Jakub Batko [3,4,*], Krzysztof Greberski [5,6], Artur Słomka [7] and Radosław Litwinowicz [1,2,4,8,*]

1 Department of Cardiac Surgery, Regional Specialist Hospital, 86-300 Grudziądz, Poland
2 Thoracic Research Centre, Collegium Medicum Nicolaus Copernicus University, Innovative Medical Forum, 85-094 Bydgoszcz, Poland
3 Department of Anatomy, Jagiellonian University Medical College, 30-688 Krakow, Poland
4 CAROL—Cardiothoracic Anatomy Research Operative Lab, Department of Cardiovascular Surgery and Transplantology, Institute of Cardiology, Jagiellonian University Medical College, 30-688 Krakow, Poland
5 Department of Cardiac Surgery, J. Strus Municipal Hospital, 61-285 Poznan, Poland
6 Faculty of Health Sciences, University of Medical Sciences, 60-572 Poznan, Poland
7 Department of Pathophysiology, Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, 85-094 Bydgoszcz, Poland; artur.slomka@cm.umk.pl
8 National Medical Institute of the Ministry of Interior and Administration, 02-507 Warsaw, Poland
* Correspondence: kubabatko5@gmail.com (J.B.); radek.litwinowicz@gmail.com (R.L.); Tel.: +48-56-641-4109 (R.L.)

Abstract: Background: The incidence of thoracic aortic aneurysms is estimated at 3.0–8.3/100,000 persons per year. There is a lack of reports in the literature on the outcomes of small- and medium-sized thoracic endovascular aortic repairs. The aim of this study is to present the results of thoracic endovascular aortic repairs at a single medium-sized center performed exclusively by a cardiac surgeon. **Methods**: Ninety patients who had undergone aortic stent graft implantations for the treatment of thoracic aortic anomalies were comprehensively, retrospectively evaluated. The detailed preoperative, surgical, and postoperative parameters of the patients, including the survival rate up to five years, were recorded and further analyzed. **Results**: The patients' Euroscores were four (2.1–9). The 30-day mortality rate was 8.9%, the 1-year mortality rate was 15.6%, and the 5-year mortality rate was 38.9% for all causes. Postoperative complications were observed in 10% of the patients. Statistically significant differences were observed between the urgency of surgery at 30 days and survival at one year, but not at five years. The most common complications were related to respiratory (4.4%), renal (3.3%), and neurological (3.3%) dysfunction. **Conclusions**: Thoracic endovascular aortic repair can be safely performed in small- and medium-sized centers with optimal long-term results.

Keywords: TEVAR; thoracic aortic aneurysm; stent graft; endovascular treatment; aortic rupture; aortic trauma

1. Introduction

Thoracic aortic aneurysms incidence is estimated to occur in 3.0–8.3/100,000 individuals per year [1]. It may not be associated with any specific symptoms, thus leading to the rupture associated mortality of up to 90%. Ruptures are observed in 1.3–2.1/100,000 individuals per year [1]. The American Heart Association in their most recent guidelines underlines the importance of the thoracic endovascular aortic repair in patients with an aortic aneurysm rupture [2]. Additionally, it should be noted that endovascular procedure implementation in the treatment of thoracic aortic pathologies grows exponentially with the use of commercially available or customized aortic stent grafts [3].

Thoracic endovascular aortic repair was introduced and performed for the first time in 1987 by Dr. Nikolay Volodos in Ukraine [4]. This procedure provides a safe and effective

approach for the treatment of aortic pathology located below the aortic arch, including an aortic aneurysm, an intramural hematoma, and a penetrating aortic ulcer or traumatic aortic injury. It includes the visualization of the pathologically altered aorta, the implantation of a stent graft, and the final confirmation of the correct location of the device without the presence of endoleaks. The procedure is performed exclusively via vascular access, so that a sternotomy can be avoided. The stent graft implantation can be performed as a second stage after the implantation of a frozen elephant trunk for pathologies of the aortic arch. The most common complications of the procedure are a progression of aortic disease, spinal cord ischemia, negative cardiac remodeling, and endoleaks [5–15].

There is a lack of reports in the literature on the outcomes of small- and medium-sized thoracic endovascular aortic repairs, which may be helpful for future development and improved access to this procedure for a broader patient population.

The aim of this study is to present detailed results of thoracic endovascular aortic repairs at a single mid-sized center performed exclusively by a cardiac surgeon, including detailed information on the postoperative outcomes based on the indication for the procedure, urgency, and patient gender.

2. Materials and Methods

2.1. Patients' Characteristics

All patients who underwent an aortic stent graft implantation for treatment of thoracic aorta abnormalities between 1 May 2015 and 1 May 2024 at the Regional Specialized Hospital in Grudziadz, Poland, were comprehensively analyzed retrospectively. Patients' demographic characteristics, preoperative comorbidities, intervention indications, intervention urgency, and detailed surgical and postoperative parameters, including up to five years survivability, were collected and further analyzed. The 30-day, 1-year, and 5-year mortality rates were collected from the National Health Fund, the obligatory public health insurance institution in Poland, and incorporated into the KROK (Polish National Registry of Cardiac Surgery Procedures) registry (available at: https://krok.csioz.gov.pl) on 1 August 2024. Due to the retrospective nature of this study, the approval of the Bioethics Committee was waived. This study's protocol complies with the ethical guidelines of the Declaration of Helsinki of 1975.

2.2. Procedure

Briefly, all thoracic endovascular aortic repair procedures at our institution are conducted under general anesthesia in a hybrid operating room, utilizing a C-arm fluoroscope. The patient is positioned with their groin, abdomen, and chest exposed. The right femoral artery is the preferred access route for the procedure. The femoral artery is surgically exposed under direct visualization, followed by the placement of a Prolene 6.0 suture. Access is established using a standard 5 Fr sheath. The patient is then heparinized to achieve an activated clotting time of 200 s. A pigtail catheter is introduced via the femoral or brachial/radial artery to perform an aortogram of the area of interest.

After the angiogram, the aneurysm is evaluated, with the length and diameter of the proximal and distal neck measured using both the preoperative computed tomography scan and the angiogram. Through femoral access, a diagnostic catheter is advanced and subsequently exchanged for extra stiff wire guides. Based on these measurements, the appropriate stent graft is selected, flushed with heparinized solution, and advanced to the proximal neck. If necessary, a repeat angiogram is performed to reconfirm the positioning of the device within the aorta and the landing zone. Before deploying the device, rapid pacing through the jugular vein is performed to ensure precise deployment and prevent migration due to forward arterial blood flow. After deployment, a completion angiogram is conducted to confirm the absence of a gross endoleak. At this point, the stent graft may be ballooned to reduce the risk of Type I or III endoleaks.

2.3. Definitions

We defined a small-sized aortic center as a center performing less than 15 procedures on a thoracic aorta annually. We defined a medium-sized aortic center as a center performing more than 15 procedures and less than 30 procedures on a thoracic aorta annually. We defined a large-sized aortic center as a center performing more than 30 procedures on a thoracic aorta annually. Our center fits the definition of the medium-sized aortic center. This division was inspired by the 2022 ACC/AHA aortic treatment guidelines [2].

2.4. Statistical Analysis

Data were analyzed using IBM SPSS Statistics 29.0 (Predictive Solutions, Pittsburgh, PA, USA). Categorical variables are presented as numbers (*n*) or percentages. Quantitative variables are presented as the median with first and third quartiles. The normal distribution was analyzed using the Shapiro–Wilk test. A continuous variables simple group comparison was performed with the U-Mann–Whitney test. A continuous variables multi-group comparison was assessed using the Kruskal and Wallis test with the Dunn's post hoc test with Bonferroni correction if the results of the Kruskal and Wallis test were statistically significant. For the categorical variables, the chi-square test for independence or Fischer's exact test was used. Survival curves were performed for all patients, with an additional analysis including the following subgroups: sex, intervention urgency, and intervention indications. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the Patients

Between 1 May 2015 and 1 May 2024, 90 patients (median age: 64 years (55–70), with 72.2% male) were admitted to our hospital and underwent an aortic stent graft implantation.

3.1.1. Characteristics of the Patients—Sex Comparison

A comparison of the detailed preoperative characteristics of the patients based on sex are presented in Table 1.

Table 1. Preoperative characteristics patients, a comparison based on sex. BMI—body mass index, TIA—transient ischemic attack, GFR—glomerular filtration rate.

		Female (n = 25)	**Male (n = 65)**	**General**	p
Age (years)		66 (59–73)	63 (55–68)	64 (55–70)	0.168
BMI (kg/m^2)		29.4 (26–33.7)	26.6 (24.5–30.8)	27 (24.7–32.7)	0.340
CCS Class	1 2 3 4	15 (60%) 9 (36%) 1 (4%) 0 (0%)	48 (73.8%) 13 (20%) 2 (3.1%) 2 (3.1%)	63 (15.6%) 22 (24.4%) 3 (3.3%) 2 (2.2%)	0.346
NYHA class	1 2 3 4	12 (48%) 8 (32%) 2 (8%) 3 (12%)	44 (67.7%) 15 (23.1%) 2 (3.1%) 4 (6.2%)	56 (11.1%) 23 (25.6%) 4 (4.4%) 7 (7.8%)	0.481
Eversmoker	actual previous	6 (24%) 11 (44%)	19 (29.2%) 25 (38.5%)	25 (27.8%) 36 (40%)	0.853
Diabetes mellitus type 2	diet pharmacological insulin	0 (0%) 3 (12%) 4 (16%)	1 (1.5%) 2 (3.1%) 4 (6.2%)	1 (1.1%) 5 (5.6%) 8 (8.9%)	0.134

Table 1. *Cont.*

		Female (n = 25)	Male (n = 65)	General	p
Hypertension	treated untreated	19 (76%) 4 (16%)	47 (72.3%) 7 (10.8%)	66 (73.3%) 11 (12.2%)	0.488
Hyperlipidemia		10 (40%)	23 (35.4%)	33 (36.7%)	0.684
TIA		1 (4%)	2 (3.1%)	3 (3.3%)	0.239
Peripheral vascular disease		11 (44%)	17 (26.2%)	28 (31.1%)	0.248
Renal impairment	GFR > 85 50 < GFR < 86 GFR < 50 dialysis	13 (52%) 5 (20%) 6 (24%) 1 (4%)	35 (53.8%) 24 (36.9%) 6 (9.2%) 0 (0%)	48 (53.3%) 29 (32.2%) 12 (13.3%) 1 (1.1%)	0.067
Poor mobility		10 (40%)	15 (23.1%)	25 (27.8%)	0.108
Chronic lung disease		3 (12%)	4 (6.2%)	7 (7.8%)	0.354
Critical preoperative condition		7 (28%)	15 (23.1%)	22 (24.4%)	0.626
Preoperative mechanical ventilation		0 (0%)	5 (7.7%)	5 (5.6%)	0.317
Cardiogenic shock		2 (8%)	7 (10.8%)	9 (10%)	1.000
Previous thoraflex implantation		0 (0%)	6 (9.2%)	6 (6.7%)	0.181
Time from thoraflex implantation (months)		0 (0–0)	2.5 (1.6–4.1)	2.5 (1.6–4.1)	-

No significant differences were observed in sex comparison.

3.1.2. Characteristics of the Patients—Surgery Urgency

A comparison of the detailed preoperative characteristics of the patients with surgery urgency is presented in Table A1 in Appendix A.

Statistically significant differences were observed between the groups with hypertension (the post-hoc comparison was significantly different between acute and chronic aortic dissection), peripheral vascular disease (the post-hoc comparison was significantly different between acute aortic dissection and aortic aneurysm), and with poor mobility (the post-hoc comparison was significantly different between acute aortic dissection and aortic aneurysm).

3.1.3. Characteristics of the Patients—Surgery Indication

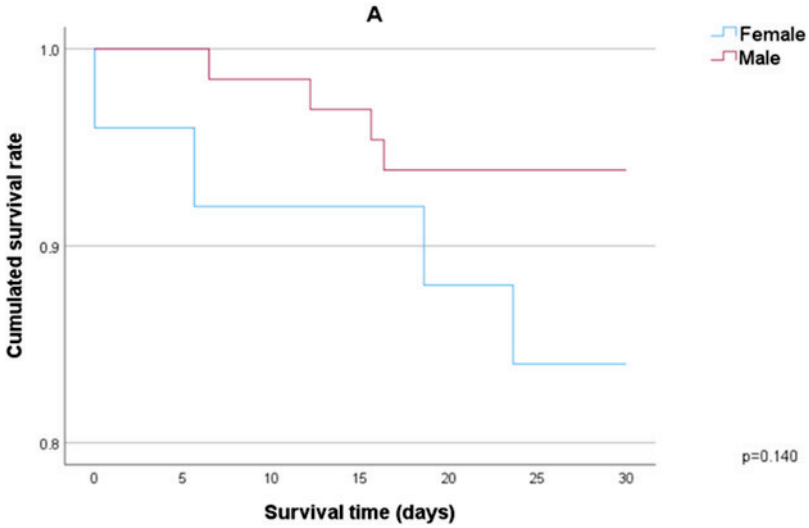
A comparison of the detailed preoperative characteristics of the patients with surgery indication is presented in Table A2 in Appendix A. Statistically significant differences were observed between the groups with hypertension (the post-hoc comparison was significantly different between acute and chronic aortic dissection), with peripheral vascular disease (the post-hoc comparison was significantly different between acute aortic dissection and aortic aneurysm), and with poor mobility (the post-hoc comparison was significantly different between acute aortic dissection and aortic aneurysm).

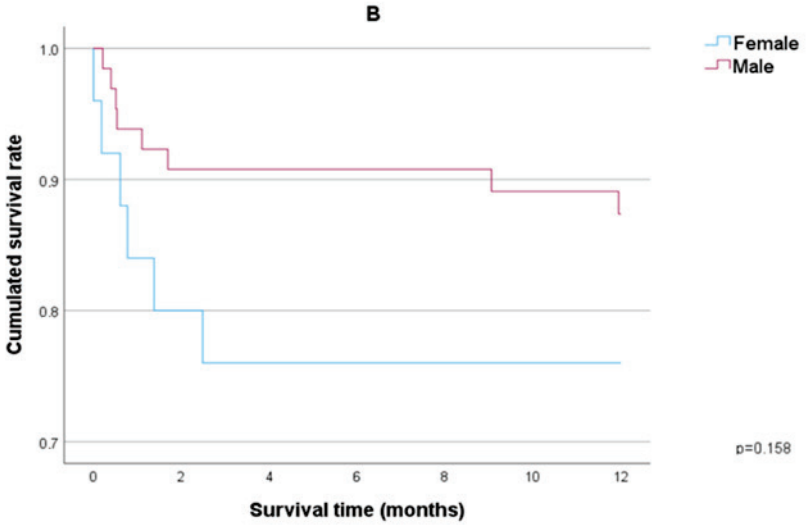
3.2. Intraoperative and Postoperative Outcomes

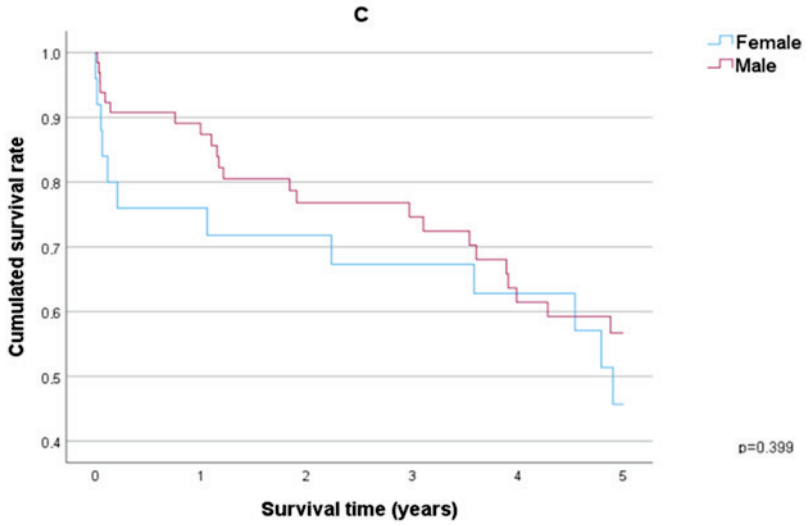
3.2.1. Intraoperative and Postoperative Outcomes—Sex Comparison

A comparison of the detailed intraoperative and postoperative outcomes for males and females can be found in Table 2. The 30-day, 1-year and 5-year survival curves with a sex comparison can be found in Figure 1A–C.

Significant differences were observed only in the Euroscores (significantly larger in females). No statistically significant differences were observed between the sexes in relation to 30-day, 1-year and 5-year survivability.







Nr at risk	Baseline	1 yr	2 yrs	3 yrs	4yrs	5yrs
Female	25	19	18	17	16	13
Male	65	57	51	50	44	42

Figure 1. Survival curves with sex comparison. (**A**) 30 days survival curve, (**B**) 1 year survival curve, (**C**) 5 years survival curve. Yr—year.

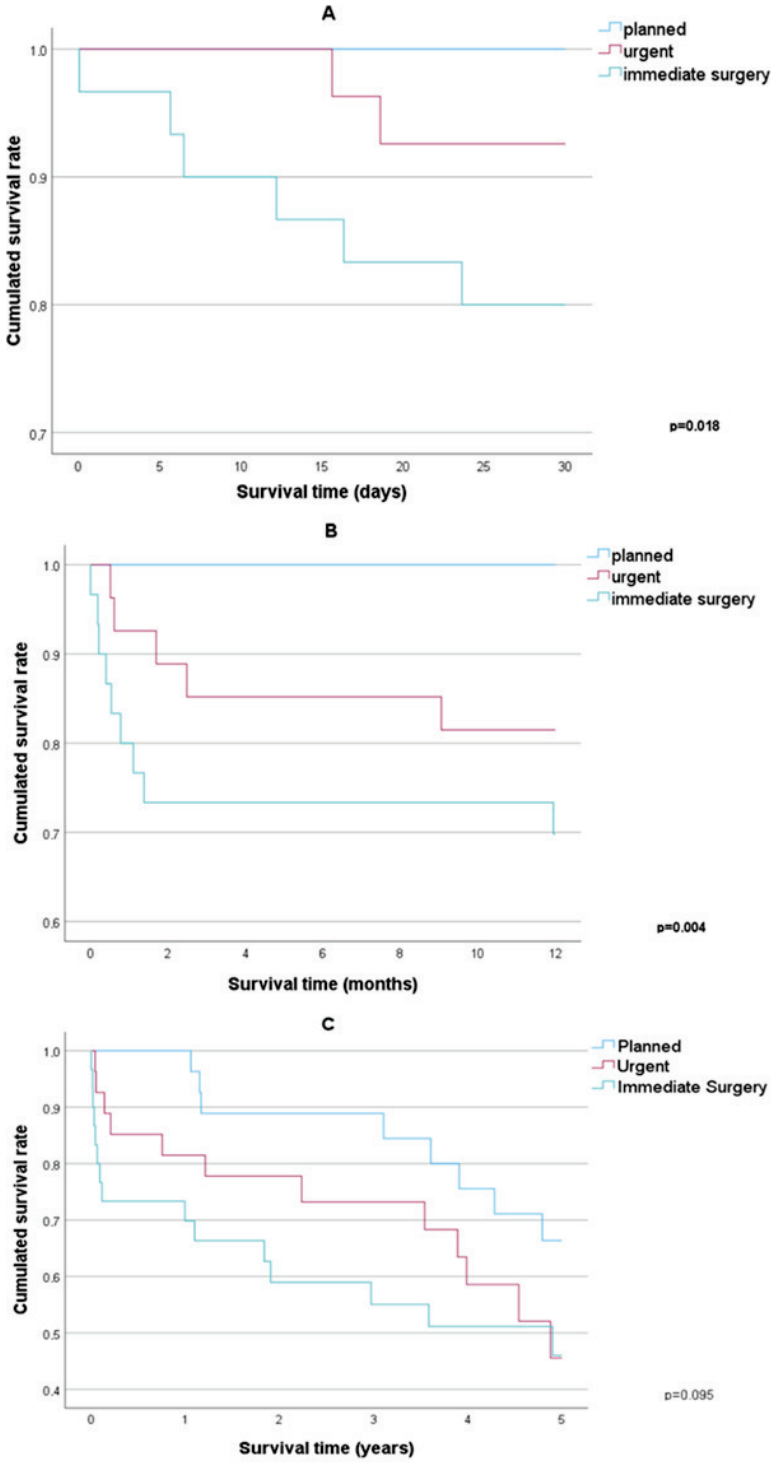
Table 2. Comparison of intraoperative and postoperative outcomes of patients' based on sex. ICU—intensive care unit. Significant *p* values bolded.

		Female (*n* = 25)	Male (*n* = 65)	General	*p*
Euroscore		6.7 (3.7–16.8)	3.5 (1.7–7.2)	4 (2.1–9)	**0.011**
Procedure urgency	planned urgent immediate surgery	6 (24%) 10 (40%) 9 (36%)	27 (41.5%) 17 (26.2%) 21 (32.3%)	33 (36.7%) 27 (30%) 30 (33.3%)	0.254
Surgery indication	acute aortic dissection chronic aortic dissection aortic aneurysm penetrating trauma	13 (52%) 4 (16%) 8 (32%) 0 (0%)	28 (43.1%) 13 (20%) 22 (33.8%) 2 (3.1%)	41 (45.6%) 17 (18.9%) 30 (33.3%) 2 (2.2%)	0.740
Aortic segments involved	thoracic descending thoracic and abdominal distal arch and thoracic	17 (68%) 2 (8%) 6 (24%)	48 (73.8%) 4 (6.2%) 13 (20%)	65 (72.2%) 6 (6.7%) 19 (21.1%)	0.854
Type of anesthesia	general sedation	21 (84%) 3 (12%)	59 (90.8%) 6 (9.2%)	80 (89.9%) 9 (10.1%)	0.698
Surgery time (min)		95 (80–120)	90 (70–120)	90 (70–120)	0.658
Intubation time (h)		5.7 (3.3–8.3)	3.5 (1.8–8.3)	3.9 (1.9–8.3)	0.152
Postoperative transfusion		7 (28%)	25 (38.5%)	32 (35.6%)	0.353
ICU stay (days)		0.9 (0.2–1.1)	0.8 (0.1–1.1)	0.9 (0.1–1.1)	0.432
Hospitalization time (days)		9 (6–12.5)	7 (5–11.5)	7.5 (5–11.5)	0.321
30 days mortality		4 (16%)	4 (6.2%)	8 (8.9%)	0.211
1 year mortality		6 (24%)	8 (12.3%)	14 (15.6%)	0.200
5 years mortality		12 (48%)	23 (35.4%)	35 (38.9%)	0.272
Postoperative complications		3 (12%)	6 (9.2%)	9 (10%)	0.695
Reoperation Fresh miocardial infarction		0 (0%) 0 (0%)	1 (1.5%) 1 (1.5%)	1 (1.1%) 1 (1.1%)	- -
Hemodialysis		0 (0%)	1 (1.5%)	1 (1.1%)	-
Respiratory system complications		1 (4%)	3 (4.6%)	4 (4.4%)	1.000
Renal complications		1 (4%)	2 (3.1%)	3 (3.3%)	1.000
Neurological complications		2 (8%)	1 (1.5%)	3 (3.3%)	0.186
Tamponade		1 (4%)	2 (3.1%)	3 (3.3%)	1.000

3.2.2. Intraoperative and Postoperative Outcomes—Surgery Urgency

The detailed intraoperative and postoperative outcomes with a surgery urgency comparison can be found in Table 3. The 30-day, 1-year and 5-year survival curves with a surgery urgency comparison can be found in Figure 2A–C.

Significant differences were observed in the Euroscores (significantly lower in the planned procedures vs. the urgent and immediate surgeries), surgery indication, and intubation time (significantly longer in immediate surgeries). Statistically significant differences were observed between surgery urgency in relation to the 30-day and 1-year survivability rates; however, it was not observed in the 5-year survivability rate.



Nr at risk	Baseline	1 yr	2 yrs	3 yrs	4yrs	5yrs
Planned	33	33	30	30	27	25
Urgent	27	22	21	20	17	15
Immediate surgery	30	21	18	17	16	15

Figure 2. Survival curves with surgery urgency comparison. (**A**) 30-day survival curve, (**B**) 1-year survival curve, (**C**) 5-year survival curve. Yr—year.

Table 3. Intraoperative and postoperative outcomes for patients with a comparison based on surgery urgency. ICU—intensive care unit.

		Planned (*n* = 33)	Urgent (*n* = 27)	Immediate Surgery (*n* = 30)	*p*
Euroscore		1.7 (1.3–3.4)	4.5 (3.3–13.8)	7.5 (4.1–16.8)	<0.001
Surgery indication	acute aortic dissection chronic aortic dissection aortic aneurysm penetrating trauma	4 (12.1%) 9 (27.3%) 20 (60.6%) 0 (0%)	12 (44.4%) 6 (22.2%) 9 (33.3%) 0 (0%)	25 (83.3%) 2 (6.7%) 1 (3.3%) 2 (6.7%)	<0.001
Aortic segments involved	thoracic descending thoracic and abdominal distal arch and thoracic	24 (72.7%) 3 (9.1%) 6 (18.2%)	20 (74.1%) 3 (11.1%) 4 (14.8%)	21 (70%) 0 (0%) 9 (30%)	0.299
Type of anesthesia	general sedation	27 (81.8%) 6 (18.2%)	26 (96.3%) 1 (3.7%)	27 (93.1%) 2 (6.9%)	0.141
Surgery time (min)		90 (75–120)	90 (60–120)	95 (69–150)	0.582
Intubation time (h)		2.6 (1.8–6.5)	2.8 (1.3–5.1)	8.3 (3.3–33.9)	0.008
Postoperative transfusion		10 (30.3%)	8 (29.6%)	14 (46.7%)	0.297
ICU stay (days)		0.9 (0–1.1)	0.9 (0.1–1.1)	0.9 (0.4–3)	0.115
Hospitalization time (days)		7 (5–9)	11 (6–15)	7 (4–11.5)	0.196
1 year mortality		0 (0%)	5 (18.5%)	9 (30%)	0.004
5 years mortality		8 (24.2%)	12 (44.4%)	15 (50%)	0.087
Postoperative complications		1 (3%)	3 (11.1%)	5 (16.7%)	0.192
Reoperation		1 (3%)	0 (0%)	0 (0%)	-
Fresh miocardial infarction		0 (0%)	0 (0%)	1 (3.3%)	-
Hemodialysis		0 (0%)	0 (0%)	1 (3.3%)	-
Respiratory system complications		0 (0%)	2 (7.4%)	2 (6.7%)	-
Renal complications		0 (0%)	0 (0%)	3 (10%)	-
Neurological complications		0 (0%)	0 (0%)	3 (10%)	-
Tamponade		1 (3%)	1 (3.7%)	1 (3.3%)	0.990

3.2.3. Intraoperative and Postoperative Outcomes—Surgery Indication

The detailed intraoperative and postoperative outcomes with a surgery indication comparison can be found in Table A3. The 30-day, 1-year, and 5-year survival curves with a surgery indication comparison can be found in Figure A1A–C.

Significant differences were observed in Euroscores (significantly larger in acute aortic dissections vs. chronic aortic dissections and aortic aneurysms), procedure urgency (immediate surgery was most commonly in acute aortic dissections), and postoperative transfusion (least common in aortic aneurysms). No statistically significant differences were observed between the surgery indications in relation to the 30-day, 1-year, and 5-year survivability rates.

4. Discussion

4.1. Results Discussion

An analysis of the outcomes of the thoracic endovascular aortic repairs in our population revealed a 30-day and 1-year mortality of 8.9% and 15.6%, respectively, which should be considered great, especially with a 63.3% rate of urgent surgery and a comparable mortality rate previously reported in the literature for large aortic centers [16]. The five-year mortality rate of 38.9% should be interpreted with caution as the exact cause of death of the patients is unknown. Only one case required reoperation due to an endoleak, which establishes a prevalence at 1.1%, compared to 9.5% in the literature [6]. There were no significant differences between women and men in the 30-day, 1-year, and 5-year observations. It is especially important in regard to patient qualification, as patients should not be taken into account as an additional risk factor in such a procedure.

It should be noted that in patients grouped based on procedure urgency, a significant difference was observed in age and hypertension—especially untreated, peripheral vascular disease—which was mostly observed in patients that qualified for an urgent procedure. In those populations, the main differences were observed in the 30-day and 1-year mortality rates, with no significant difference in the 5-year mortality rate, which proves that aortic disease, especially its aneurysm or dissection, increases the long-term mortality in all patients. However, a planned character for the procedure is the most optimal approach, and if possible it should be performed in every patient with aortic pathology, as procedure urgency increases intraoperative and postoperative mortality.

Recently, we have introduced sedation as the main anesthetic procedure for stent graft implantation. However, due to the small number of patients (10), it is still too early to assess the long-term benefits of such a procedure. We achieved a shorter operation time (90 vs. 154.2 min) and a shorter stay in the intensive care unit (0.9 vs. 1.95 days) than in the previously published study [17].

We observed complications in 10% of the patients. The most common complications, including respiratory (4.4%) and renal (3.3%) complications, were related to the critical preoperative condition of the patients. In three patients, we observed neurological complications, including spinal cord ischemia (2 cases) and transient ischemic attack (one case), at a rate similar to previous studies [10–13].

4.2. Thoracic Endovascular Aortic Repair Indications

4.2.1. Acute Aortic Dissection

The urgent treatment of acute aortic dissection is required in patients with diagnosed malperfusion, persistent pain, unstable or rapid hypertension, and a radiologically confirmed extension of the dissection. General indications for thoracic endovascular aortic repair for subacute aortic dissection include a total aortic diameter greater than 40 mm, a false lumen diameter greater than 25 mm, a primary entry tear greater than 10 mm, and an entry tear communication in the internal aortic curvature [18].

4.2.2. Descending Aortic Aneurysms

Thoracic endovascular aortic repair should be performed in patients with an aneurysm larger than 55 mm, although this may be lower in patients with connective tissue disorders such as Marfan syndrome or in women. The procedure should be performed in patients with a rapidly growing aneurysm, which is defined as growth rate of more than 10 mm/year [2,18,19].

4.2.3. Intramural Hematomas and Penetrating Aortic Ulcers

According to the most recent guidelines, penetrating aortic ulcers with a depth of more than 10 mm and a diameter of more than 20 mm are an indication of the need for thoracic endovascular aortic repair. It should be noted that patients with intramural hematomas that occur concomitantly with an aortic ulcer require more frequent follow-up [20].

4.2.4. Traumatic Aortic Injuries

For traumatic aortic injuries, thoracic endovascular aortic repair should be considered first, as it is less invasive and provides excellent results [21]. Even penetrating aortic trauma with a penetrating factor remaining in the aortic lumen can be successfully treated in this way [22].

4.3. Preoperative Imaging

The gold standard for aortic imaging in patients with a suspected or confirmed pathology of the thoracic aorta is electrocardiography-guided, contrast-enhanced computed tomography of the entire aorta [2,19]. It enables the correct measurement of the aorta, which is necessary for the adjustment of the stent graft, the assessment of the entry site and the vessels involved in aortic pathology, and provides additional information on the possible

restrictions to vascular access. It also provides detailed information about the patient's vascular anatomy, which may be helpful for future interventions in this region [23,24].

4.4. Postoperative Aftercare

Strict follow-up care is required to achieve good early and long-term results. Great care must be taken during the short-term follow-up and during hospitalization to detect an early air embolism or other ischemic complications that may be iatrogenic [16,25]. A computed tomographic angiography is recommended at 6 and 12 months postoperation and then annually. Regular imaging helps to detect late complications such as progression of aortic disease, including a type A retrograde aortic dissection, or endoleaks [6–14,17,20,25]. Left ventricular fraction and blood pressure should be closely monitored as there are previous reports of adverse cardiac remodeling with a decreased ejection fraction and increased blood pressure in patients undergoing thoracic endovascular aortic repair [13]. We did not observe such changes in our patients.

4.5. Limitations

This is a retrospective, observational study, the results of which should be interpreted with caution. We did not receive complete information regarding mortality causes, which may be connected with the lower rates of cardiac-associated mortality. We did not collect information regarding patients' quality of life postoperation. Future studies should focus on refining the risk stratification tools, especially in identifying high-risk patients for a tailored management.

5. Conclusions

Thoracic endovascular aortic repair can be safely performed in small- and medium-sized centers with optimal long-term results.

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Informed Consent Statement: Patient consent was waived due to the retrospective character of this study.

Data Availability Statement: Data are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Table A1. Preoperative characteristics of patients, a comparison based on surgery urgency. BMI—body mass index, TIA—transient ischemic attack, GFR—glomerular filtration rate.

	Planned (*n* = 33)	**Urgent (*n* = 27)**	**Immediate Surgery (*n* = 30)**	***p***
Age (years)	63 (56–68)	67 (61–74)	58.5 (53–66)	0.036
Male	27 (81.8%)	17 (63%)	21 (70%)	0.254
BMI (kg/m^2)	28.1 (25.9–33.6)	26.5 (24.1–33.7)	26.6 (24.2–30.7)	0.254

Table A1. *Cont.*

		Planned (n = 33)	Urgent (n = 27)	Immediate Surgery (n = 30)	p
CCS Class	1 2 3 4	26 (21.2%) 6 (18.2%) 0 (0%) 1 (3%)	17 (7.4%) 8 (29.6%) 2 (7.4%) 0 (0%)	20 (16.7%) 8 (26.7%) 1 (3.3%) 1 (3.3%)	0.622
NYHA class	1 2 3 4	22 (6.1%) 10 (30.3%) 1 (3%) 0 (0%)	15 (7.4%) 7 (25.9%) 2 (7.4%) 3 (11.1%)	19 (20%) 6 (20%) 1 (3.3%) 4 (13.3%)	0.281
Eversmoker	actual previous	5 (15.2%) 14 (42.4%)	8 (29.6%) 10 (37%)	12 (40%) 12 (40%)	0.191
Diabetes mellitus type 2	diet pharmacological insulin	0 (0%) 2 (6.1%) 2 (6.1%)	0 (0%) 2 (7.4%) 6 (22.2%)	1 (3.3%) 1 (3.3%) 0 (0%)	0.067
Hypertension	treated untreated	27 (81.8%) 0 (0%)	24 (88.9%) 2 (7.4%)	15 (50%) 9 (30%)	<0.001
Hyperlipidemia		9 (27.3%)	14 (51.9%)	10 (33.3%)	0.130
TIA		0 (0%)	3 (11.1%)	0 (0%)	-
Peripheral vascular disease		7 (21.2%)	14 (51.9%)	7 (23.3%)	0.001
Renal impairment	GFR > 85 50 < GFR < 86 GFR < 50 dialysis	20 (60.6%) 12 (36.4%) 1 (3%) 0 (0%)	10 (37%) 11 (40.7%) 6 (22.2%) 0 (0%)	18 (60%) 6 (20%) 5 (16.7%) 1 (3.3%)	0.102
Poor mobility		1 (3%)	6 (22.2%)	18 (60%)	<0.001
Chronic lung disease		1 (3%)	3 (11.1%)	3 (10%)	0.436
Critical preoperative condition		0 (0%)	5 (18.5%)	17 (56.7%)	-
Preoperative mechanical ventilation		0 (0%)	0 (0%)	5 (16.7%)	-
Cardiogenic shock		0 (0%)	0 (0%)	9 (30%)	-
Previous thoraflex implantation		6 (18.2%)	0 (0%)	0 (0%)	-
Time from thoraflex implantation (months)		2.5 (1.6–4.1)	0 (0–0)	0 (0–0)	-

Table A2. Preoperative characteristics of patients, a comparison based on surgery indication. BMI—body mass index, TIA—transient ischemic attack, GFR—glomerular filtration rate.

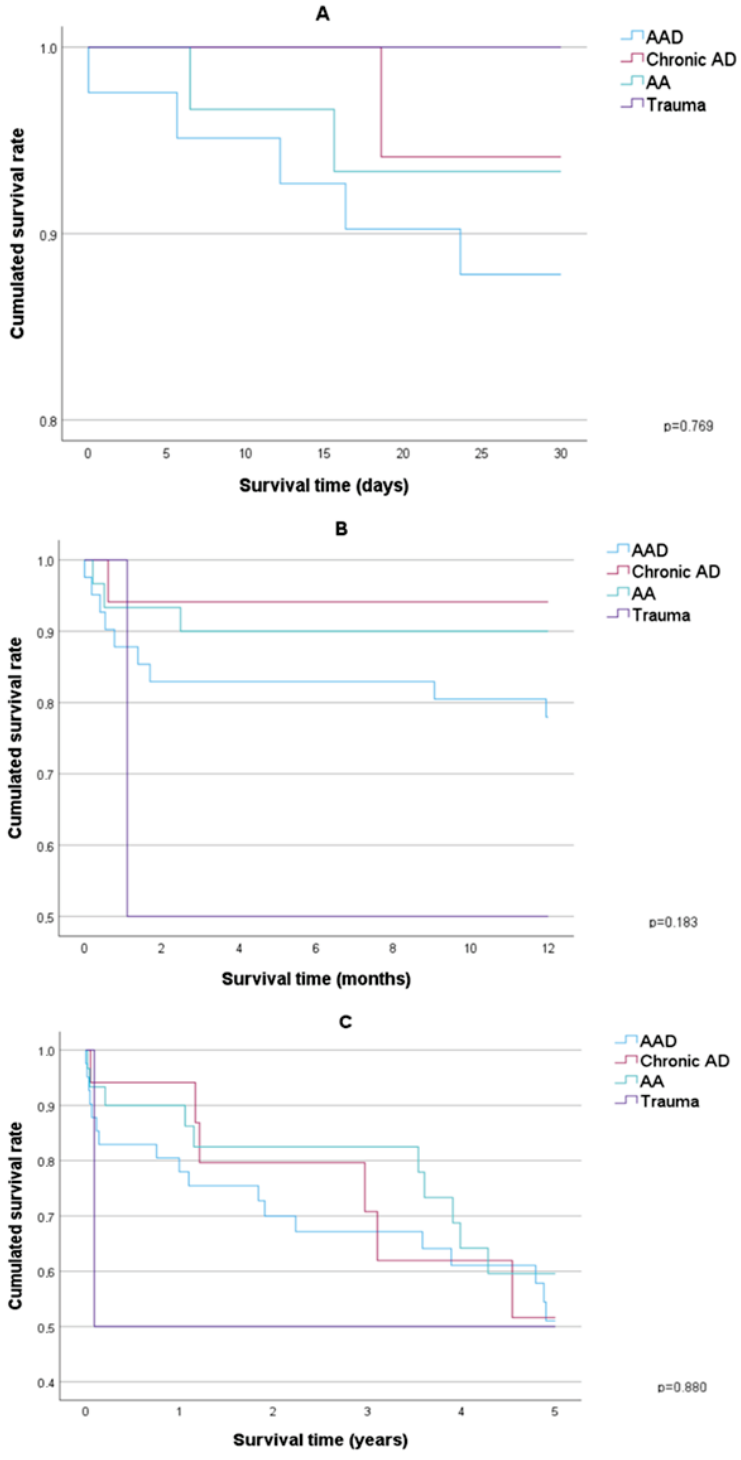
		Acute Aortic Dissection (n = 41)	Chronic Aortic Dissection (n = 17)	Aortic Aneurysm (n = 30)	Penetrating Trauma (n = 2)	p
Age (years)		65 (53–72)	64 (57–68)	63 (59–69)	34.5 (25–44)	0.2
Male		28 (68.3%)	13 (76.5%)	22 (73.3%)	2 (100%)	0.740
BMI (kg/m^2)		26.5 (24.3–30)	27 (23.7–34.2)	27.6 (26–33.7)	27.5 (24.2–30.7)	0.452
CCS Class	1 2 3 4	25 (12.2%) 13 (31.7%) 2 (4.9%) 1 (2.4%)	13 (17.6%) 3 (17.6%) 1 (5.9%) 0 (0%)	23 (16.7%) 6 (20%) 0 (0%) 1 (3.3%)	2 (50%) 0 (0%) 0 (0%) 0 (0%)	0.883
NYHA class	1 2 3 4	25 (19.5%) 8 (19.5%) 2 (4.9%) 6 (14.6%)	11 (0%) 6 (35.3%) 0 (0%) 0 (0%)	19 (6.7%) 9 (30%) 2 (6.7%) 0 (0%)	1 (0%) 0 (0%) 0 (0%) 1 (50%)	0.056
Eversmoker	actual previous	11 (26.8%) 21 (51.2%)	6 (35.3%) 6 (35.3%)	7 (23.3%) 9 (30%)	1 (50%) 0 (0%)	0.287
Diabetes mellitus type 2	diet pharmacological insulin	1 (2.4%) 1 (2.4%) 2 (4.9%)	0 (0%) 2 (11.8%) 2 (11.8%)	0 (0%) 2 (6.7%) 4 (13.3%)	0 (0%) 0 (0%) 0 (0%)	0.795
Hypertension	treated untreated	26 (63.4%) 10 (24.4%)	13 (76.5%) 0 (0%)	26 (86.7%) 1 (3.3%)	1 (50%) 0 (0%)	0.03

Table A2. *Cont.*

		Acute Aortic Dissection (*n* = 41)	Chronic Aortic Dissection (*n* = 17)	Aortic Aneurysm (*n* = 30)	Penetrating Trauma (*n* = 2)	*p*
Hyperlipidemia		16 (39%)	7 (41.2%)	10 (33.3%)	0 (0%)	-
TIA		0 (0%)	1 (5.9%)	2 (6.7%)	0 (0%)	-
Peripheral vascular disease		20 (48.8%)	4 (23.5%)	3 (10%)	1 (50%)	0.024
Renal impairment	GFR > 85 50 < GFR < 86 GFR < 50 dialysis	20 (48.8%) 12 (29.3%) 8 (19.5%) 1 (2.4%)	10 (58.8%) 5 (29.4%) 2 (11.8%) 0 (0%)	17 (56.7%) 11 (36.7%) 2 (6.7%) 0 (0%)	1 (50%) 1 (50%) 0 (0%) 0 (0%)	0.874
Poor mobility		17 (41.5%)	3 (17.6%)	3 (10%)	2 (100%)	0.002
Chronic lung disease		6 (14.6%)	0 (0%)	1 (3.3%)	0 (0%)	-
Critical preoperative condition		20 (48.8%)	0 (0%)	1 (3.3%)	1 (50%)	-
Preoperative mechanical ventilation		4 (9.8%)	1 (5.9%)	0 (0%)	0 (0%)	-
Cardiogenic shock		6 (14.6%)	1 (5.9%)	0 (0%)	2 (100%)	-
Previous thoraflex implantation		2 (4.9%)	3 (17.6%)	1 (3.3%)	0 (0%)	-
Time from thoraflex implantation (months)		1.6 (1.6–1.6)	4.1 (3.5–19.6)	1.2 (1.2–1.2)	0 (0–0)	0.11

Table A3. Intraoperative and postoperative outcomes of patients, a comparison based on surgery indication. ICU—intensive care unit.

		Acute Aortic Dissection (*n* = 41)	Chronic Aortic Dissection (*n* = 17)	Aortic Aneurysm (*n* = 30)	Penetrating Trauma (*n* = 2)	*p*
Euroscore		8.3 (3.9–25.1)	3.2 (1.6–4.3)	2.5 (1.3–4.1)	5.8 (2.4–9.1)	<0.001
Procedure urgency	planned urgent immediate surgery	4 (9.8%) 12 (29.3%) 25 (61%)	9 (52.9%) 6 (35.3%) 2 (11.8%)	20 (66.7%) 9 (30%) 1 (3.3%)	0 (0%) 0 (0%) 2 (100%)	<0.001
Aortic segments involved	thoracic descending thoracic and abdominal distal arch and thoracic	29 (70.7%) 3 (7.3%) 9 (22%)	13 (76.5%) 1 (5.9%) 3 (17.6%)	21 (70%) 2 (6.7%) 7 (23.3%)	2 (100%) 0 (0%) 0 (0%)	0.983
Type of anesthesia	general sedation	38 (95%) 2 (5%)	14 (82.4%) 3 (17.6%)	26 (86.7%) 4 (13.3%)	2 (100%) 0 (0%)	0.427
Surgery time (min)		90 (69–120)	90 (70–120)	92.5 (70–115)	117.5 (115–120)	0.697
Intubation time (h)		3.8 (1.9–9.2)	5.5 (2–7.7)	3.6 (1.4–5.2)	18.8 (3.5–34.1)	0.313
Postoperative transfusion		18 (43.9%)	8 (47.1%)	4 (13.3%)	2 (100%)	0.006
ICU stay (days)		0.9 (0.2–1.7)	1 (0.4–1.4)	0.6 (0.1–1)	1.5 (0.1–3)	0.340
Hospitalization time (days)		9 (6–12)	8 (6–16)	7 (5–9)	2 (0–4)	0.081
30-day mortality		5 (12.2%)	1 (5.9%)	2 (6.7%)	0 (0%)	-
1-year mortality		9 (22%)	1 (5.9%)	3 (10%)	1 (50%)	0.172
5-year mortality		18 (43.9%)	6 (35.3%)	10 (33.3%)	1 (50%)	0.797
Postoperative complications		7 (17.1%)	1 (5.9%)	1 (3.3%)	0 (0%)	-
Reoperation		0 (0%)	0 (0%)	1 (3.3%)	0 (0%)	-
Fresh miocardial infarction		1 (2.4%)	0 (0%)	0 (0%)	0 (0%)	-
Hemodialysis		1 (2.4%)	0 (0%)	0 (0%)	0 (0%)	-
Respiratory system complications		3 (7.3%)	1 (5.9%)	0 (0%)	0 (0%)	-
Renal complications		3 (7.3%)	0 (0%)	0 (0%)	0 (0%)	-
Neurological complications		3 (7.3%)	0 (0%)	0 (0%)	0 (0%)	-
Tamponade		2 (4.9%)	0 (0%)	1 (3.3%)	0 (0%)	-



Nr at risk	Baseline	1 yr	2 yrs	3 yrs	4yrs	5yrs
AAD	41	32	29	28	26	23
Chronic AD	17	16	14	13	12	11
AA	30	27	25	25	21	20
Trauma	2	1	1	1	1	1

Figure A1. Survival curves with a surgery indication comparison. (**A**) 30-day survival curve, (**B**) 1-year survival curve, (**C**) 5-year survival curve. AAD—acute aortic dissection, AD—aortic dissection, AA—aortic aneurysm.

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Transthoracic Cross Clamp versus Endoaortic Balloon Occlusion in Minimally Invasive Mitral Valve Surgery: A Pooled Study with Subgroup Analyses

Dimitrios E. Magouliotis [1,*], Serge Sicouri [1], Massimo Baudo [1,2], Yoshiyuki Yamashita [1,2], Andrew Xanthopoulos [3], Arian Arjomandi Rad [4], Thanos Athanasiou [5] and Basel Ramlawi [1,2]

[1] Department of Cardiac Surgery Research, Lankenau Institute for Medical Research, Main Line Health, Wynnewood, PA 19096, USA; sicouris@mlhs.org (S.S.); massimo.baudo@icloud.com (M.B.); yamashitay@mlhs.org (Y.Y.); basel.ramlawi@gmail.com (B.R.)
[2] Department of Cardiac Surgery, Lankenau Heart Institute, Main Line Health, Wynnewood, PA 19096, USA
[3] Department of Cardiology, University of Thessaly, 412 23 Larissa, Greece; andrewvxanth@gmail.com
[4] Division of Medical Sciences, University of Oxford, Oxford OX1 2JD, UK; arian.arjomandirad@medsci.ox.ac.uk
[5] Department of Surgery and Cancer, Imperial College London, St Mary's Hospital, London W2 1NY, UK; t.athanasiou@imperial.ac.uk
* Correspondence: magouliotisd@mlhs.org

Abstract: Objective: We assessed the available literature regarding patients undergoing minimally invasive mitral valve surgery (MIMVS) with either transthoracic clamping (TTC) or endoaortic balloon occlusion (EABO). **Methods**: Original research studies that evaluated the perioperative outcomes of TTC versus EABO group were identified from 2000 to 2024. The incidence of all-cause mortality, cerebrovascular accidents (CVA), and aortic dissections were the primary endpoints. The cardiopulmonary bypass (CPB), cross-clamp, and ventilation time, along with the incidence of conversion to sternotomy, re-exploration, new-onset atrial fibrillation (AF), postoperative acute kidney injury (AKI), ICU stay, and LOS were the secondary endpoints. Subgroup analyses were performed regarding the EABO cannulation approach (femoral and aortic) and MIMVS approach (video-assisted and robotic-assisted). Sensitivity analyses were performed with the leave-one-out method and by including risk-adjusted populations. **Results**: Sixteen studies were included in both the qualitative and quantitative syntheses. After pooling data from 6335 patients, both groups demonstrated similar outcomes on all primary and secondary endpoints in the non-adjusted and adjusted total cohort analyses. These outcomes were further validated by the leave-one-out sensitivity analysis. In addition, the aortic cannulation EABO was associated with a lower cross-clamp time, followed by TTC and the femoral cannulation EABO approach. Furthermore, in the video-assisted subgroup analysis, the EABO approach was associated with a higher incidence of CVA, conversion to sternotomy, and longer ICU stay compared to the TTC group. **Conclusions**: The present meta-analysis indicates that both aortic occlusion techniques are safe and feasible in the context of MIMVS. A future well-designed randomized-control trial should further validate the current outcomes.

Keywords: MIMVS; mitral valve surgery; transthoracic clamping; balloon occlusion; TTC; EABO

1. Introduction

Surgery remains the gold standard treatment approach for severe mitral valve regurgitation [1]. In fact, the wide adoption of minimally invasive, endoscopic, and robot-assisted techniques in numerous centers is driven by their feasibility and effectiveness, reduced risk of infection, and enhanced patient satisfaction in terms of cosmesis and pain, along with a shorter length of hospital stay [2]. The DeBakey cross-clamp has been the mainstay of aortic occlusion during open cardiac surgery [3]. Nonetheless, aortic occlusion and

myocardial protection strategies underwent further adaptations following the increasing adoption of minimally invasive approaches in mitral valve surgery [4]. In the context of minimally invasive mitral valve surgery (MIMVS), the transthoracic clamp (TTC) and the endoaortic balloon occlusion (EABO) approaches have been employed as alternative strategies for aortic occlusion and myocardial protection [5]. TTC incorporates a longer DeBakey-type clamp inserted through the intercostal spaces [5]. On the other hand, EABO employs a transcatheter intraluminal balloon as an alternative strategy for aortic occlusion and myocardial protection [4].

To date, there have been two previous meta-analyses on this topic available in the literature [5,6]. The first meta-analysis [6] was associated with limitations related to the lack of a sensitivity analysis regarding the cannulation site in the EABO approach. Moreover, both meta-analyses were associated with two additional limitations: (1) they did not include larger multicentric studies with adjusted outcomes published in the five-year interval since the last meta-analysis [5], (2) they did not perform sensitivity analyses (a) with risk-adjusted populations and (b) using the leave-one-out method, and (3) they did not perform subgroup analyses regarding the MIMVS setting (video-assisted or robotic-assisted). The first point is important since there are no available randomized control trials and most of the previous studies were small with most surgeons exclusively using one technique or the other, especially given the steep learning curve of the EABO approach, thus posing a certain bias. The second point (sensitivity analysis) is necessary to provide the best up-to-date level of evidence given the increasing popularity of robot-assisted mitral valve surgery. Aiming to address these issues, we performed an updated meta-analysis comparing TTC and EABO as two alternative strategies for aortic occlusion and myocardial protection in the setting of minimally invasive and robot-assisted mitral valve surgery.

2. Materials and Methods

2.1. Literature Search and Articles Selection Strategy

We conducted the present study in accordance with the protocol agreed by all participating authors following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [7]. The PRISMA Checklist 2020 is demonstrated in Table S1. A thorough literature search was performed in three databases: PubMed/Medline, Scopus/ELSEVIER, and the Cochrane Central Register of Controlled Studies (CENTRAL) (the last search was performed on 24 June 2024). The following terms were employed in every possible combination: "transthoracic clamp", "cross-clamp", "ttc", "aortic balloon", "eabo", "aortic occlusion", "mitral valve replacement", "mitral valve surgery", "mitral valve repair", "mvr", "mimvs", and "minimally invasive mitral valve surgery". Inclusion criteria were (1) original reports written in English, (2) with $\geq$ 10 patients, (3) published between 2000 and 2024, (4) conducted on human subjects, and (5) reporting comparative outcomes of patients undergoing MIMVS (including robot-assisted) with the employment of either the TTC or EABO approach for aortic occlusion. All duplicate articles were excluded. We also reviewed the reference lists of all included articles for additional studies. Two authors (DEM, SS) worked independently and extracted data from the included studies. Any potential discrepancies between the two investigators were further discussed with the senior author (BR) to include only articles that best matched the criteria until consensus was reached.

2.2. Data Extraction and Endpoints

Data were extracted from each eligible study relative to the demographics (number of patients, gender, age, type of TTC, type of EABO, previous cerebrovascular events), along with the incidence of all-cause mortality, cerebrovascular accident (CVA), aortic dissection, aortic cross-clamp and cardiopulmonary bypass (CPB) time, the incidence of conversion to sternotomy, re-exploration, new onset atrial fibrillation (AF), postoperative acute kidney injury (AKI), ventilation time, intensive care unit (ICU) stay, and length of hospital stay (LOS). The incidence of all-cause mortality, CVA, and aortic dissection were the primary

endpoints. Aortic cross-clamp and CPB time, along with the incidence of conversion to sternotomy, re-exploration, new onset AF, postoperative AKI, ventilation time, ICU stay, and LOS were the secondary endpoints.

2.3. Sensitivity Analysis on Primary Endpoints

Aiming to validate our findings, we conducted further sensitivity analyses regarding both the primary and secondary endpoints. First, we performed subgroup analyses using the following subgroups: (1) EABO with aortic cannulation, (2) EABO with femoral cannulation, (3) video-assisted approach, (4) robotic-assisted approach, and (5) only studies with risk-adjusted patient groups. Second, we conducted further sensitivity analyses by employing the leave-one-out method. The leave-one-out method involves conducting separate meta-analyses on each subset of the studies remaining after leaving out exactly one study.

2.4. Quality and Publication Bias Assessment

We evaluated the non-randomized controlled trials (RCTs) for their quality using the Newcastle–Ottawa Quality Assessment Scale (NOS) [8] as an assessment tool. The scale's range varies from zero to nine stars. Studies with a score equal to or higher than five were considered to have adequate methodological quality and were finally included. All studies with a score lower than five stars were excluded. The Risk of Bias in Non-Randomized Studies of Interventions tool (ROBINS-I) was also employed to assess the risk of bias of the included studies [9]. No RCTs were included in the present meta-analysis. Two reviewers (DEM, SS) rated the studies in an independent manner, and a final decision was reached by consensus. The risk of publication bias was evaluated by visual inspection of the funnel plots.

2.5. Statistical Analysis

The odds ratio (ORs) and 95% confidence interval (95% CI) were estimated for the categorical outcomes using the random-effects model (Mantel–Haenszel statistical method). OR < 1 denoted an outcome that was more frequent in the EABO group. The weighted mean difference (WMD) with its 95% CI was calculated for the continuous outcomes using the random-effects (inverse variance statistical method) models. In cases where the WMD was lower than zero, values in the EABO group were higher. We chose the random-effects model since we did not expect that all included studies would share a common effect size. Inter-study heterogeneity was assessed through the Cochran Q statistic and by estimating I^2 [10]. Forest plots were also produced regarding the variables that were analyzed. We employed the Cochrane Collaboration Review Manager version 5.4.1 to perform all of the analyses.

3. Results

3.1. Search Strategy and Patient Demographics

The search strategy is demonstrated in the flow diagram in Figure 1 and the PRISMA Checklist 2020 (Supplementary Materials). The characteristics of the included studies are summarized in Table 1. Among the 3239 articles in PubMed/Medline, Scopus/Elsevier, and CENTRAL that were originally identified, sixteen studies [11–26] were included in the qualitative and quantitative syntheses. The level of agreement between the two reviewers was "almost perfect" (kappa = 0.91; 95% CI: 0.81, 1.00). Figure 2a,b shows the qualitative assessment with the ROBINS-I tool. The main concerns posed by the authors were related to biases due to the selection of participants and performance. The study design was prospective in four studies [14,16,22,24], and retrospective in twelve studies [11–13,15,17–21,23,25,26]. PSM was performed in four studies [12,16,18,19]. Three studies [20–22] were retrospective using a prospectively collected database. No RCTs were included in the current meta-analysis. The included studies were conducted in Germany [11, 24,25], the USA [12,16,17,26], Italy [13,14,19–22], the Netherlands [15], Canada [23], and

one was multinational [18]. The studies were published between 2000 and 2023. The total sample size was 6335 patients (TTC: 3271; EABO: 3064). The ratio of mitral valve repair (MVR) operations ranged from 9% to 73% with significant heterogeneity among studies. The comparison of the two groups in terms of the baseline characteristics is demonstrated in Table 2. The TTC and EABO groups had similar baseline characteristics, except for the previous cardiac surgery variable, with more redo cases incorporated into the EABO group (OR: 0.45; 95% CI: 0.22–0.91; $p = 0.03$). The primary and secondary endpoints, along with the sensitivity subgroup analyses, are demonstrated cumulatively in Table 3.

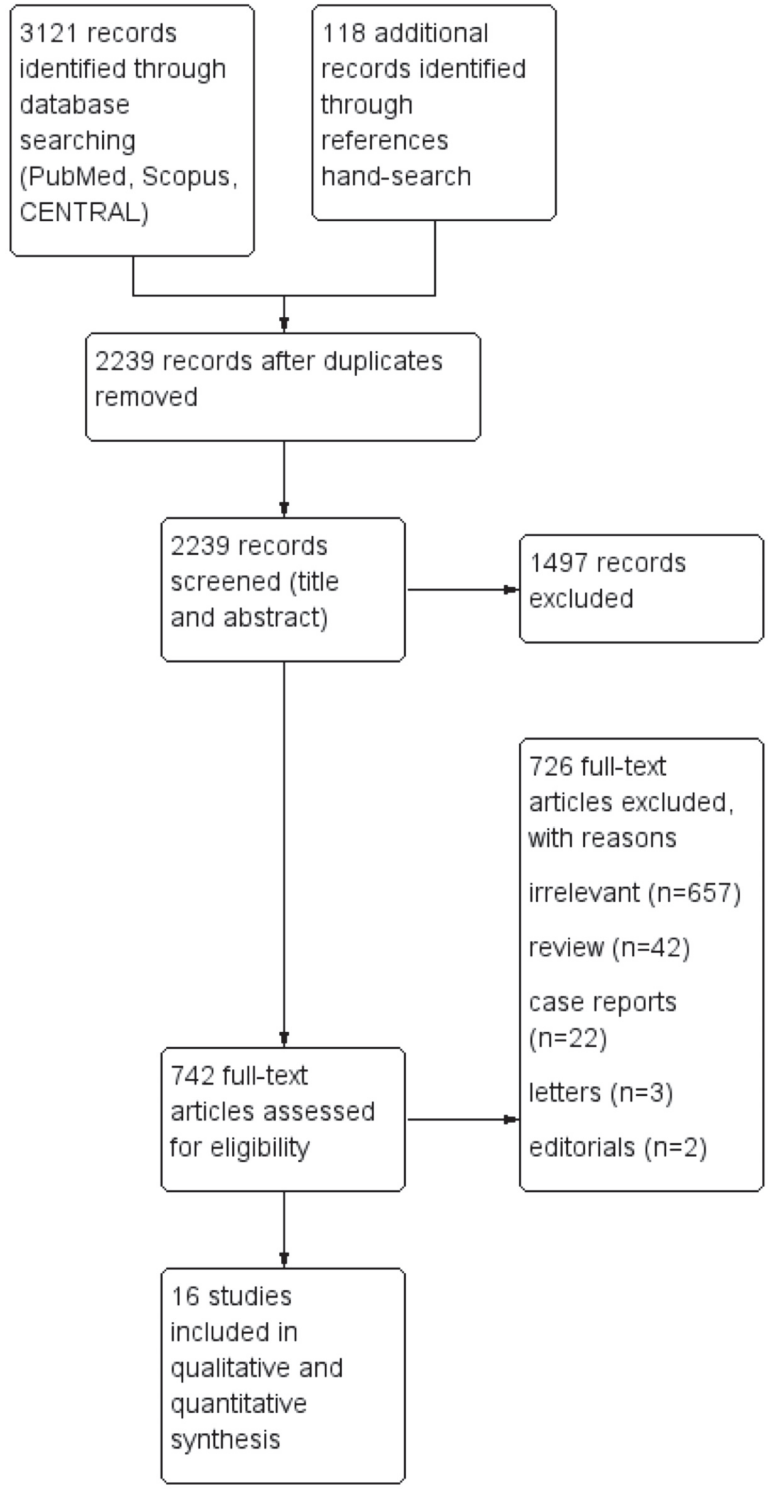

Figure 1. Trial flow of the current meta-analysis.

Table 1. Baseline characteristics and the quality assessment according to the Newcastle–Ottawa Scale (NOS) of the studies finally included in the meta-analysis.

Study ID, Year	Study Design	Patients, n TTC/EABO	Age, Mean ± SD TTC/EABO	Female Sex, % TTC/EABO	LVEF, Mean ± SD, TTC/EABO	NYHA Class 3/4, % TTC/EABO	Previous CVA, % TTC/EABO	Previous CS, % TTC/EABO	Type of TTC	Type of EABO Cannulation Approach	MVR:MVRe, % TTC/EABO	NOS
Aybek, 2000 [11]	R	35/23	56 ± 13/58 ± 16	46/52	61 ± 11/66 ± 13	3 ± 1/3 ± 1	3/0	N/A	Chitwood	Heartport Endoaortic Clamp	37:63/26:74	5
Balkhy, 2022 [12]	R-STS-A	1163/1163	62 ± 12/62 ± 12	36/36	EF < 30: 1/1	23/23	8/8	6/5	N/A	Intraclude	14:86/14:86	8
Barbero, 2016 [13]	R	150/301	67 ± 12/P:61 ± 14 C: 69 ± 9	43/P: 52 C: 24	61 ± 10/P: 59 ± 11 C: 57 ± 13	N/A	11/P: 6 C: 10	6/P: 32 C: 25	Chitwood	Intraclude	38:62/40:60	6
Barbero, 2021 [14]	P	37/80	62 ± 9/55 ± 12	30/35	63 ± 8/62 ± 7	N/A	N/A	3/10	Chitwood	Intraclude	10:90/21:79	6
Bentala, 2015 [15]	R	57/164	62 (57–73)/66 (60–74)	44/44	EF < 30: 9/4	NYHA III: 54/52	7/2	N/A	Chitwood	Intraclude	16:84/9:91	6
Ergi, 2023 [16]	P-A	168/56	65 (56–70)/66 (55–72)	32/27	63 (59–65)/61.5 (59–65)	17/17	0/0	N/A	Chitwood	IntraClude	N/A	8
Glower, 2010 [17]	R	436/235	59 ± 13/58 ± 14	53/59	51 ± 12/53 ± 10	72/56	N/A	20/14	Cosgrove	Intraclude	22:78/33:67	6
Grazioli, 2022 [18]	R-A	78/102	60 ± 14/6 ± 12	35/49	58 ± 6/56 ± 8	31/48	N/A	N/A	Chitwood, Cygnet	Intraclude	14:86/23:77	7
Ius, 2009 [19]	R-A	95/32	62 ± 11/63 ± 9	49/59	65 ± 8/64 ± 8	26/22	N/A	N/A	Cygnet, Portaclamp, Chitwood	Intraclude	23:77/41:59	7
Loforte, 2010 [20]	R *	93/45	59 ± 8/58 ± 11	73/78	60 ± 10/58 ± 9	40/40	N/A	0/0	Cygnet	Intraclude	77:23/73:27	6
Malvindi, 2018 [21]	R *	165/93	63 ± 13/56 ± 15	47/51	55 ± 7/55 ± 9	N/A	N/A	N/A	N/A	N/A	30:70/42:58	6
Maselli, 2006 [22]	P	16/20	55 ± 5/57 ± 6	63/70	N/A	N/A	N/A	N/A	Chitwood	Intraclude	38:62/45:55	6
Mazine, 2013 [23]	R *	103/140	62 ± 11/55 ± 2	39/40	61 ± 9/61 ± 8	32/31	6/6	3/7	Chitwood	N/A	13:87/20:80	6
Modi, 2009 [24]	P	573/479	61 ± 14	51	N/A	N/A	N/A	7/15	N/A	N/A	20:80/15:85	6
Reichenspurner, 2005 [25]	R	60/60	62 ± 11	71	56 ± 16	N/A	N/A	N/A	Chitwood	Intraclude	33:67	5
Yost, 2023 [26]	R	42/71	62 (56–69)/65 (56–72)	40/30	N/A	N/A	7/11	N/A	Chitwood	IntraClude	2:98/9:91	6

Abbreviations: TTC = transthoracic clamping; EABO = endoaortic balloon occlusion; R = retrospective; P = prospective; A = adjusted; N/A = not available; LVEF = left ventricle ejection fraction; NYHA = New York Heart Association; CVA = cerebrovascular accidents; CS = cardiac surgery; MVR = mitral valve replacement; MVRe = mitral valve repair; SD = standard deviation; Chitwood = Chitwood clamp (Scanlan International, Inc., Minneapolis, MN, USA); Cygnet = Cygnet (Novare Surgical Systems Inc., Cupertino, CA, USA); Portaclamp = Portaclamp (Cardio Life Research SA, Louvain-la-Neuve, Belgium); Cosgrove = Cosgrove Flexible Clamp (Cardinal Health V, Edwards Lifesciences Corporation, Irvine, CA, USA); Intraclude = Intraclude (Edwards Lifesciences, Irvine, CA, USA); Heartport = Heartport Endoaortic Clamp (Heartport, Redwood City, CA, USA). * Retrospective analysis of a prospectively collected database.

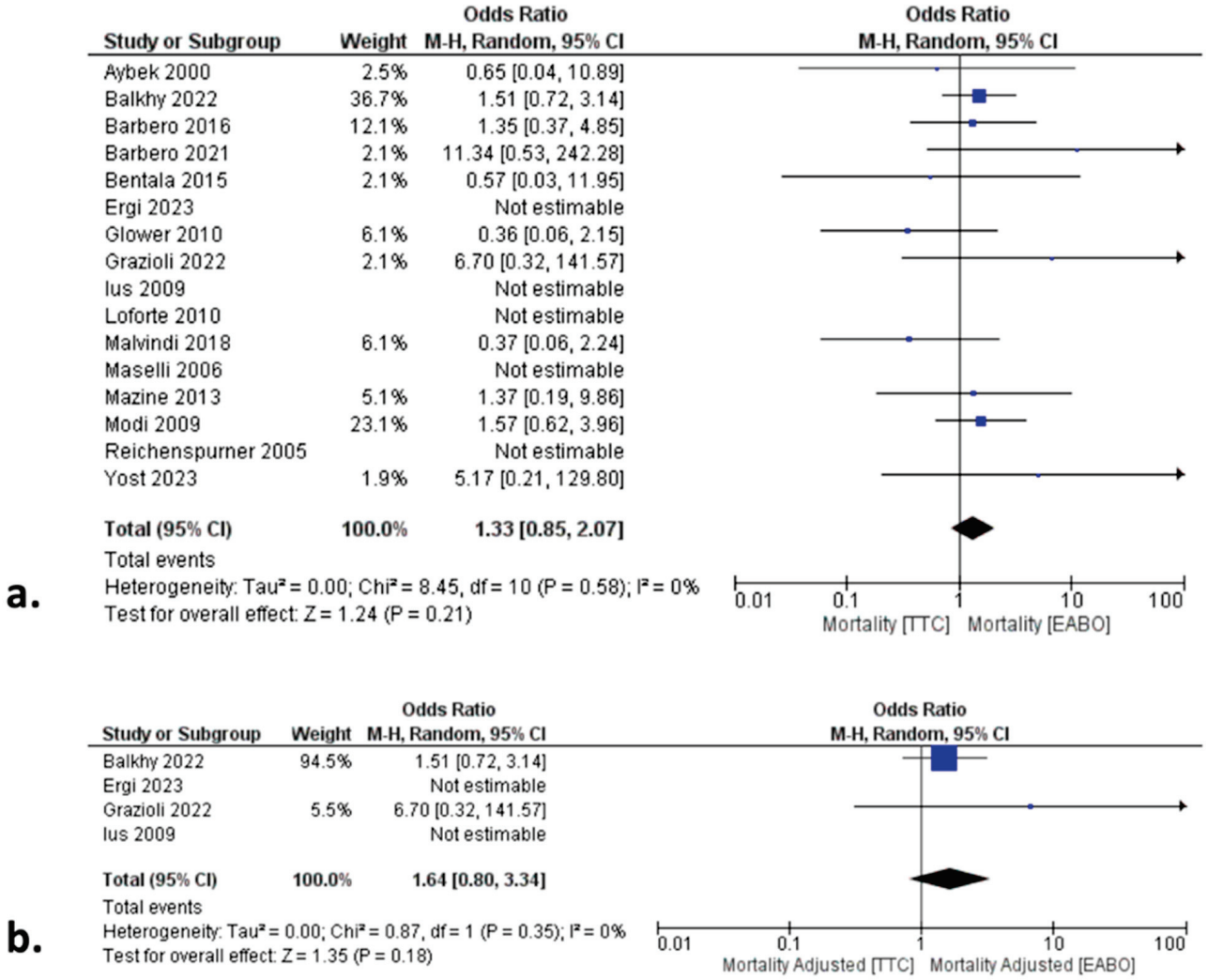

Figure 2. Forest plots regarding all-cause mortality in the (**a**) non-adjusted and (**b**) adjusted total cohort. There were no significant differences between the transthoracic clamping (TTC) and endoaortic balloon occlusion (EABO) groups [11–26].

Table 2. Comparison of baseline characteristics.

Baseline Characteristics	Arms	OR *	95% CI	*p*-Value	Heterogeneity	
					I^2	*p*-Value
Age	14	0.21	−1.5, 1.93	0.81	90%	<0.01
Female ratio	14	0.92	0.82, 0.73	0.15	0%	0.82
LVEF	10	0.55	−0.49, 1.59	0.30	63%	<0.01
NYHA III/IV	8	1.08	0.80, 1.47	0.06	66%	<0.01
Previous CVA	7	1.04	0.79, 1.36	0.80	0%	0.57
Previous CS	8	0.45	0.22, 0.91	0.03	88%	<0.01
MVR rate	15	0.83	0.65, 1.05	0.12	55%	<0.01

Abbreviations: LVEF = left ventricle ejection fraction; NYHA = New York Heart Association; CVA = cerebrovascular accidents; CS = cardiac surgery; MVR = mitral valve replacement; OR = odds ratio; 95% CI = 95% confidence intervals. * Mantel–Haenszel (M–H) method was employed for categorical variables and inverse variance (IV) for continuous variables.

Table 3. Summary of primary and secondary endpoints in the total cohort and subgroup analyses.

Endpoints	Arms	OR *	95% CI	*p*-Value	Heterogeneity	
					I^2	*p*-Value
Total cohort						
All-cause mortality	16	1.33	0.85, 2.07	0.21	0%	0.58
CPB time	17	−1.68	−8.21, 4.85	0.61	95%	<0.01
Aortic cross-clamp time	16	−3.27	−7.61, 1.07	0.14	92%	<0.01
Conversion to sternotomy	14	0.51	0.19, 1.39	0.19	65%	<0.01
Aortic dissection	15	0.51	0.20, 1.33	0.17	0%	0.50
CVA	15	0.68	0.44, 1.04	0.07	0%	0.59
Re-exploration	14	0.90	0.64, 1.28	0.57	0%	0.61
Ventilation	8	−0.03	−0.58, 0.52	0.92	0%	0.71
New onset AF	10	0.86	0.61, 1.21	0.37	54%	0.03
AKI	11	1.22	0.91, 1.65	0.19	0%	0.85
ICU stay	10	−0.27	−0.72, 0.19	0.25	97%	<0.01
LOS	15	−0.20	−0.99, 0.58	0.61	99%	<0.01
Femoral cannulation EABO						
All-cause mortality	14	1.44	0.91, 2.28	0.12	0%	0.71
CPB time	14	−3.78	−9.84, 2.28	0.22	94%	<0.01
Aortic cross-clamp time	13	−5.60	−10.47, −0.73	0.02	93%	<0.01
Conversion to sternotomy	14	0.52	0.19, 1.40	0.20	65%	<0.01
Aortic dissection	14	0.51	0.20, 1.33	0.17	0%	0.50
CVA	15	0.66	0.43, 1.02	0.06	0%	0.65
Re-exploration	13	0.87	0.61, 1.24	0.45	0%	0.59
Ventilation	7	−0.04	−0.59, 0.51	0.89	0%	0.64
New onset AF	9	1.12	0.93, 1.35	0.22	0%	0.44
AKI	10	1.27	0.93, 1.72	0.13	0%	0.88
ICU stay	9	−0.30	−0.78, 0.18	0.22	98%	<0.01
LOS	13	−0.20	−1.17, 0.77	0.69	99%	<0.01
Aortic cannulation EABO						
All-cause mortality	2	1.51	0.72, 3.14	0.21	N/A	–
CPB time	3	10.07	−35.55, 55.49	0.66	98%	<0.01
Aortic cross-clamp time	3	7.89	3.65, 12.12	<0.01	0%	0.42
Conversion to sternotomy	2	0.14	0.01, 3.44	0.23	N/A	–
Aortic dissection	2	N/E	–	–	–	–
CVA	2	3.01	0.15, 59.20	0.47	N/A	–
Re-exploration	2	1.60	0.51, 4.97	0.42	0%	0.75
Ventilation	1	2.60	−6.73, 11.93	0.58	N/A	–
New onset AF	1	0.45	0.27, 0.76	<0.01	N/A	–
AKI	2	0.73	0.25, 2.08	0.13	0%	0.88
ICU stay	1	0.10	−0.70, 0.90	0.81	N/A	–
LOS	2	0.00	−0.10, 0.10	0.99	0%	0.40
Video-assisted approach						
All-cause mortality	12	1.18	0.67, 2.08	0.57	0%	0.48
CPB time	13	−4.85	−14.51, 4.80	0.32	94%	<0.01
Aortic cross-clamp time	12	−5.41	−11.54, 0.72	0.08	89%	<0.01
Conversion to sternotomy	10	0.31	0.16, 0.61	<0.01	0%	0.69
Aortic dissection	11	0.39	0.14, 1.13	0.08	0%	0.45
CVA	11	0.55	0.31, 0.98	0.04	0%	0.52
Re-exploration	12	0.87	0.61, 1.23	0.43	0%	0.43
Ventilation	8	−0.03	−0.58, 0.52	0.92	0%	0.71
New onset AF	8	0.77	0.52, 1.14	0.19	37%	0.14
AKI	10	1.08	0.59, 1.97	0.81	0%	0.79
ICU stay	8	−0.07	−0.09, −0.05	<0.01	0%	0.88
LOS	12	−0.40	−1.36, 0.57	0.42	99%	<0.01

Table 3. *Cont.*

Endpoints	Arms	OR *	95% CI	*p*-Value	Heterogeneity	
					I^2	*p*-Value
Robotic-assisted approach						
All-cause mortality	2	5.17	0.21, 129.80	0.32	N/A	–
CPB time	2	13.68	7.31, 20.05	<0.01	94%	<0.01
Aortic cross-clamp time	2	4.46	−4.36, 13.28	0.32	98%	<0.01
Conversion to sternotomy	2	1.71	0.10, 280.03	0.71	N/A	–
Aortic dissection	2	1.01	0.04, 25.20	0.99	N/A	–
CVA	2	0.55	0.02, 13.88	0.72	N/A	–
Re-exploration	2	5.38	0.54, 53.54	0.15	N/A	–
Ventilation	0	–	–	–	–	–
New onset AF	1	1.38	0.49, 3.86	0.54	N/A	–
AKI	0	–	–	–	–	–
ICU stay	0	–	–	–	–	–
LOS	1	0.00	−0.14, 0.14	1.00	N/A	–
Risk-Adjusted Total Cohort						
All-cause mortality	4	1.64	0.80, 3.34	0.18	0%	0.35
CPB time	4	0.51	−9.03, 10.06	0.92	89%	<0.01
Aortic cross-clamp time	4	−3.84	−9.16, 1.49	0.16	81%	<0.01
Conversion to sternotomy	4	0.51	0.05, 5.54	0.58	84%	<0.01
Aortic dissection	4	0.90	0.14, 5.93	0.91	29%	0.24
CVA	4	0.71	0.35, 1.44	0.34	7%	0.34
Re-exploration	3	1.03	0.04, 25.96	0.98	N/A	–
Ventilation	2	−5.77	−19.75, 8.21	0.42	58%	0.12
New onset AF	4	1.18	0.97, 1.44	0.10	0%	0.50
AKI	4	1.33	0.96, 1.84	0.09	0%	0.39
ICU stay	4	−0.50	−1.28, 0.28	0.21	99%	<0.01
LOS	4	0.30	−0.60, 1.21	0.51	95%	<0.01

Abbreviations: EABO = endoaortic balloon occlusion; CVA = cerebrovascular accidents; AF = atrial fibrillation; CPB = cardiopulmonary bypass; AKI = acute kidney injury; ICU = intensive care unit; LOS = length of hospital stay; OR = odds ratio; 95% CI = 95% confidence intervals; N/A = Not available. * Mantel–Haenszel (M–H) method was employed for categorical variables and inverse variance (IV) for continuous variables.

3.2. Primary Endpoints: All-Cause Mortality, CVA, and Aortic Dissection

In the total cohort analysis, there was no significant difference between the two groups in terms of all-cause mortality (HR: 1.33; 95% CI:0.85, 2.07; $p = 0.21$) (Figure 2a), incidence of CVA (OR: 0.68; 95% CI: 0.44, 1.04; $p = 0.07$), and aortic dissection (OR: 0.51; 95% CI: 0.20, 1.33; $p = 0.17$) (Table 3).

3.3. Secondary Endpoints

In the total cohort analysis, both groups demonstrated similar CPB (OR: −1.68; 95% CI: −8.21, 4.85; $p = 0.61$), cross-clamp (OR: −3.27; 95% CI: −7.61, 1.07; $p = 0.14$), and ventilation (OR: −0.03; 95% CI: −0.58, 0.52; $p = 0.92$) time. In addition, there was no significant difference between the two groups regarding the incidence of conversion to sternotomy (OR: 0.51; 95% CI: 0.19, 1.39; $p = 0.19$), re-exploration (OR: 0.90; 95% CI: 0.64, 1.28; $p = 0.57$), new-onset AF (OR: 0.86; 95% CI: 0.61, 1.21; $p = 0.37$), and postoperative AKI (OR: 1.22; 95% CI: 0.91, 1.65; $p = 0.19$). Finally, both groups were similar regarding ICU stay (OR: −0.27; 95% CI: −0.72, 0.19; $p = 0.25$) and LOS (OR: 0.30; 95% CI: −0.60, 1.21; $p = 0.51$).

3.4. Subgroup and Sensitivity Analyses

To further validate our outcomes, we performed subgroup analyses comparing TTC vs. EABO in patients (a) with femoral cannulation EABO, (b) aortic cannulation EABO, (c) undergoing video-assisted, and (d) robotic-assisted MIMVS. In the femoral EABO subgroup, all outcomes were similar to the TTC group, except for the aortic cross-clamp time, which was higher in the EABO group. In contrast, the aortic EABO subgroup demonstrated

significantly lower cross-clamp time compared to the TTC group. Consequently, the aortic cannulation EABO approach was associated with the shortest cross-clamp time of all three subgroups. In the video-assisted subgroup analysis, EABO was associated with a higher incidence of CVA, conversion to sternotomy, and longer ICU stay compared to the TTC group.

Moreover, the validity of the total cohort analysis outcomes was further affirmed by the risk-adjusted subgroup analyses, in which patients were matched with the baseline characteristics to minimize the risk of bias related to cofounders. In fact, the outcomes of this subgroup analysis were similar to the total cohort analysis outcomes, with no difference between the two groups in any of the primary or secondary endpoints (Figure 2b, Table 3). Finally, no difference was found when we applied the leave-one out sensitivity analysis method, thus further supporting the validity of our outcomes.

3.5. Quality and Publication Bias Assessment

The quality evaluation according to the Newcastle–Ottawa Scale for all studies is shown in Table 1. Figure 3 demonstrates the qualitative assessment of the studies according to the ROBINS-I tool. Figure 3a,b shows the qualitative assessment with the ROBINS-I tool. The authors' main concerns were mainly related to biases associated with the outcome data and selective reporting. The primary endpoints were associated with low heterogeneity. Most of the secondary endpoints were related to low heterogeneity. In contrast, the CPB and cross-clamp time, along with the incidence of conversion to sternotomy, ICU stay, and LOS, were associated with high heterogeneity. The main factors affecting and increasing heterogeneity in these variables were the level of expertise, the volume of cases, the differences in operation setting, and aortic occlusion devices, along with the differences in the perioperative pathway protocols among different institutions. The funnel plots (Figure S1) seemed asymmetrical, with studies being absent from either the top or bottom of the graph, thus suggesting the presence of certain publication bias. The relatively small number of included studies was the main reason for the reported asymmetry.

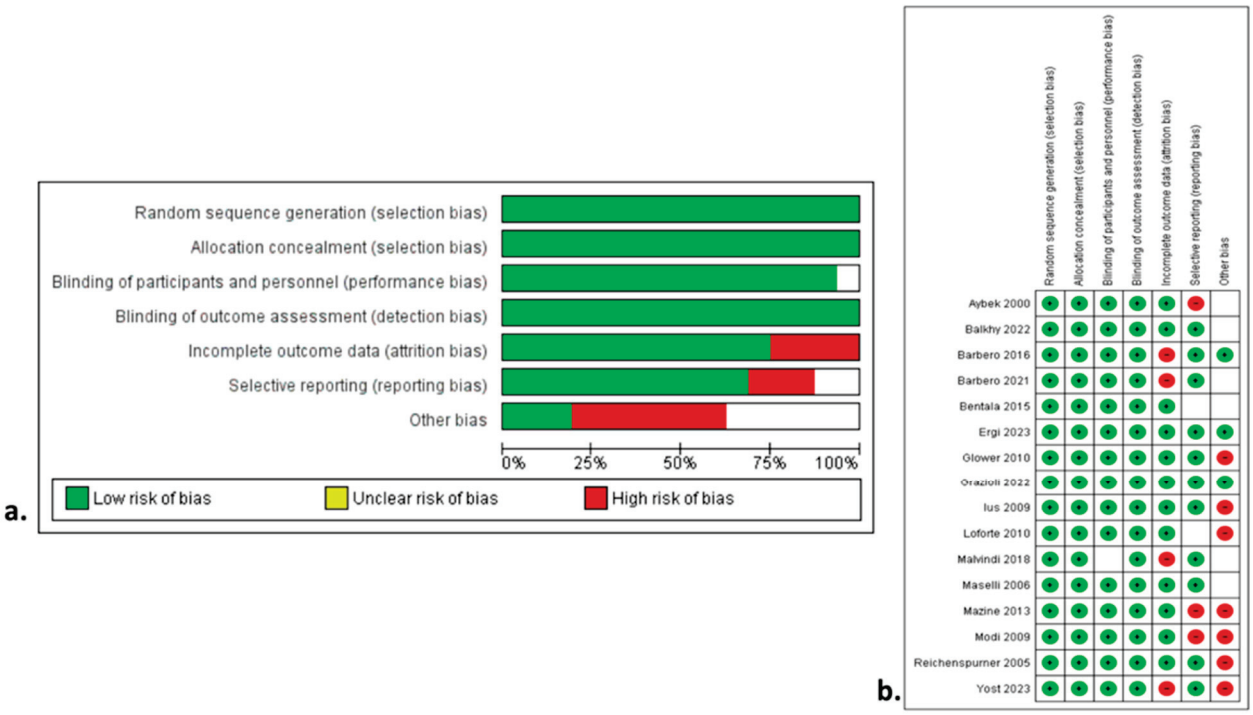

Figure 3. Risk of Bias in Non-Randomized Studies of Interventions with (**a**) summary plot and (**b**) traffic lights [11–26].

4. Discussion

The current meta-analysis identified sixteen articles comparing the TTC versus EABO as two alternative methods of aortic occlusion for minimally invasive mitral valve surgery and incorporated 6335 patients. According to our total cohort analysis, TTC and EABO demonstrated comparable outcomes with regard to the primary and secondary outcomes. Although a previous meta-analysis [5] was conducted in 2019 (study period until December 2018), numerous newer studies have been published with important characteristics (PSM study design in three of them [12,16,18] and robotic-assisted MIMVS in two studies [16,26]), and the sensitivity analyses were limited. Given the lack of a randomized trial, the present meta-analysis provides the best currently available level of evidence on this topic.

All included studies reported postoperative all-cause mortality. According to the whole cohort analysis and all related sensitivity analyses, both techniques were associated with a similar all-cause mortality rate. This was an expected outcome given the growing evidence, suggesting that baseline characteristics and CPB time, rather than aortic clamping technique, are predictors of mortality [13,24]. In fact, in the present study, we tried to limit the impact of potential cofounders by assessing the similarity of the baseline characteristics in the total cohort and by performing a PSM sensitivity analysis. Given the low heterogeneity, similarity, and replicability of these outcomes in all sensitivity analyses, we suggest that both techniques are equally safe in terms of all-cause mortality and that survival is not influenced by the aortic occlusion technique.

Fifteen studies reported outcomes on postoperative CVA. The overall cohort analysis showed no difference between the two groups in the risk of CVA with either technique. In addition, the incidence of CVA was similar between the TTC and EABO in either the femoral or the aortic cannulation EABO subgroup. However, in the video-assisted MIMVS subgroup analysis, the incidence of CVA was higher in the EABO cohort. A potential mechanism is the increased risk of embolus derived from the aortic wall of patients with severe atheromatous disease and porcelain aorta during the manipulation of the balloon catheter, and the inflation–deflation–reinflation circles that may occur in cases of balloon migration. Overall, both the TTC and EABO are associated with a similarly low risk of CVA; however, EABO (aortic) seems the least risk prone for this outcome. Nonetheless, the PSM and leave-one-out sensitivity analyses confirmed the equal outcomes demonstrated by the total cohort analysis. Finally, there was zero heterogeneity in all analyses regarding CVA incidence.

Seventeen studies reported CPB time and sixteen studies reported aortic cross-clamp time. There was no difference between the two groups in terms of CPB and cross-clamp time in the total cohort, PSM, and video-assisted approach analyses. Nonetheless, there was high heterogeneity among the included studies, probably attributed to differences in terms of the level of expertise, the point of standing in the learning curve, the volume of cases, the operation setting, the cross-clamp devices, and the perioperative pathway protocols among different institutions. Outcomes were different in the cannulation approach subgroup analyses. However, there was no difference regarding the CPB time in all analyses, and the cross-clamp time was higher in the femoral EABO and lower in the aortic EABO group compared to the TTC group. These results are consistent with the previous meta-analysis [5] regarding cross-clamp time, but differ with respect to CPB time. The main reasons for this difference from the previous meta-analysis were the inclusion of six newer studies with a larger number of patients included as well as surgeons more experienced in MIMVS. However, the difference between the femoral cannulation approach EABO and TTC technique remains, mainly due to the more straightforward nature and shorter learning curve of the TTC occlusion maneuver [27].

Fifteen studies were included in the aortic dissection assessment. According to the total and PSM analyses, both techniques were associated with a similar incidence of aortic dissections. This finding is in contrast with the previous meta-analysis that reported a higher incidence of aortic dissection for the EABO group. In addition, the cannulation approach (femoral or aortic) did not affect our outcomes. There is evidence demonstrating

the correlation between the learning curve and the incidence of iatrogenic aortic dissections [28]. Because we included newer studies with larger patient volumes, the impact of learning was limited, and the outcomes were similar between the two groups. Furthermore, according to the total cohort and PSM analyses, there was no difference between the two groups regarding the perioperative morbidity.

The limitations of the current meta-analysis are relevant to the limitations posed by the included studies. No RCTs were included. Although most studies were retrospective in nature, seven of them provided either risk-adjusted/PSM analyses or used prospectively collected data. In addition, the included studies were related to potential biases regarding the outcome data and selective reporting. Moreover, differences among institutions in selection criteria, surgeon expertise, different occlusion devices, and perioperative management pose certain limitations.

On the other hand, the present study was associated with certain strengths such as (1) the clear data-extraction protocol, (2) the well-specified inclusion/exclusion criteria, (3) the literature search performed in three different databases, (4) the quality assessment of the included studies, (5) the detailed presentation of the results of data-extraction and analyses, (6) the significantly larger patient sample compared to the previous meta-analyses, (7) the groups were similar in almost all baseline characteristics, and (8) the thorough sensitivity and subgroups analyses performed.

5. Conclusions

In the context of patients undergoing MIMVS, aortic occlusion with either the TTC or EABO approach is similarly safe and feasible. There was no difference between the two groups regarding the primary endpoints (all-cause mortality, CVA, aortic dissections) between the two groups in the non-adjusted and adjusted total cohort analyses. Furthermore, the aortic cannulation EABO approach was associated with the shortest cross-clamp time. The current study represents the best currently available level of evidence on the topic and should be further supported by a well-designed future RCT.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm13174989/s1, Figure S1: Funnel plots describing the publication bias regarding (a) mean operative time (MOT), (b) intraoperative blood loss, (c) length of stay (LOS), (d) complications; Table S1: PRISMA 2020 Checklist.

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Contemporary Use of Sodium Glucose Co-Transporter 2 Inhibitors in Hospitalized Heart Failure Patients: A "Real-World" Experience

Andrew Xanthopoulos [1,*], Nikolaos Katsiadas [2], Grigorios Giamouzis [1], Kleoniki Vangelakou [1], Dimitris Balaskas [1], Michail Papamichalis [1], Angeliki Bourazana [1], Nikolaos Chrysakis [1], Sotirios Kiokas [3], Christos Kourek [4], Alexandros Briasoulis [4], Niki Skopeliti [1], Konstantinos P. Makaritsis [5,6], John Parissis [7], Ioannis Stefanidis [8], Dimitrios Magouliotis [9], Thanos Athanasiou [9], Filippos Triposkiadis [1] and John Skoularigis [1]

[1] Department of Cardiology, University Hospital of Larissa, 41100 Larissa, Greece; grgiamouzis@gmail.com (G.G.); kleonikivag@hotmail.com (K.V.); balaskasdim@gmail.com (D.B.); mic_pap@yahoo.gr (M.P.); angi3bou@gmail.com (A.B.); nikoschrisakis8@yahoo.gr (N.C.); n.skopeliti@gmail.com (N.S.); ftriposk@med.uth.gr (F.T.); iskoular@gmail.com (J.S.)
[2] Department of Cardiology, Konstantopouleio General Hospital of Athens, 14233 Athens, Greece; nikos5189@hotmail.com
[3] Department of Cardiology, General Hospital of Larissa, 41221 Larissa, Greece; sotkiokas@gmail.com
[4] Department of Clinical Therapeutic, Alexandra Hospital, National and Kapodistrian University of Athens, 11528 Athens, Greece; chris.kourek.92@gmail.com (C.K.); alexbriasoulis@gmail.com (A.B.)
[5] Department of Medicine & Research Laboratory of Internal Medicine, Faculty of Medicine, University of Thessaly, 41334 Larissa, Greece; makaritsis@gmail.com
[6] National Expertise Center of Greece in Autoimmune Liver Diseases, General University Hospital of Larissa, 41110 Larissa, Greece
[7] Emergency Medicine Department, Attikon University Hospital, National and Kapodistrian University of Athens, 10679 Athens, Greece; jparissis@yahoo.com
[8] Department of Nephrology, Faculty of Medicine, University of Thessaly, 41334 Larissa, Greece; stefanid@med.uth.gr
[9] Department of Cardiothoracic Surgery, University Hospital of Larissa, 41110 Larissa, Greece; dimitrios.magouliotis.18@alumni.ucl.ac.uk (D.M.); t.athanasiou@imperial.ac.uk (T.A.)
* Correspondence: andrewvxanth@gmail.com

Abstract: Background/Objectives: The aim of this study was to examine the association between in-hospital initiation of sodium glucose co-transporter 2 inhibitors (SGLT2is) and outcomes in hospitalized heart failure (HHF) patients utilizing data from a Greek center. **Methods**: The present work was a single-center, retrospective, observational study of consecutive HF patients hospitalized in a tertiary center. The study endpoint was all-cause mortality or HF rehospitalization. Univariate and multivariate Cox proportional-hazard models were conducted to investigate the association between SGLT2i administration at discharge and the study endpoint. **Results**: Sample consisted of 171 patients, 55 of whom (32.2%) received SGLT2is at discharge. Overall, mean follow-up period was 6.1 months (SD = 4.8 months). Patients who received SGLT2is at discharge had a 43% lower probability of the study endpoint compared to those who did not receive SGLT2is at discharge (HR = 0.57; 95% CI: 0.36–0.91; $p = 0.018$). After adjusting for age, gender, smoking, hemoglobin (Hgb), use of SGLT2is at admission, use of Angiotensin-Converting Enzyme Inhibitors (ACEI-Is)/Angiotensin Receptor Blockers (ARBs) at discharge and Sacubitril/Valsartan at discharge, the aforementioned result remained significant (HR = 0.38; 95% CI: 0.19–0.73; $p = 0.004$). The 55 patients who received SGLT2is at discharge were propensity score matched with the 116 patients who did not receive SGLT2is at discharge. Receiving SGLT2is at discharge continued to be significantly associated with a lower probability of the study endpoint (HR= 0.43; 95% CI: 0.20–0.89; $p = 0.024$). **Conclusions**: Initiation of SGLT2is in HHF patients may be associated with better outcomes.

Keywords: hospitalization; heart failure; acute; sodium glucose co-transporter 2 inhibitors; outcomes

1. Introduction

Acute heart failure (HF) refers to the rapid or gradual onset of symptoms and/or signs of HF that results in either the patients' urgent visit to the emergency department (ED) or an unplanned hospital admission [1,2]. Although it can manifest as a first clinical episode of HF (new onset), signs usually occur as an acutely decompensated chronic HF [2]. Acute HF continues to be the leading reason for hospitalization in people over 65 years of age and it is associated with high rates of mortality and rehospitalization for HF [3]. More specifically, in Europe and the USA over 1 million patients are admitted for HF each year, with a rehospitalization rate that reaches 50% at six months and a one-year mortality rate reaching 30% [4]. This results in an overload of health systems and an increase in medical costs [5]. Despite the development of new innovative treatments for the management of chronic HF, in-hospital treatment for acute HF is mainly symptomatic and involves the use of decongestive drugs with loop diuretics [1–3]. Therefore, there is an urgent need to find new treatments that will improve outcomes in these patients.

Sodium glucose co-transporter 2 inhibitors (SGLT2is) are a class of drugs that act on the proximal tubule and cause glycosuria and natriuresis [6]. Although initially used to treat patients with diabetes mellitus, SGLT2is have shown beneficial effects in the management of patients with HF [6]. These agents have been shown in large randomized trials to reduce both cardiovascular mortality and readmissions in patients with chronic HF with either reduced or preserved left ventricular ejection fraction (LVEF) [7–10]. As a result, they have become an integral part of the management of patients with chronic HF regardless of LVEF and they are an important weapon in the quiver of clinicians [2]. Although their value in chronic HF is indisputable, their role in patients with acute HF dysregulation is still under investigation. Recent studies have shown beneficial effects from the rapid initiation of SGLT2is and especially empagliflozin in patients with hospitalized HF (HHF) [11,12]. The aim of this study was to examine the association of in-hospital initiation of SGLT2is and outcomes in HHF patients utilizing "real world" data.

2. Materials and Methods

2.1. Study Population

The present work was a single-center observational study of 221 single consecutive patients who were admitted in the Cardiology Department of the University Hospital of Larissa between 1 April 2022 and 15 March 2023. The data were obtained from the patients' medical records. All patients had to be over 18 years of age with or without a known history of HF, regardless of LVEF. Patients with active cancer, sepsis, eGFR < 20 mL/min/1.73 m^2 and missing data were excluded from the analysis. After the implementation of inclusion and exclusion criteria, the 171 patients that remained were divided into two cohorts. The first cohort consisted of 116 hospitalized HF patients who were not on SGLT2is at discharge and the second cohort consisted of 55 hospitalized HF patients who received SGLT2is at discharge (Figure 1).

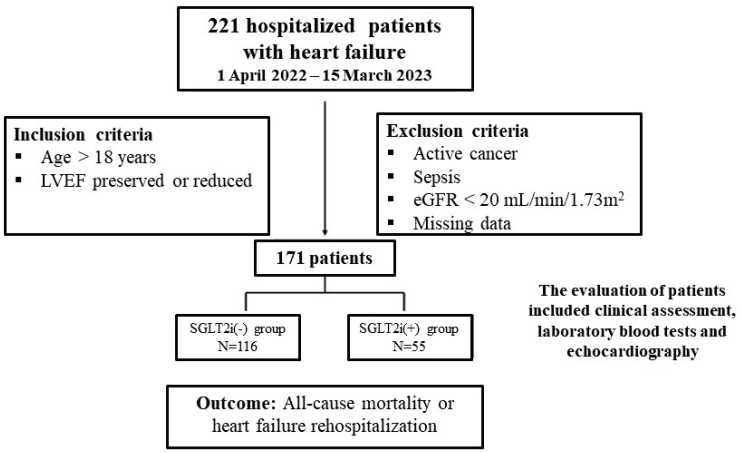

Figure 1. Study flowchart.

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of the University of Thessaly (protocol code: 53326; date of approval: 29 November 2023). Informed consent was waived due to the retrospective nature of the study.

2.2. Patient Assessment

The evaluation of patients at admission, during hospitalization and before discharge included a clinical assessment, laboratory blood tests and echocardiography. Levels of hematocrit (Ht), hemoglobin (Hgb) and Red Blood Cell Distribution Width (RDW) were measured with the use of a Unicel DxH 900 Hematology Analyzer (Beckman, USA) on samples obtained for standard of care evaluation, while urea, creatinine, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and electrolytes were measured with the use of a Cobas 8000 (Roche, Germany). The echocardiography was reviewed by two independent echocardiographers with the use of a Vivid T8 v206 (General Electric Medical Systems, China). Standard echocardiographic measurements were obtained in accordance with the current guidelines of the European Association of Cardiovascular Imaging [13].

2.3. Outcomes

The outcome of the study was the combined endpoint of all-cause mortality or HF rehospitalization (whichever occurred first). Follow-up data were collected through outpatient clinic visits, telephone calls and death certificates.

2.4. Statistical Analysis

Quantitative variables were expressed as mean (Standard Deviation) or as median (interquartile range). Categorical variables were expressed as absolute and relative frequencies. For the comparison of proportions, chi-square and Fisher's exact tests were used. Students' *t*-tests and Mann–Whitney tests were used for the comparison of continuous variables between two groups. Kaplan–Meier survival curves for the study outcome were graphed over the follow-up period for the SGLT2i and non-SGLT2i at discharge groups. Univariate and multivariate Cox proportional-hazard models were conducted in order to find if receiving SGLT2is at discharge was significantly associated with all-cause mortality or HF rehospitalization. Moreover, the aforementioned Cox proportional-hazard model was also conducted in the subsample, where the 55 patients who received SGLT2is at discharge were propensity score matched, using a ratio 1:1, with the 116 patients who did not receive SGLT2is at discharge in order to ensure similar baseline characteristics. All reported p values are two-tailed. Statistical significance was set at $p < 0.05$ and analyses were conducted using SPSS statistical software (version 26.0).

3. Results

3.1. Patient Characteristics

Patients' characteristics are presented in Table 1, in total sample and by administration of SGLT2is at discharge. Regarding the phenotypes of the HHF patients, 34 (20%) presented with acute pulmonary edema, 116 (68%) with acute decompensated HF, 14 (8%) with isolated right HF and 7 (4%) with cardiogenic shock. The percentage of males was significantly greater in the SGLT2i group vs. the no-SGLT2i group. Further, patients in the SGLT2i group were significantly younger and more frequently smokers. Hct and Hgb values were significantly higher in the SGLT2i group. Patients in the SGLT2i group were less frequently on ACE-Is/ARBs but were more often on Sac/Valsartan at discharge.

Table 1. Sample characteristics in total sample and by group.

	Total Sample (1 April 2022–15 March 2023) (*n* = 171; 100%)	SGLT2i (at Discharge)		
		No (*n* = 116; 67.8%)	Yes (*n* = 55; 32.2%)	
	n (%)	*n* (%)	*n* (%)	*p*
Gender				
Females	83 (48.5)	63 (54.3)	20 (36.4)	0.028 +
Males	88 (51.5)	53 (45.7)	35 (63.6)	
Age, mean (SD)	76 (11.8)	78.2 (11.4)	71.5 (11.4)	<0.001 ‡
SBP, mean (SD)	132.5 (28.9)	131.6 (27.9)	134.4 (30.9)	0.562 ‡
DBP, mean (SD)	77.4 (15.7)	77.2 (16.1)	77.7 (15.1)	0.859 ‡
Pulse Rate, mean (SD)	82.5 (20.4)	83 (20.9)	81.6 (19.7)	0.696 ‡
NYHA				
III	59 (40.7)	38 (40.0)	21 (42.0)	0.816 +
IV	86 (59.3)	57 (60.0)	29 (58.0)	
LVEF, median (IQR)	35 (22.5–47.5)	35 (25–50)	35 (20–45)	0.180 ‡‡
HFrEF/HFmrEF/HFpEF				
HFrEF	103 (65.2)	63 (59.4)	40 (76.9)	0.094 +
HFmrEF	10 (6.3)	8 (7.5)	2 (3.8)	
HFpEF	45 (28.5)	35 (33)	10 (19.2)	
E/e' (echocardiography)	14 (12–16)	14 (12–15)	14 (11.5–16)	0.764 ‡‡
NT-proBNP, median (IQR)	6490 (3410–10,500)	6520 (3185–10,350)	6385 (3880–10,800)	0.849 ‡‡
Cancer	9 (5.3)	5 (4.3)	4 (7.3)	0.471 ++
Hypertension	164 (95.9)	112 (96.6)	52 (94.5)	0.682 ++
Diabetes	67 (39.2)	46 (39.7)	21 (38.2)	0.854 +
COPD	12 (7)	10 (8.6)	2 (3.6)	0.342 ++
Dyslipidemia	116 (67.8)	80 (69)	36 (65.5)	0.646 +
Coronary disease	85 (49.7)	56 (48.3)	29 (52.7)	0.587 +
eGFR	60 (37–83)	56 (36–79.5)	64 (42–85)	0.138 ‡‡
Anemia	121 (70.8)	87 (75)	34 (61.8)	0.077 +
Atrial fibrillation	94 (55)	64 (55.2)	30 (54.5)	0.939 +
Obstructive Sleep Apnea	2 (1.2)	1 (0.9)	1 (1.8)	0.541 ++
Smoking				
Yes	16 (9.4)	7 (6.1)	9 (16.4)	0.032 +
No	130 (76.5)	88 (76.5)	42 (76.4)	
In the past	24 (14.1)	20 (17.4)	4 (7.3)	
Ht, mean (SD)	37.2 (6)	36.4 (5.6)	38.8 (6.5)	0.011 ‡
Hgb, mean (SD)	11.9 (2)	11.6 (1.9)	12.5 (2.2)	0.008 ‡
RDW, median (IQR)	16.2 (14.6–18.4)	16.5 (14.7–18.8)	15.5 (14.4–17.2)	0.075 ‡‡
Creatinine, median (IQR)	1.1 (0.9–1.6)	1.1 (0.9–1.6)	1.1 (0.9–1.5)	0.708 ‡‡
Urea, median (IQR)	51 (38.5–79)	55.5 (38.9–78.5)	47 (37–79.2)	0.442 ‡‡
K^+, median (IQR)	4.5 (4.1–5)	4.5 (4.2–5)	4.4 (3.9–4.9)	0.160 ‡‡
Na^+, median (IQR)	138 (134–140)	137.1 (133.1–140)	138.2 (136–140)	0.089 ‡‡
SGOT, median (IQR)	21 (16–31.4)	21.4 (16.4–32)	21 (15.2–29)	0.223 ‡‡
SGPT, median (IQR)	16 (11–24)	16 (10–23.5)	16 (12–25)	0.662 ‡‡
ACEI-Is/ARBs (at admission) *	58 (33.9)	43 (37.1)	15 (27.3)	0.206 +
B-Blocker (at admission) *	127 (74.3)	89 (76.7)	38 (69.1)	0.286 +
MRAs (at admission) *	57 (33.3)	42 (36.2)	15 (27.3)	0.247 +
Furosemide (at admission) *	104 (60.8)	76 (65.5)	28 (50.9)	0.068 +
Sacubitril/Valsartan (at admission) *	21 (12.3)	15 (12.9)	6 (10.9)	0.707 +
SGLT2i (at admission) *	23 (13.5)	0 (0)	23 (41.8)	<0.001 +
Inotropes/Vasopressors (during hospitalization)	20 (11.7)	13 (11.2)	7 (12.7)	0.776 +
ACE-Is/ARBs (at discharge)	58 (33.9)	47 (40.5)	11 (20)	0.008 +
B-Blocker (at discharge)	151 (88.3)	100 (86.2)	51 (92.7)	0.215 +
MRAs (at discharge)	113 (66.1)	72 (62.1)	41 (74.5)	0.107 +
Furosemide (at discharge)	146 (85.4)	99 (85.3)	47 (85.5)	0.985 +
Sacubitril/Valsartan (at discharge)	43 (25.1)	18 (15.5)	25 (45.5)	<0.001 +
ICD/CRT	33 (19.2)	22 (18.9)	11 (20)	0.865 +
All-cause death or HF rehospitalization	97 (56.7)	73 (62.9)	24 (43.6)	0.017 +

+ Pearson's chi-square test; ++ Fisher's exact test; ‡ Student's *t*-test; ‡‡ Mann–Whitney test. * Patient's previous medical treatment when arrived at the hospital. Abbreviations: ACE-Is, Angiotensin Converting Enzyme Inhibitors; ARBs, Angiotensin Receptor Blockers; COPD, Chronic Obstructive Pulmonary Disease; CRT, Cardiac Resynchronization Therapy; DBP, Diastolic Blood Pressure; eGFR, estimated Glomerular Filtration Rate; HFmrEF, Heart Failure with mildly reduced Ejection Fraction; HFpEF, Heart Failure with Preserved Ejection Fraction; HFrEF, Heart Failure with Reduced Ejection Fraction; Ht, hematocrit; Hgb, hemoglobin; ICD, Implantable Cardioverter Defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; MRAs, Mineralocorticoid Receptor Antagonists; NT-proBNP, N-terminal pro B-type natriuretic peptide; RDW, Red Blood Cell Distribution Width; SBP, Systolic Blood Pressure; SGLT2is, sodium glucose co-transporter 2 inhibitors; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

3.2. Study Outcomes

More than half of the sample (56.7%) experienced HF rehospitalization or died. The aforementioned outcome in patients who received SGLT2is at discharge was significantly less frequent compared to those who did not receive SGLT2is at discharge (43.6% vs. 62.9%; $p = 0.017$; Figure 2).

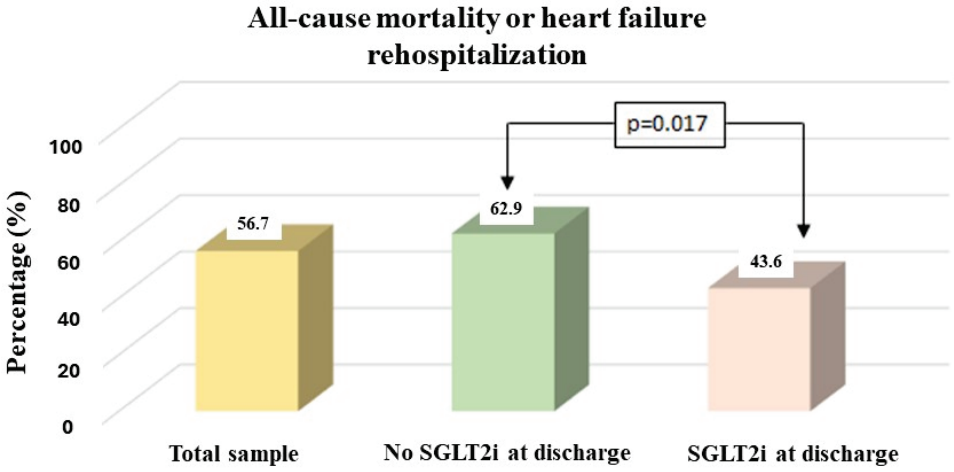

Figure 2. Percentages of all-cause mortality and heart failure rehospitalization, in total sample and by group.

Patients who were on SGLT2is at discharge had a 43% lower probability of all-cause mortality or HF rehospitalization in comparison to those who were not on SGLT2is at discharge (Table 2, Figure 3).

After adjusting for age, gender, smoking, Hgb, administration of SGLT2is at admission, ACEI-Is/ARBs at discharge and Sacubitril/Valsartan at discharge, the aforementioned result remained significant, HR = 0.38; 95% CI: 0.19–0.73; $p = 0.004$.

Table 2. Cox regression results for patients' all-cause mortality and HF rehospitalization as dependent variable and administration of SGLT2is at discharge as independent variable.

	HR (95% CI) [1]	*p*	HR (95% CI) [2]	*p*	*p* Interaction Term [3]
Total sample	0.57 (0.36–0.91)	0.018	0.38 (0.19–0.73)	0.004	-
Diabetes: Yes	0.69 (0.33–1.47)	0.341	0.54 (0.20–1.48)	0.229	0.612
Diabetes: No	0.51 (0.28–0.91)	0.023	0.26 (0.10–0.67)	0.005	
LVEF < 50	0.56 (0.31–0.99)	0.049	0.37 (0.15–0.93)	0.035	0.768
LVEF ≥ 50	0.47 (0.16–1.42)	0.182	0.20 (0.05–0.75)	0.017	
NYHA: III	0.41 (0.17–1.02)	0.054	0.22 (0.07–0.76)	0.017	0.317
NYHA: IV	0.73 (0.40–1.31)	0.285	0.49 (0.21–1.14)	0.098	
Gender: Females	0.44 (0.20–0.99)	0.046	0.42 (0.17–1.05)	0.065	0.485
Gender: Males	0.64 (0.36–1.15)	0.139	0.34 (0.13–0.91)	0.031	
ACEI-Is/ARBs (discharge): No	0.53 (0.31–0.89)	0.017	0.35 (0.16–0.76)	0.008	0.949
ACEI-Is/ARBs (discharge): Yes	0.53 (0.18–1.52)	0.235	0.39 (0.10–1.58)	0.188	
MRAs (discharge): No	0.89 (0.40–2.00)	0.777	0.54 (0.15–1.93)	0.344	0.179
MRAs (discharge): Yes	0.47 (0.26–0.82)	0.008	0.30 (0.13–0.69)	0.005	

[1] Unadjusted hazard ratio (95% confidence interval) for use of SGLT2is at discharge. [2] Hazard ratio (95% confidence interval) for receiving SGLT2is at discharge adjusted for age, gender (except for when analysis was conducted separately in males and females), smoking, Hgb, receiving SGLT2is at admission, ACEI-Is/ARBs at discharge (except for when analysis was conducted separately in these groups) and Sacubitril/Valsartan at discharge. [3] Interaction term for testing if the effect of receiving SGLT2is at discharge was different within each subgroups' levels. Abbreviations: As in Table 1.

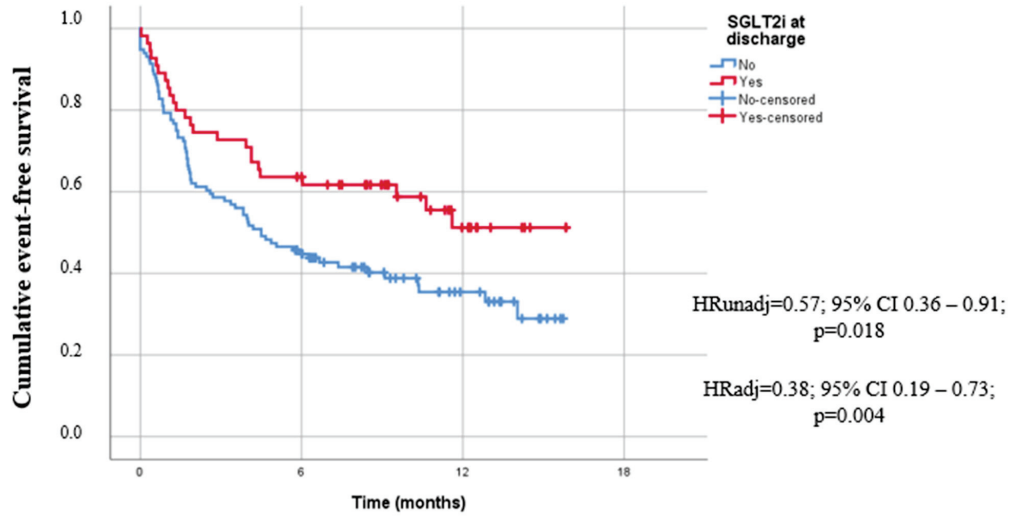

Figure 3. Kaplan–Meier curves for all-cause mortality or HF rehospitalization for patients receiving SGLT2is vs. no SGLT2is at discharge.

Overall, mean follow-up period was 6.1 months (SD = 4.8 months). Mean overall event-free time was 8.20 months (SE = 0.52). For patients who received SGLT2is at discharge, mean event-free time was 10.03 months (SE = 0.90), and for those who did not receive SGLT2is at discharge, mean event-free time was significantly lower and equal to 7.29 months (SE = 0.61), *p* log-rank test = 0.018.

3.3. Subgroup Analysis

When subgroup analysis was conducted, it was found that receiving SGLT2is at discharge was significantly associated with a significantly lower probability of all-cause mortality or HF rehospitalization in males, in patients without diabetes, those with NYHA III, those who did not receive ACEI-Is/ARBs at discharge and in those who received MRAs at discharge (Figure 4, Table 2). In addition, receiving SGLT2is at discharge was significantly associated with a significantly lower probability of all-cause mortality or HF rehospitalization regardless of patients' LVEF. However, none of the interaction terms were found to be significant ($p > 0.05$), indicating that the effect of SGLT2i administration at discharge was similar within each subgroup.

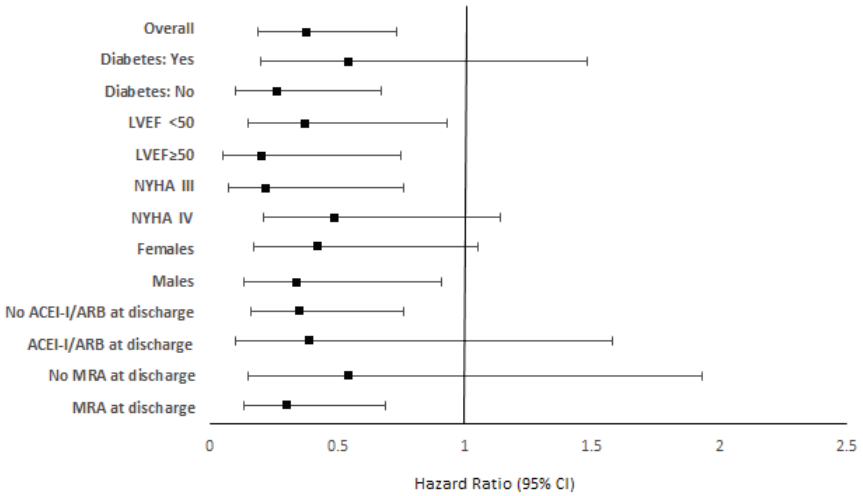

Figure 4. Adjusted hazard ratios (95% confidence intervals) for subgroup analyses. Abbreviations: LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; ACE-Is, Angiotensin-Converting Enzyme Inhibitors; ARBs, Angiotensin Receptor Blockers; MRAs, Mineralocorticoid Receptor Antagonists.

3.4. Propensity Matching Analysis

The 55 patients who received SGLT2is at discharge were propensity score matched, using a ratio 1:1, with the 116 patients who did not receive SGLT2is at discharge. The propensity score matching was done using all baseline characteristics that differed between the two groups, i.e., age, gender, smoking, Hgb, use of SGLT2is at admission, ACEI-Is/ARBs at discharge and Sacubitril/Valsartan at discharge. Afterwards, 32 matching pairs of patients remained in the sample, whose characteristics are presented in Supplementary Table S1. In this sample, receiving SGLT2is at discharge continued to be significantly associated with a lower probability of all-cause mortality or HF rehospitalization, HR= 0.43; 95% CI: 0.20–0.89; $p = 0.024$ (Figure S1).

4. Discussion

In the present study, utilizing real world data from 171 consecutive HHF patients, we demonstrated that in-hospital initiation of SGLT2is was associated with a reduction in the composite endpoint of all-cause mortality or HF rehospitalization.

HF is a major health system problem which has been increasing in recent years, mainly due to the aging of the world population [14]. The natural course of HF syndrome is progressive, with periods of relative stabilization interspersed with periods of decompensation [1,4]. Acute HF refers to the rapid or gradual onset of HF signs and/or symptoms that prompt the patient to seek emergency medical attention [2]. This leads to either a visit to the ED or an unscheduled admission to the hospital [2]. Acute HF includes a wide range of clinical conditions with diverse etiologies and triggers [1,4]. It may involve either the first onset of HF or, more commonly, acute dysregulation of chronic stable HF [4,15]. Acute HF is a complex pathophysiological syndrome that includes several hemodynamic abnormalities associated with increased ventricular filling pressure and/or decreased cardiac output. Clinically, it manifests mainly with cardiac congestion, while hypoperfusion can also occur [4,15]. Patients presenting with acute HF have high rates of mortality and rehospitalization for HF decompensation [16]. In the present study, more than half of patients experienced HF rehospitalization or died during the follow-up.

Compared with chronic HF, there are fewer robust data to guide diagnosis, risk stratification and treatment in these patients [4]. Although new and innovative treatments have been developed for chronic HF in recent years, resulting in significant clinical benefits, in acute HF, treatment options are still limited [2].

Congestion is an important cause for cardiac decompensation, and therefore it is arguably considered a key therapeutic target in acute HF [4]. In fact, achieving complete decongestion at hospital discharge and maintaining it during the early period after discharge has been associated with better outcomes [17,18]. The main therapeutic option for the decongestion of these patients continues to be the use of diuretics and especially intravenous loop diuretics [17]. However, the management of these patients during hospitalization is still based on clinical expertise and experience [12,19].

One class of drugs that has shown great benefit in patients with chronic HF is SGLT2is [20]. SGLT2is act on the proximal convoluted tubule of the kidney and inhibit SGLT2 co-transporters, which causes a decrease in glucose reabsorption along the tubule, resulting in glycosuria [6,21]. Along with glycosuria, SGLT2 inhibition also causes natriuresis associated with negative salt and water balance [21]. Increased natriuresis and sodium delivery to the distal nephron is important for renal protection, as it normalizes the tubuloglomerular feedback mechanism [6]. Although initially used for their anti-diabetic properties, SGLT2is have resulted in great benefits in patients with chronic HF [2]. Large randomized trials on the use of SGLT2is in patients with chronic HF have showed a reduction in cardiovascular mortality and readmissions for HF decompensation [7–10,22]. These benefits were seen in both patients with reduced and preserved LVEF. The use of SGLT2is in patients with chronic HF is now an integral part and mainstay of treatment for all patients with chronic HF [2].

Although the role of SGLT2is in patients with chronic HF is well established through large randomized trials and meta-analyses, their role in patients with acute HF has not been fully established. There are some data showing a possible benefit of rapid initiation of SGLT2is in patients with HHF [11,12]. The first study that examined the effect of SGLT2is in patients with acute HF was SOLOIST-WHF [23]. This multi-center, double-blind, randomized study involved 1222 patients with type 2 DM who had recently been hospitalized for worsening HF and were randomized to receive sotagliflozin or a placebo. The aim was to examine the rate of cardiovascular death and rehospitalization for HF [23]. The group initiated on sotagliflozin before or soon after discharge had fewer cardiovascular deaths or rehospitalizations or emergency visits for HF over a 9-month follow-up period compared with the placebo group (245 vs. 355 events, HR 0.67, 95% CI 0.52–0.85). EMPA-RESPONSE-AHF was a randomized, placebo-controlled, double-blind pilot study in which 80 patients with acute HF with or without DM were randomized to receive empagliflozin 10 mg/day or a placebo for 30 days [24]. No significant differences were observed in the primary endpoints (change in visual analogue scale dyspnea score, diuretic response, change in NT-proBNP and length of stay). However, the empagliflozin group showed an increased in urinary output [difference 3449 (95% confidence interval 578–6321) mL; p <0.01] and a reduced combined endpoint of worsening HF, rehospitalization for HF or death at 60 days compared to the placebo group [4 (10%) vs. 13 (33%); p = 0.014] [24].

The most recent study that examined the effect of empagliflozin on decongestion in patients with acute HF was the EMPULSE trial [11]. In this randomized double-blind study, 530 patients who were hospitalized with acute HF with elevated NT-proBNP ($\geq$1600 pg/mL) requiring at least 40 mg of iv furosemide per day and an eGFR $\geq$ 20 mL/min/m^2 were randomized 1:1 to either empagliflozin 10 mg once daily or a placebo for 90 days [11]. The empagliflozin group resulted in an early, effective and sustained decongestion which was associated with clinical benefit at day 90. More specifically, using a win-ratio approach, empagliflozin significantly reduced the combined primary endpoint of death, the number of HF events, time to first HF event and change from baseline in KCCQ total symptom score at 90 days (clinical benefit of 53.9% vs. 39.7%, win ratio 1.36, 95% CI 1.09–1.68) [11]. In the present retrospective analysis, initiation of SGLT2is in HHF patients was associated with clinical benefits in these patients as it reduced deaths from any cause and HF readmissions.

Although SGLT2is in patients with chronic HF are part of first-line therapy, the mechanisms through which they exert their beneficial effects are still not fully clarified and even less is known about their actions in patients with HHF. For chronic HF, it has been hypothesized that the benefits of SGLT2is are mediated through pleiotropic actions involving metabolic, renal, cardiac and hemodynamic effects on the body. Regarding acute HF, the mechanism of action is more complicated [25,26]. The initiation of SGLT2is in patients with acute HF during their hospitalization or immediately after is suspected to lead to a rapid and sustained volume unloading and improvement of left ventricular filling pressure and diastolic function, which may contribute to the significant reduction in the risk of rehospitalization [27].

It is well documented that in patients with acute HF and volume overload, the first-line treatment is loop diuretics, aiming to produce natriuresis and a negative fluid balance [28]. Studies have shown that a higher urinary sodium concentration in patients with acute HF has been associated with better in-hospital and post-discharge outcomes [29,30]. However, the resulting volume depletion from loop diuretics can lead to activation of the renin–angiotensin–aldosterone system and the sympathetic nervous system, especially in tubular sites that cannot be acted upon by these diuretics, which can lead to the emergence of diuretic resistance [31,32]. This obstacle could be overcome by using a combination of diuretics that act at different sites, and SGLT2is could be a good choice since they act at a different site than loop diuretics to increase natriuresis [12]. Recent studies have shown that SGLT2i treatments in patients with acute HF increased urinary sodium excretion and increased diuresis, possibly due to the osmotic diuresis they cause [33,34]. Interestingly, SGLT2is are quite effective in removing fluid from the interstitial space rather than from the

intravascular space, acting mainly as an anti-edematous agent without causing electrolyte disturbances [35]. Acute decompensated HF frequently causes kidney impairment and treatment may lead to acute kidney injury [36]. However, the use of SGLT2is in patients with acute HF appears to reduce the required doses of loop diuretics to decongest these patients, which may mitigate the risk of renal damage [37]. In a study by Thiele et al., it was shown that the use of empagliflozin in patients with acute decompensated HF did not affect hemodynamic parameters and instead significantly reduced markers of tubular injury, suggesting that SGLT2 inhibitor treatment may prevent acute kidney injury [38]. Although some studies have shown an initial decrease in eGFR in patients with acute HF receiving SGLT2is, this decrease appears to be transient as eGFR increased during follow-up [39]. The renoprotective effects of SGLT2 inhibitors have been attributed to kidney tubular–glomerular feedback with subsequent reduction of glomerular filtration pressure as the driving mechanism [38]. Another parameter possibly playing a role in the benefit of SGLT2is in acute HF is that they can lead to significantly lower NT-proBNP and BNP levels and a significantly higher incidence of hemoconcentration, all of which have been associated with a better prognosis [40,41].

Regarding the optimal timing for initiation of SGLT2is in patients with acute HF, it appears that an early initiation (within the first 5 days) is safe and effective as long as patients do not experience symptomatic hypotension or a need for inotropes or vasodilators within the previous six hours of their start [41]. Interestingly, in the present analysis approximately 1/3 of HHF received SGLT2is at discharge, which is in accordance with the current literature [42,43]. Lastly, since hospitalization is the result of progressive decompensation which occurs outside of the hospital, outpatient management is of utmost importance, including urgent ambulatory visits for the management of diuretics and optimal medical therapy (i.e., neurohormonal inhibitors and SGLT2is), to halt or reduce the worsening of the disease [44].

Limitations

The major limitation associated with the present study is its observational nature; therefore, an inherent risk of confounding and bias cannot be excluded. However, different statistical methods (multiple adjustments and propensity matching) have been conducted to eliminate this risk. Furthermore, the studied sample was not large (171 consecutive patients) and the follow-up period was relatively short; however, each patient was presented once in this analysis. The number of patients with available NT-proBNP values at discharge was very small (n = 18, 10.5%), precluding any statistical analysis comparing cardiac biomarkers at admission versus at discharge in both subgroups. Lastly, the decision to initiate SGLT2is was up to the attending physician's discretion, which may have led to a selection bias. Nevertheless, the aim of this study was to present "real world" data from a single center in Greece.

5. Conclusions

In the present "real world" analysis, the in-hospital initiation of SGLT2is in HHF patients was associated with improved prognosis. Further efforts are needed to overcome implementation barriers and improve use of SGLT2is among HHF patients.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm13123562/s1, Figure S1: Kaplan–Meier curves for patients receiving vs. not receiving SGLT2is at discharge in the propensity score matched sample; Table S1: Sample characteristics after propensity matching, by administration of SGLT2is at discharge.

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preparation, A.X.; writing—review and editing, all authors; supervision, A.X. and J.S. All authors have read and agreed to the published version of the manuscript.

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Review

The Role of Anesthetic Management in Lung Cancer Recurrence and Metastasis: A Comprehensive Review

Jaewon Huh and Wonjung Hwang *

Department of Anesthesiology and Pain Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea; ether@catholic.ac.kr
* Correspondence: amoeba79@catholic.ac.kr; Tel.: +82-2-2258-6162; Fax: +82-2-537-1951

Abstract: Lung cancer remains a leading cause of cancer-related mortality worldwide. Although surgical treatment is a primary approach, residual cancer cells and surgery-induced pathophysiological changes may promote cancer recurrence and metastasis. Anesthetic agents and techniques have recently been shown to potentially impact these processes by modulating surgical stress responses, immune function, inflammatory pathways, and the tumor microenvironment. Anesthetics can influence immune-modulating cytokines, induce pro-inflammatory factors such as HIF-1α, and alter natural-killer cell activity, affecting cancer cell survival and spread. Preclinical studies suggest volatile anesthetics may promote tumor progression by triggering pro-inflammatory signaling, while propofol shows potential antitumor properties through immune-preserving effects and reductions in IL-6 and other inflammatory markers. Additionally, opioids are known to suppress immune responses and stimulate pathways that may support cancer cell proliferation, whereas regional anesthesia may reduce these risks by decreasing the need for systemic opioids and volatile agents. Despite these findings, clinical data remain inconclusive, with studies showing mixed outcomes across patient populations. Current clinical trials, including comparisons of volatile agents with propofol-based total intravenous anesthesia, aim to provide clarity but highlight the need for further investigation. Large-scale, well-designed studies are essential to validate the true impact of anesthetic choice on cancer recurrence and to optimize perioperative strategies that support long-term oncologic outcomes for lung cancer patients.

Keywords: anesthesia; cancer recurrence; lung cancer; metastasis; perioperative care

1. Introduction

Lung cancer remains one of the most prevalent cancers with a high mortality rate [1]. According to 2020 data, it is the most frequently diagnosed cancer worldwide, accounting for 11.4% of all cancer cases and causing approximately 1.8 million deaths annually. Non-small cell lung cancer (NSCLC), which comprises about 85% of all lung cancer cases, is primarily treated with surgical resection. However, despite the successful removal of the primary tumor, microscopic residual cancer cells often persist, leading to recurrence and metastasis. Postoperative recurrence and metastasis rates in NSCLC patients range from 30% to 55%, with a median survival time of approximately 21 months.

Ideally, the immune system would eliminate residual cancer cells after surgery [2]. However, surgical interventions often exacerbate pathophysiological changes that hinder this process. The surgical stress response plays a crucial role in disrupting inflammatory balance, resulting in immunosuppression [3,4]. Additionally, the preoperative period, characterized by patient anxiety and stress, can elevate cortisol and catecholamine levels, leading to reduced natural-killer (NK) cell activity and weakened immune readiness. The postoperative period also poses challenges, such as pain, surgical site inflammation, and potential infections, which further compromise immune recovery and promote an environment conducive to tumor growth. These stressors collectively contribute to inflammatory and immune system alterations that affect cancer outcomes.

The anesthesiologist's role extends beyond the intraoperative period to include managing these preoperative and postoperative stress responses. Techniques such as preemptive analgesia, multimodal pain management, and the targeted use of sedatives can mitigate these stress-induced effects. Through these strategies, anesthesiologists play a vital role in maintaining immune function and reducing the risk of cancer recurrence. Thus, understanding these mechanisms is essential for developing strategies to mitigate surgery-induced effects that contribute to cancer progression.

Emerging evidence suggests that anesthetic agents and techniques may also influence cancer progression. This review aims to provide an in-depth analysis of the mechanisms underlying cancer recurrence and metastasis following surgery. Additionally, we will explore perioperative strategies and their role in mitigating cancer recurrence risk, particularly focusing on lung cancer patients.

2. Materials and Methods

A comprehensive literature search was conducted using electronic databases, including PubMed, EMBASE, Web of Science, Google Scholar, and the Cochrane Library. The search utilized the following keywords: "cancer recurrence", "metastasis", "anesthesia", "analgesia", "anesthetic agent", and "lung cancer". Studies published in English up to December 2023 were included, and there were no restrictions on study type, ensuring a broad and inclusive scope for eligible studies.

We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines in identifying, screening, and selecting studies (Figure 1). All retrieved articles were manually examined, and additional studies were identified by screening the reference lists of relevant reviews and articles. The selection criteria included both preclinical and clinical studies examining the role of anesthetic agents and techniques in cancer recurrence and metastasis, with a specific focus on lung cancer surgery. Studies investigating the effects of general and regional anesthesia, volatile anesthetics, opioids, and non-opioid agents were prioritized.

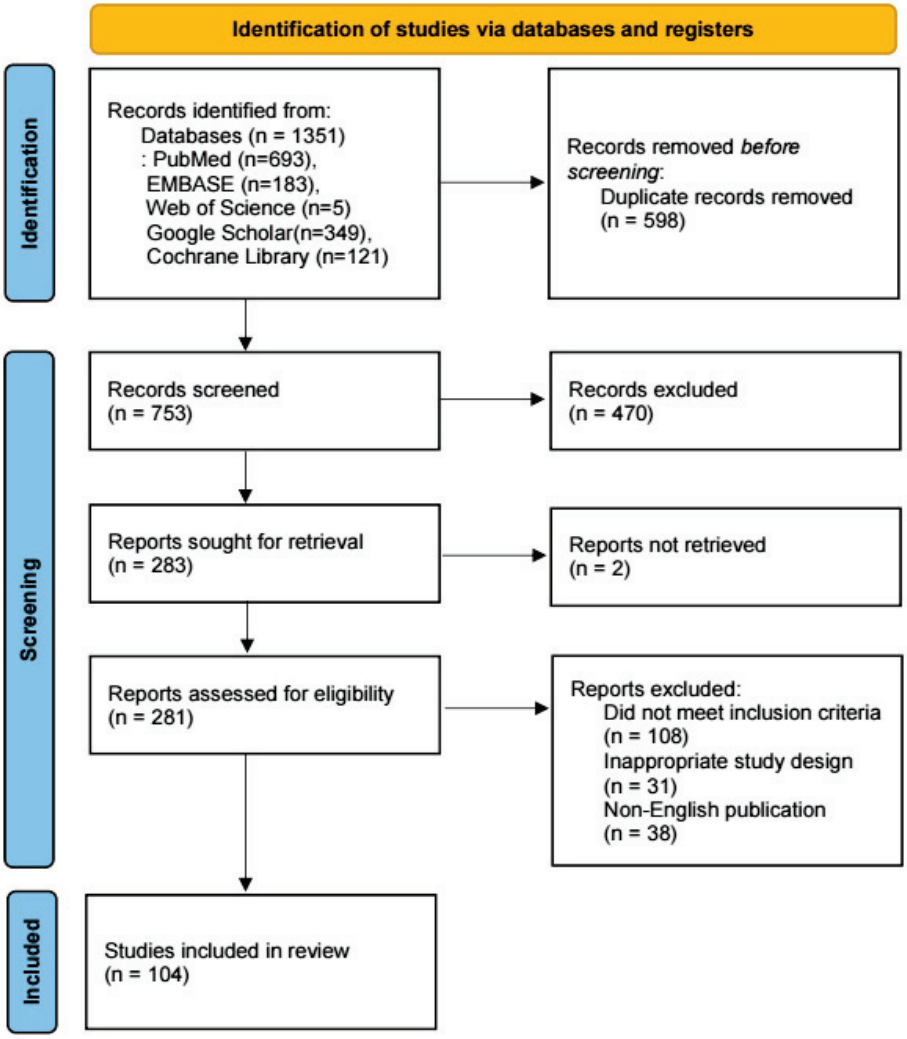

Figure 1. PRISMA flow diagram.

3. Mechanisms of Cancer Recurrence After Surgery

3.1. Remnants of Cancer Cells and Circulating Tumor Cells

Despite curative surgical resection being the primary treatment for solid tumors, microscopic residual cancer cells often persist, leading to local recurrence, lymphatic or vascular invasion, and transcoelomic dissemination, such as intrapleural or intraperitoneal spread [5]. Circulating tumor cells (CTCs) play a critical role in distant metastasis, as they can escape the primary tumor site and travel through the bloodstream [6]. CTCs are frequently detected in patients with solid tumors, and several studies have shown elevated CTC levels following surgery for cancers such as lung, hepatocellular, gastric, colorectal, and breast [7–11]. Elevated CTC counts are generally associated with a poor prognosis; however, not all CTCs lead to metastasis. For metastasis to occur, CTCs must evade immune surveillance, survive in the circulatory system, and successfully colonize distant organs. This process is facilitated by postoperative stress responses, inflammation, and immunosuppression, which collectively create an environment favorable for tumor cell survival and progression. The ability of CTCs to evade immune destruction and establish secondary tumors is significantly influenced by perioperative disruptions in immune and inflammatory pathways.

3.2. Tumor Microenvironment and Metastasis

Cancer cells reside within a tumor microenvironment (TME), composed of various elements, including inflammatory and immune cells, stromal cells, blood vessels, and

extracellular matrix components [12,13]. Surgical manipulation and perioperative stress response can significantly disrupt the TME, triggering a cascade of events that facilitate cancer cell migration to distant sites [12,14]. First, cancer cells acquire invasive and migratory properties through epithelial–mesenchymal transition (EMT), during which they transform into fibroblast-like cells. Second, the transformed cancer cells infiltrate adjacent tissues, eventually entering the circulation by penetrating lymphatic or blood vessels. During this phase, CTCs may be recognized and targeted by immune surveillance mechanisms, such as NK cells or cytotoxic T (Tc) cells. Third, surviving CTCs travel to distant sites and function as progenitor cells. Finally, these progenitor cells interact with local tissue, inflammatory cells, and other components to proliferate within the newly formed TME.

The complex and dynamic interactions between cancer cells and surrounding non-malignant cells within the TME are pivotal in cancer progression and metastasis. Inflammatory cells, for instance, contribute to cancer invasion and proliferation by releasing cytokines, chemokines, growth factors, and enzymes [15,16]. Cytokines and chemokines produced by inflammatory cells attract and activate immune cells while also promoting cancer cell migration and invasion. Growth factors, such as epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF), stimulate cancer cell proliferation, survival, and angiogenesis. Additionally, enzymes such as matrix metalloproteinases (MMPs) degrade the extracellular matrix at the invasive front, facilitating cancer cell invasion into surrounding tissues.

3.3. Surgery-Induced Pathophysiologic Changes and Cancer Recurrence

Surgical stress is induced not only by tissue trauma but also by several factors such as hypothermia, tissue hypoxia, transfusion, and patient anxiety. These stressors initiate a cascade of sympathetic, inflammatory, and immune system changes, each of which can influence the metastatic process [4,17] (Figure 2).

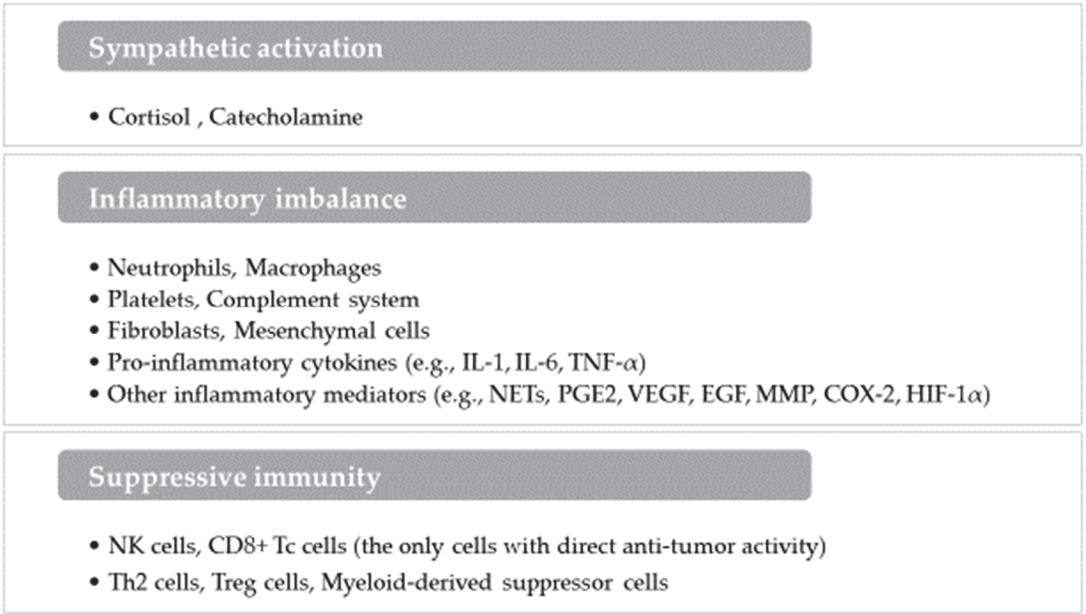

Figure 2. Overview of tumor-promoting mechanisms during surgical treatment. The diagram illustrates the key mechanisms and related factors influencing cancer progression during the perioperative period. Notably, NK cells and CD8+ Tc cells are indicated as the only immune elements providing direct anti-tumor activity, contrasting with other factors that promote tumor growth. IL: interleukin, TNF-α: tumor necrosis factor—alpha, NETs: neutrophil extracellular traps, PGE2: prostaglandin E2, VEGF: vascular endothelial growth factor, EGF: epidermal growth factor, MMP: matrix metalloproteinase, COX-2: cyclooxygenase-2, HIF-1α: hypoxia-inducible factor-1 alpha, NK cells: natural killer cells, CD8+ Tc cells: CD8+ cytotoxic T cells, Th2 cells: helper T2 cells, Treg cells: regulatory T cells.

3.3.1. Sympathetic Activation

Surgical stress primarily activates the sympathetic nervous system, resulting in an increased secretion of cortisol and catecholamines. These neuroendocrine mediators elevate inflammatory cytokines (e.g., IL-6, IL-8) and immunosuppressive cytokines (e.g., IL-4, IL-10, VEGF), suppressing NK cell and Tc cell activity while promoting regulatory T (Treg) cell expansion, ultimately contributing to tumor progression [5].

Catecholamine can directly bind to β-receptors on tumor cells, inducing morphological changes that promote EMT [18]. Additionally, it can indirectly contribute to the remodeling of the TME by stimulating the secretion of IL-6 (an inflammatory cytokine), VEGF (a proangiogenic factor), and MMP-2/9 (enzymes involved in extracellular matrix degradation). The activation of β-receptors on the surface of cancer cells has been shown to accelerate metastasis and tumor growth in breast, colon, liver, prostate, and lung cancers [19,20].

3.3.2. Inflammatory Imbalance

Surgical tissue damage and sympathetic stimulation trigger an inflammatory response as part of the normal wound-healing process [21]. The acute inflammatory response is primarily mediated by macrophages and neutrophils, which secrete pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α. This response initially promotes a helper T (Th)1-dominant profile, essential for cell-mediated immunity through the secretion of interferon gamma (IFN-γ) and IL-2. However, persistent inflammatory cell stimulation results in excessive cytokine production, altering the Th1/Th2 ratio and leading to an inflammatory imbalance [22,23]. This suppresses the activity of NK cells and CD8+ Tc cells while enhancing the functions of Th2 cells and Treg cells, thereby weakening anti-tumor immunity and facilitating tumor progression. Additionally, fibroblasts and mesenchymal cells secrete several factors, including growth factors (e.g., VEGF, EGF), enzymes (e.g., MMP, COX-2), transcription factors (e.g., HIF-1α, NF-kB, STAT-3), and chemokines (e.g., CXCR-2). These molecules are pivotal in tumor growth, angiogenesis, and consequent dissemination.

IL-6 stimulates macrophages to secrete prostaglandin E2 (PGE2), further amplifying the inflammatory response and inhibiting cell-mediated immunity. PGE2 also enhances tumor cell migration and angiogenesis, facilitating metastasis [24,25]. In lung cancer models, PGE2 has been shown to upregulate MMP-9 mRNA expression while downregulating E-cadherin mRNA expression [26]. These changes enhance extracellular matrix degradation and reduce cell adhesion, promoting cancer cell invasion and metastasis.

Neutrophils also contribute to cancer progression and dissemination by releasing neutrophil extracellular traps (NETs) [27]. While NETs play an essential role in clearing microorganisms, they promote tumor cell proliferation, migration, and invasion in the context of cancer. In addition, NETs interact with CTCs, facilitating their implantation in distant tissues and promoting metastasis. [28]. These processes are mediated by releasing high mobility group box 1 (HMGB1) and activating Toll-like receptor (TLR) 9-dependent pathways.

Platelets play a dual role in their interaction with CTCs. First, they can form platelet-CTC aggregates, shielding CTCs from immune surveillance [29]. Second, activated platelets release factors such as TGF-β, platelet-derived growth factor (PDGF), and ATP, which further modulate the TME to favor cancer growth [30]. TGF-β suppresses NK cell activity and other immune responses, creating an immunosuppressive environment, while PDGF promotes tumor growth and angiogenesis. Furthermore, ATP enhances vascular permeability, facilitating the infiltration of immune cells and other factors into the TME. Perioperative increases in platelet levels have been linked to poor cancer prognosis [31].

Recent studies have highlighted the role of fibrinogen and the complement system in enhancing the metastatic process. Surgery-induced pro-inflammatory cytokines elevate fibrinogen levels, forming fibrin complexes around tumor cells that protect them from NK cell surveillance and promote tumor adhesion to endothelial cells [32,33]. The complement system is also activated during surgery, contributing to cancer recurrence by promoting cancer cell stemness, enhancing angiogenesis, and inhibiting anti-tumor immunity [34–37]. In lung cancer, complement activation through the C3a receptor has been

shown to promote tumor progression by influencing T cell differentiation and fostering an immunosuppressive microenvironment [38].

Tissue hypoxia, a common consequence of surgery, induces the expression of hypoxia-inducible factor (HIF)-1α, which promotes angiogenesis by upregulating VEGF [39,40]. This pathway not only aids tissue repair but also provides cancer cells with a route for distant metastasis. The overexpression of HIF-1α and VEGF has been associated with poor prognosis in various cancer types [41,42].

3.3.3. Suppressive Immunity

Perioperative stress and inflammatory imbalances can impair the body's anti-tumor immune response, reducing its ability to eliminate residual cancer cells after tumor resection [43]. The peak suppression of immune function typically occurs around the third day after surgery, with full recovery taking up to two weeks [44]. During this period, cancer cells may evade immune detection and establish a tumor-promoting microenvironment conducive to metastasis [45]. Tumor cells can express surface ligands that inhibit NK cell cytotoxicity, allowing them to evade immunosurveillance. Additionally, tumor cells release inflammatory mediators that create a pro-tumor environment, promoting their survival and metastasis.

NK cells and T cells are crucial in post-surgical immunosurveillance [46]. NK cells are capable of destroying cancer cells without prior sensitization, while Tc cells and Th cells coordinate the immune response against tumor cells. However, surgery significantly reduces the levels of circulating NK and T cells, mainly through the activation of the programmed death-1 (PD-1) and programmed death–ligand 1 (PD-L1) pathway [47]. Cytokine imbalances further exacerbate immune suppression, increasing anti-inflammatory cytokines like IL-10 while reducing pro-inflammatory cytokines such as IFN-γ, thereby shifting the immune response in favor of tumor survival [48].

Treg cells, which are known for their immunosuppressive role, also increase after surgery, promoting a tolerant environment that allows cancer cells to thrive [49]. Elevated Treg levels have been associated with poor prognosis lung cancer and other malignancies [50–52]. Furthermore, myeloid-derived suppressor cells (MDSCs), another immunosuppressive cell type, increase after surgery. The recruitment of MDSCs is facilitated by a reduction in chemokine ligand 4 (CXCL4), which is known to inhibit MDSC activity [53]. Elevated MDSC levels have been linked to cancer recurrence and a poor prognosis [54–56], as these cells promote tumor progression through angiogenesis and immune suppression [57]. In lung cancer patients, the increased presence of MDSCs after surgery supports angiogenesis and facilitates tumor growth [58].

4. Effect of Thoracic Anesthesia on Lung Cancer Recurrence

Given the potential impact of perioperative changes on tumor growth and survival, optimizing anesthetic management to mitigate these effects is essential for improving patient outcomes. In this section, we review commonly used anesthetic agents and techniques in lung cancer resection, focusing on their influence on stress responses, inflammation, and immune function, as well as their potential effects on cancer recurrence and metastasis. To provide a comprehensive overview of current evidence regarding anesthetic agents and techniques used in lung cancer surgeries, we have summarized the major findings from clinical studies in Table 1.

4.1. General vs. Regional Anesthesia

Anesthetic techniques may influence cancer outcomes by modulating the immune system and the body's stress response during surgery, both of which are associated with tumor progression. Regional anesthesia (RA), such as neuraxial and peripheral nerve blocks, has been shown to reduce surgical stress by attenuating the neuroendocrine response, thus preserving immune function [59–61]. Preclinical studies suggest that RA may reduce circulating levels of cortisol and catecholamines, potentially limiting tumor cell invasion

and metastasis by reducing EMT and maintaining NK cell activity [62,63]. In clinical practice, RA is hypothesized to decrease recurrence risk by modulating the balance between Th1 and Th2 immune responses, thereby enhancing the body's ability to eliminate residual cancer cells [64]. Additionally, RA may have direct inhibitory effects on cancer cells [65,66] while reducing the need for volatile anesthetics and opioids, both of which are associated with immunosuppression [67,68].

Despite the theoretical advantages, clinical trials have not consistently shown a significant reduction in cancer recurrence or improved survival with RA compared to general anesthesia (GA) alone. A randomized controlled trial (RCT) involving 400 patients undergoing video-assisted thoracoscopic surgery (VATS) for lung cancer compared the use of combined epidural–GA with GA alone [69]. After a median follow-up of 32 months, no significant differences were found between the two groups in terms of recurrence-free survival (RFS), cancer-specific survival, or overall survival (OS) between the two groups. Hazard ratios were 0.90 for RFS (95% CI: 0.60–1.35, $p = 0.068$), 1.08 for cancer-specific survival (95% CI: 0.61–1.91, $p = 0.802$), and 1.12 for OS (95% CI: 0.64–1.96, $p = 0.697$). Similar findings have been reported in other trials assessing RA's impact on oncologic outcomes [70,71].

One explanation for these mixed results may lie in the complexity of the TME and the variable biological behavior of different cancers. While RA reduces stress hormone levels and preserves immune function, these effects may not be sufficient to counteract the multifactorial nature of tumor recurrence and metastasis. Additionally, the concentration of local anesthetics at micro-metastatic niches may not be high enough to exert a robust anti-tumor effect [72,73].

In summary, although RA offers potential physiological benefits, including reduced stress response and opioid-sparing effects, current clinical evidence does not consistently demonstrate a significant impact on long-term cancer outcomes when compared to GA alone.

4.2. Volatile vs. Total Intravenous Anesthetics (Propofol)

Volatile anesthetics, such as isoflurane and sevoflurane, have been extensively studied for their potential impact on cancer progression. Inhalation anesthetics may promote metastasis by activating the hypothalamic–pituitary–adrenal axis and sympathetic nervous system, leading to the release of neuroendocrine mediators such as cortisol and catecholamine [61,74]. These agents suppress immune responses by reducing NK cell activity and increasing the release of immunosuppressive cytokines [75–77]. Additionally, volatile anesthetics induce T lymphocyte apoptosis and increase the expression of HIF-1, which is associated with cancer cell proliferation and metastasis via the Akt/mTOR and VEGF pathways [78–80]. Studies in NSCLC have demonstrated that isoflurane concentrations of 1–3% enhance both cancer cell proliferation and invasion [78], although other studies suggest that sevoflurane may inhibit invasion by downregulating MMPs and HIF-1α [81–83]. This duality highlights the complexity of volatile anesthetics' effects, which may vary based on the specific cancer cell type and experimental conditions.

In contrast, propofol, a commonly used intravenous anesthetic, has demonstrated anti-tumor properties in both preclinical and clinical studies. Preclinical studies indicate that propofol inhibits tumor cell viability, migration, and invasion by modulating molecular pathways such as STAT3/HOTAIR and by reducing the expression of critical factors like Slug and HIF-1α [79,84–88]. Additionally, propofol promotes apoptosis in lung cancer cells by activating p53 and suppressing ERK signaling, both of which are key regulators of cell survival and metastasis [89]. Propofol also downregulates oncogenes such as neuroepithelial cell-transforming gene 1 and sex-determining region Y box (SOX)4 [86,90,91]. Furthermore, propofol inhibits EMT markers, including N-cadherin and MMPs, reducing the potential for metastasis [92–95]. Its immune-modulating effects, such as enhanced NK cell activity and reduced levels of pro-inflammatory cytokines like IL-6 and TNF-α, may further contribute to its anti-cancer properties [96–98].

Clinical studies have also shown promising results for propofol-based total intravenous anesthesia (TIVA) in cancer surgery [99–102]. Several retrospective analyses have reported better OS in patients undergoing cancer surgery with propofol compared to volatile anesthetics [103–105]. Recent meta-analysis studies found that propofol-based TIVA was associated with improved OS and RFS compared to volatile agents [106,107]. However, not all studies support these findings. Some retrospective studies have reported no significant differences in RFS or OS between TIVA and volatile anesthetics, including in lung cancer cases [108,109]. Other studies have similarly produced mixed results, indicating that propofol may offer some oncological advantages, but the evidence remains inconclusive [110,111].

In summary, while propofol appears to exert anti-tumor effects through immune modulation and the direct inhibition of cancer cell activity, volatile anesthetics may promote tumor progression in certain contexts. However, the available data from both preclinical and clinical studies remain inconclusive, and further research is required to establish a definitive link between anesthetic type and long-term cancer outcomes.

4.3. Opioid Agents

Opioids, widely used for perioperative analgesia in cancer surgeries, have raised concerns about their potential role in cancer progression. Laboratory studies indicate opioids can modulate immune function, often leading to immunosuppression [112,113]. Morphine and fentanyl, for instance, reduce NK cell activity, promote lymphocyte apoptosis, and inhibit T cell proliferation [114–116]. However, different opioids may have varying immunomodulatory effects. While morphine has been shown to promote tumor growth by enhancing angiogenesis and suppressing immune responses [117], oxycodone has been found to have minimal impact on immune function [118]. Conversely, tramadol may possess immune-stimulating properties, potentially reducing the risk of metastasis [119].

Opioids can directly influence tumor growth by activating transcription factors and promoting angiogenesis through the activation of VEGF receptors [120,121]. These agents also affect cell proliferation through Akt and ERK signaling, while higher doses can induce tumor cell death through NF-κB inhibition and p53 stabilization [122,123].

Additionally, opioids have been linked to enhanced angiogenesis and tumor growth, primarily through the activation of mu-opioid receptors (MOR) in cancer cells [114,124,125]. Preclinical models of NSCLC have demonstrated that MOR activation promotes tumor growth pathways such as Akt/mTOR and VEGF signaling [126–129]. At the same time, opioid antagonists like methylnaltrexone have shown potential in reducing tumor growth and metastasis [130,131]. The overexpression of MOR in cancer cells is associated with poorer outcomes, including higher rates of recurrence and metastasis, particularly in cancers such as prostate and NSCLC [126,132]. A continuous infusion of methylnaltrexone has been shown to decrease primary tumor growth and lung metastasis [133], suggesting the potential of MOR antagonism as a therapeutic strategy in limiting opioid-driven tumor progression.

The clinical evidence regarding opioid use in cancer patients remains mixed. Some studies suggest that fentanyl administered during or immediately after surgery is associated with poorer OS and RFS in NSCLC [134,135]. However, other studies report no significant impact of perioperative opioid use on long-term oncologic outcomes in NSCLC [136]. Conflicting data also exist for other cancer types, such as colorectal cancer and esophageal cancer [137,138].

Despite the potential cancer-promoting effects of opioids, poorly managed pain may also contribute to tumor progression by increasing sympathetic and adrenal activity, which elevates catecholamine and glucocorticoid levels and suppresses immune function. A retrospective study has linked poorly controlled pain or higher opioid needs to worse survival outcomes in advanced NSCLC patients [139]. Therefore, balancing effective pain management with minimizing opioid use is crucial in determining their impact on cancer recurrence.

4.4. Non-Opioid Agents

4.4.1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs exhibit anticancer effects primarily by reducing inflammation and inhibiting PGE2 synthesis [140–142]. By inhibiting cyclooxygenase (COX) enzymes, NSAIDs reduce PGE2 levels, suppressing tumor-promoting pathways and enhancing immune responses, particularly Tc cell and NK cell activity [143]. In vitro studies demonstrate that NSAIDs like aspirin and celecoxib reduce cancer cell viability, migration, and proliferation through both COX-dependent and COX-independent mechanisms [144–146]. Animal models further show that NSAIDs downregulate oncogenes like SOX2 and reduce VEGF expression, inhibiting tumor growth and metastasis [147].

Clinical studies regarding NSAIDs' impact on cancer recurrence have yielded mixed results [148–151]. Regular NSAID use, especially aspirin, has been associated with reduced cancer incidence and improved RFS in some retrospective studies, including NSCLC [152,153]. However, other studies found no significant survival benefits with perioperative NSAID use alone [154,155]. A review of 16 studies concluded that the perioperative effects of NSAIDs on reducing cancer recurrence remain inconclusive [156].

4.4.2. Dexmedetomidine

Dexmedetomidine, a selective α2-adrenoceptor agonist, has demonstrated both pro-tumor and anti-tumor effects depending on the context [157,158]. It interacts with α2 adrenoceptors on both immune and tumor cells, potentially influencing immune regulation and tumor progression.

Preclinical studies suggest that dexmedetomidine may promote cancer cell survival through the upregulation of HIF-1α, enhance metastasis via MMPs, and stimulate angiogenesis by increasing VEGF expression [159–161]. In contrast, dexmedetomidine infusion has been shown to increase NK cells, B cells, and CD4+ T cells while improving the CD4+/CD8+ and Th1/Th2 ratios [158]. In animal models, dexmedetomidine has been associated with increased metastasis in cancers such as lung, liver, and colon, particularly through MMP expression and the induction of MDSCs [162–165]. However, other studies show that dexmedetomidine may reduce metastasis by upregulating miR-143-3p and downregulating EGFR expression [166].

A retrospective study of NSCLC patients reported worse OS with intraoperative dexmedetomidine use, although RFS was not significantly affected [167]. These findings still require confirmation through further clinical trials.

4.4.3. Thiopental

Thiopental, a barbiturate that acts on the GABA-A receptor, has demonstrated immunosuppressive effects in preclinical studies. It suppresses NK cell and neutrophil activity while protecting T lymphocytes from apoptosis [168,169]. This immunosuppression, primarily due to the inhibition of the NF-κB pathway, may contribute to cancer cell survival and metastasis, particularly in lung cancer [77,170]. However, clinical studies have not yet established a definitive link between perioperative thiopental use and oncologic outcomes.

4.4.4. Ketamine

Ketamine, an NMDA receptor antagonist, is widely used for its anesthetic and analgesic properties. Preclinical studies suggest that ketamine may reduce cancer cell proliferation and migration by lowering intracellular calcium levels and inhibiting HIF-1α, p-AKT, and p-ERK expression, thereby reducing VEGF levels [171,172]. Additionally, ketamine decreases pro-inflammatory cytokines, such as IL-6 and TNF-α, which may further inhibit tumor growth [173]. However, ketamine also suppresses NK cell activity, induces lymphocyte apoptosis, and inhibits dendritic cell maturation, which may promote metastasis [77,174–176].

In lung adenocarcinoma models, ketamine has been shown to promote apoptosis and inhibit cell growth through CD69 expression [177]. However, some studies suggest an

increased risk of metastasis due to reduced NK cell activity [77,174]. Clinical evidence regarding ketamine's overall impact on cancer outcomes remains limited and inconclusive [178,179].

4.5. Local Anesthetics

Local anesthetics (LAs), commonly used for intraoperative anesthesia and postoperative analgesia, block neural transmission by inhibiting voltage-gated sodium channels (VGSCs) [180]. Recent studies suggest that LAs may also have direct anti-tumor effects by modulating cancer cell behavior [181,182]. By reducing the surgical stress response, LAs may help mitigate immunosuppression and preserve the immune system's ability to eliminate cancer cells. Additionally, LAs reduce the need for opioids and volatile anesthetics, both of which may negatively impact cancer recurrence. Recent evidence suggests that amide LAs may directly inhibit cancer cell growth.

Laboratory studies have shown that LAs, particularly amide types such as lidocaine, can inhibit cancer cell viability, migration, and proliferation in vitro [183,184]. Lidocaine has been shown to reduce lung cancer proliferation by upregulating miR-539, which blocks EGFR signaling [185]. Lidocaine also exhibits anti-inflammatory properties, reducing pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, which may help prevent perioperative immunosuppression [186,187]. Additionally, it preserves NK cell function and lymphocyte proliferation, supporting the immune system's role in targeting cancer cells [188–190].

LAs may also reduce metastasis by inhibiting VGSC activity, which is crucial for tumor cell invasion and metastasis formation. Preclinical studies suggest that LAs block the formation of invadopodia, structures that help cancer cells degrade the extracellular matrix and invade surrounding tissues [191,192]. Lidocaine reduces lung metastasis by decreasing MMP-2 levels in murine breast cancer models, limiting tumor cell invasion [193,194]. Both lidocaine and ropivacaine further inhibit cancer cell migration and invasion by blocking TNF-α-induced Src phosphorylation and reducing ICAM-1 expression, which are essential for cellular adhesion in lung cancer cells [195,196]. Furthermore, lidocaine and ropivacaine have demonstrated anti-angiogenic effects by inhibiting VEGF-induced tumor growth and promoting apoptosis in tumor-associated endothelial cells [197,198].

Despite promising preclinical data, clinical evidence on the impact of LAs on cancer recurrence remains mixed. Some retrospective studies have suggested that regional anesthesia, which reduces opioid and volatile anesthetic use, may improve OS in cancer patients [199–201]. However, more recent studies, including a Cochrane review, concluded that the evidence supporting the benefit of local anesthetics on cancer recurrence remains inadequate, with conflicting results from various retrospective studies [202–204]. Although some clinical studies have shown potential benefits, such as improved survival in patients with pancreatic cancer receiving intravenous lidocaine [205], prospective trials are needed to clarify these findings across various cancer types.

4.6. Others

4.6.1. Hypothermia

Perioperative hypothermia can suppress immune function by reducing NK cell activity and disrupting the Th1/Th2 cytokine balance, both of which promote cancer metastasis [206,207]. Retrospective studies show mixed results, with some reporting worse cancer outcomes [208,209], while others find no significant impact on recurrence or survival [210].

4.6.2. Transfusions

Perioperative blood transfusions, often necessary in cancer surgeries, have been linked to immunosuppressive effects that may contribute to cancer recurrence [211,212]. Transfusions can impair macrophage function and shift the immune balance toward a pro-tumor Th2 profile. Retrospective studies associate allogeneic transfusions with poorer OS and disease-free survival in several cancer types, including gastric, bladder, and lung can-

cers [213–216]. However, the exact relationship between transfusions and cancer prognosis remains unclear, and more research is needed to understand the underlying mechanisms.

4.6.3. β-Blockers

β-blockers, commonly used as antihypertensive agents, have shown potential anti-cancer effects by reducing catecholamine-mediated tumor progression [217,218]. In vitro studies suggest β-blockers may exert anti-metastatic effects by reducing inflammation and inhibiting pro-tumor Treg cell activity [219,220]. Retrospective studies in patients with ovarian, breast, and other cancers have indicated improved survival with perioperative β-blocker use [221,222]. Meta-analyses have shown similar trends, although results vary depending on factors such as administration time, cancer stage, and tumor type [223–225]. Further studies are needed to confirm the benefits of β-blockers in cancer surgery.

4.6.4. Steroids

Corticosteroids, such as dexamethasone, are frequently used perioperatively for their anti-inflammatory and anti-emetic properties. However, their immunosuppressive effects at higher doses have raised concerns about increased cancer recurrence. Retrospective studies have shown mixed results, with some indicating improved survival in cancers like NSCLC and pancreatic cancer with perioperative dexamethasone use [152,226], while others report worsened outcomes, particularly in colorectal cancer [227,228]. More prospective trials are needed to clarify the long-term impact of corticosteroid use on cancer recurrence and metastasis.

Table 1. Summary of clinical studies on anesthetic agents and techniques in lung cancer surgery.

Anesthetic Agents/Techniques	Study Type	Author (Year)	Patients/Studies	Findings	References
EA + GA (vs. GA alone)	RCT	Xu. et al. (2021)	n = 400	No difference in OS and RFS	[69]
EA + GA (vs. GA alone)	RCT	Du. et al. (2021)	n = 1802	No difference in OS and RFS	[70]
TIVA (vs. Volatile)	Meta-analysis	Chang. et al. (2021)	n = 19	Improved OS and RFS	[106]
TIVA (vs. Volatile)	Meta-analysis	Yap. et al. (2019)	n = 10	Improved OS and RFS	[107]
TIVA (vs. Volatile)	Retrospective	Oh. et al. (2018)	n = 943	No difference in OS and RFS	[108]
Opioid	Retrospective	Cata. et al. (2014)	n = 901	Decreased OS and RFS (in stage I)	[134]
Opioid	Retrospective	Maher. et al. (2014)	n = 99	Increased in recurrence rate	[135]
Opioid	Retrospective	Oh. et al. (2017)	n = 1009	No difference in recurrence rate and OS	[136]
NSAIDs	Retrospective	Choi. et al. (2015)	n = 1139	No difference in OS and RFS	[154]
NSAIDs	Retrospective	Lee. et al. (2016)	n = 1637	No difference in OS and RFS	[155]
Dexmedetomidine	Retrospective	Cata. et al. (2017)	n = 1404	Decreased OS and no difference in RFS	[167]

EA: epidural anesthesia, GA: general anesthesia, RCT: randomized controlled trial, TIVA: total intravenous anesthesia, OS: overall survival, RFS: recurrence-free survival, NSAIDs: non-steroidal anti-inflammatory drugs.

5. Current Large-Scale Studies and Proposed New Research Directions

Recent clinical trials have sought to elucidate the relationship between anesthetic techniques and cancer recurrence rates in surgical patients, with a particular focus on the effects of volatile anesthetics and TIVA (Table 2). The VAPOR-C trial compares the long-term impact of propofol-based TIVA with volatile anesthesia on RFS in patients with lung and colorectal cancers, aiming to determine whether TIVA provides superior oncologic outcomes. Preliminary results suggest TIVA may have a favorable impact, though comprehensive results are awaited. Similarly, the GA-CARES trial examines various anesthetic agents across multiple cancer types, including lung cancer, to assess their influence on OS and recurrence rates. The GAS-TIVA trial focuses on NSCLC, comparing the recurrence rates between propofol-based TIVA and volatile agents. These studies will provide critical insights into optimizing anesthetic strategies for improved oncologic outcomes.

Table 2. Ongoing prospective randomized clinical trials on anesthetic management and lung cancer recurrence.

Trial Registry Number	Study Title	Study Design	Interventions	Primary Outcome	Estimated Completion
NCT03034096	General Anesthetics in Cancer Resection Surgery (GA-CARES trial)	All cancer type (n = 2000)	Propofol-based TIVA vs. Sevoflurane, Isoflurane, Desflurane	All-cause mortality	December 2025
NCT04316013	Volatile Anaesthesia and Perioperative Outcomes Related to Cancer (VAPOR-C trial)	Non-small cell lung cancer, colorectal cancer (n = 3500)	Propofol-based TIVA vs. Sevoflurane	Disease-free survival	June 2028
NCT06330038	Recurrence Free Survival After Curative Resection of Non-small Cell Lung Cancer Between Inhalational Gas Anesthesia and Propofol-based Total IntraVenous Anesthesia (GAS-TIVA trial)	Non-small cell lung cancer (n = 5384)	Propofol-based TIVA vs. Sevoflurane, Isoflurane, Desflurane	Recurrence-free survival	December 2028

TIVA: total-intravenous anesthesia.

Beyond these large-scale studies, new research should investigate how anesthetic agents modulate molecular mechanisms such as ferroptosis and autophagy, which are crucial in cancer cell survival and death [229,230]. Ferroptosis is a form of regulated cell death characterized by lipid peroxidation driven by iron-dependent processes. It contrasts with apoptosis and necrosis by involving unique mechanisms such as glutathione peroxidase 4 (GPX4) inhibition, leading to cellular damage and death. Autophagy, on the other hand, plays a dual role by promoting cell survival under stress but can also trigger ferroptosis through processes like ferritinophagy, which releases free iron and generates reactive oxygen species. These mechanisms represent promising targets for therapeutic strategies, suggesting that anesthetic techniques impacting oxidative stress and autophagic activity could influence cancer outcomes. Anesthetics like propofol and dexmedetomidine are known to interact with these mechanisms; propofol can modulate oxidative stress and autophagic processes, while dexmedetomidine may inhibit ferroptosis by enhancing GPX4 expression. Understanding these interactions could reveal how perioperative anesthetic choices impact cancer cell viability and long-term recurrence, opening new therapeutic strategies that combine anesthetic management with targeted interventions.

6. Conclusions

While increasing evidence suggests that anesthetic techniques and perioperative management may influence cancer recurrence and metastasis, much of the current data come from preclinical or retrospective studies with conflicting results. Certain anesthetic agents, such as propofol, have shown promising anti-tumor effects, whereas others, such as volatile anesthetics and opioids, have been linked to tumor-promoting mechanisms. However, these findings are not entirely consistent, likely due to the complex interactions between tumor biology, surgical techniques, and patient-specific factors such as immune status, comorbidities, and genetics. This complexity makes it challenging to isolate the effects of individual agents or techniques on cancer outcomes.

In addition to anesthetic agents, future studies should focus on other perioperative factors such as pain management, blood transfusions, and perioperative hypothermia, which may significantly affect cancer prognosis. Understanding the influence of these variables is crucial to developing comprehensive perioperative strategies aimed at reducing metastasis risk and improving survival.

Effective anesthetic management in cancer surgery requires balancing immediate perioperative needs with long-term oncologic outcomes. Personalized approaches, considering each patient's risk profile—including immune status and comorbidities—are essential. Multidisciplinary collaboration between anesthesiologists, surgeons, and oncologists is key to ensuring that perioperative care effectively supports oncologic considerations.

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Systematic Review

Antiepileptic Drugs for De Novo Seizure Prevention After Craniotomy: A Systematic Review and Network Meta-Analysis of Current Evidence

Georgia Tsaousi [1,*], Adriani Nikolakopoulou [2], Parmenion P. Tsitsopoulos [3], Chryssa Pourzitaki [4], Dimitrios Mavridis [5] and Anna Bettina Haidich [2]

[1] Department of Anesthesiology and ICU, School of Medicine, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece
[2] Laboratory of Hygiene, Social & Preventive Medicine and Medical Statistics, School of Medicine, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece; anikolakopoulou@auth.gr (A.N.); haidich@auth.gr (A.B.H.)
[3] Second Department of Neurosurgery, School of Medicine, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece; ptsitsopoulos@auth.gr
[4] Laboratory of Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece; chpour@auth.gr
[5] Department of Primary Education, University of Ioannina, 45110 Ioannina, Greece; dmavridi@uoi.gr
* Correspondence: tsaousig@auth.gr

Abstract

Objective: We aimed to systematically evaluate the available clinical evidence concerning the comparable efficacy and safety of currently used anti-epileptic drugs (AEDs) for seizure prophylaxis in patients undergoing craniotomy for brain tumor excision and synthesize this with a network meta-analysis (NMA). **Methods**: A systematic literature review was performed to identify randomized controlled trials (RCTs) relevant to the prophylactic use of AEDs in seizure-naïve patients subjected to brain tumor excision. Total, early, or late post-craniotomy seizures constituted primary outcome measures, while mortality and treatment-related adverse effects served as secondary endpoints. Pairwise and network meta-analysis were conducted for each pair of interventions to obtain 'direct' treatment effect estimates, while NMA was employed to assess the relative efficacy and safety of prophylactic use of AEDs in post-craniotomy epilepsy management in brain tumor cases. **Results**: Twelve eligible RCTs involving 10 interventions were retrieved. Levetiracetam (OR 0.08; 95%CI 0.02–0.43) and phenytoin (OR 0.43; 95%CI 0.20–0.91) showed superior efficacy over placebo on early seizure control, while none of the applied interventions demonstrated any significant effect on late seizures versus placebo. With the single exception of carbamazepine (OR 3.29; 95%CI 1.21–8.91), none of the implemented AEDs exerted a notable effect on mortality. Phenytoin presented a higher incidence of treatment-related AEs, imposing drug discontinuation compared to other treatment regimens, yet this effect did not reach statistical significance. **Conclusions**: Our NMA indicates that, in seizure-naive individuals subjected to brain tumor excision, levetiracetam and phenytoin effectively prevent postoperative short-term seizure activity. Notwithstanding the fact that levetiracetam presents an enhanced safety profile over other AEDs, no statistical superiority could be demonstrated. PROSPERO registration CRD42022377136.

Keywords: anticonvulsant; antiepileptic; seizure; prophylactic; brain tumor; craniotomy

1. Introduction

Epileptic seizures constitute a well-recognized clinical entity in patients harboring a brain tumor [1–3]. An epileptic seizure could be a common clinical manifestation at the onset of tumor progression (30–80%), while a minority of patients (10–30%) with brain tumors develop late seizures [4,5]. Notably, the mass lesion per se, in conjunction with its surgical resection, could predispose to the aggravation of post-craniotomy seizure activity [5]. Although there is no clear cutoff point for the distinction between early and late seizures postoperatively, conventionally, the appearance of seizures within 1 week after surgery is defined as early seizures, while those occurring later are defined as late seizures [6].

The consequences of persistent seizure activity early after craniotomy involve the development of brain edema, traumatic brain damage, and aspiration, as well as an adverse impact on the neurological recovery and long-term quality of life of the affected individuals [6]. The goal of preventive anti-epileptic drugs (AEDs) is to reduce the development of early seizures while minimizing the incidence of late-onset seizures without the occurrence of profound adverse effects [7]. Nonetheless, it should be emphasized that only limited data affirm the efficacy of this practice, based on the absence of a class I study addressing this question [8]. On the other hand, each AED incurs potential harm, which should be taken into account before the commencement of antiseizure prophylaxis. Given the hazards of AED side effects, even if AEDs are given preoperatively in seizure-free patients with brain tumors, it is recommended that they be discontinued during the first week after surgery [9].

Nonetheless, AEDs are ordinarily commenced perioperatively, with their use being maintained for at least 1 year, provided that no seizure recurrence is recorded during that period [10]. In the current literature, several systematic reviews and meta-analyses have attempted to investigate the efficacy and safety of pairwise monotherapy comparisons or the direct comparisons of anticonvulsants to a placebo using individual participant data; however, their findings are inconclusive [11–16]. In the absence of robust evidence in this area, current practice relies on guidelines based on limited and low-quality clinical trials [5,7,17–20].

Furthermore, direct evidence from randomized controlled trials is not available for some drug comparisons or comparisons to a placebo, which might be of great importance in order to expand our knowledge in this area [11,21–23]. Thus, this study aims to systematically evaluate the available clinical evidence concerning the comparative efficacy and safety of all anticonvulsants currently used as prophylaxis for early or late de novo seizure occurrence compared with a placebo in patients undergoing elective craniotomy for brain tumor excision and synthesize this with a network meta-analysis.

2. Materials and Methods

2.1. Search Strategy

This review was performed following the Cochrane Handbook for Systematic Reviews of Interventions [24]. Furthermore, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [25] were followed (Table S1: PRISMA Checklist in Supplementary Materials), as were the subsequent additions for Network Meta-Analyses (NMA) [26]. The protocol of this review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the identifier CRD42022377136.

A methodological and comprehensive search approach was devised to retrieve all relevant papers that met the study's objectives. A meticulous database search involving the National Library of Medicine's PubMed, Scopus, Cochrane Central Register of Con-

trolled Trials (CENTRAL), and Web of Science from their inception to 15 July 2025 was conducted to detect relevant papers. Free-text and medical subject heading (MeSH) terms such as "craniotomy", "brain surgery", "brain tumor", "epilepsy", "seizure", "antiepileptic", "anticonvulsant", "prophylactic", "prophylaxis", "adverse effects" or "side effects" using appropriate Boolean operators, were applied to the literature search strategy to identify articles relevant to the objectives of this review (Tables S2, S3 and Figure S1 in Supplementary File). Our search strategy also incorporated several trial registries, namely Clinicaltrial.gov, the EU Clinical Trials Register, and the International Clinical Trials Registry Platform, to track any unpublished eligible trials. The last electronic search was performed on 10 August 2025.

2.2. Criteria for Considering Studies for This Review

Successfully screened studies were subsequently assessed for inclusion if they conformed to the following criteria: (1) original double-blind, single-blind, or unblinded RCTs involving a parallel design comparing at least two of the currently licensed AEDs prescribed as monotherapy for perioperative seizure prophylaxis in patients subjected to supratentorial or infratentorial craniotomy; (2) adult patients (age $\geq$ 18 years) undergoing brain tumor surgery with a portion of at least $\geq$50% of them being seizure-naïve; (3) direct comparison of an active treatment arm (any AED) with the control arm (alternative AED type, or no prophylaxis involving placebo and no-treatment); (4) provision of complete data on at least one of the predefined primary outcome measures; and (5) full-text publication with no language restriction. Articles focusing on the treatment of status epilepticus elicited by brain injury or involving a history of seizure disorders were excluded.

2.3. Outcome Measures

The primary study outcomes involved the presence of total and early or late seizure activity, defined as seizures occurring within the first postoperative week or beyond this period, respectively. The efficacy of the implemented AED was assessed by seizure freedom or a decline in seizure activity of $\geq$50% of the cases (seizure response).

As supplementary relevant secondary endpoints served: (1) mortality during follow-up assessment, and (2) the occurrence of major adverse effects related to the use of AEDs leading to drug discontinuation. Concerning safety outcomes, we also registered the proportion of individuals experiencing at least one major adverse event necessitating treatment or discontinuation of the implemented AEDs.

2.4. Screening and Selection Process

Complying with the selection strategy, two investigators (G.T. and C.P.) independently screened the titles and abstracts of all retrieved publications to detect articles potentially relevant to AED prophylaxis in patients subjected to brain tumor excision. Duplicate manuscripts and articles with clearly unrelated content were promptly deleted. Multiple records from the same research were compiled at the end of the data collection process. If eligibility could not be ascertained from the article title or abstract, the entire document was acquired, and studies were evaluated for eligibility based on their adherence to the stated inclusion criteria and overall clinical significance. Reference lists of recovered articles were hand-searched to ensure no relevant publications were overlooked. Disagreements in the screening and selection process were resolved by discussion or were arbitrated by the senior reviewer (D.M.) until consensus was reached.

2.5. Data Extraction

To record all pertinent data, a custom-designed abstraction form was employed. Data of interest included publication details (author, year of publication, study design, number of participants), brain pathology, details on research and control arms (type, dose/frequency, time of treatment commencement, and duration of AED prophylaxis), duration of follow-up, and findings relevant to the primary or secondary endpoints.

2.6. Quality Assessment

The Cochrane Collaboration Risk of Bias tool Version 2 for randomized trials (RoB2) [27] was applied to critically appraise the quality of the incorporated RCTs concerning the following domains: randomization process, timing of identification or recruitment of participants, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each item was assigned a low, some concerns, or high risk of bias. If a study met all of the low-risk criteria, it was classified as low risk; if it met any high-risk domains, it was classified as high risk. The risk of bias was assessed as having some concerns in all other circumstances. RoB2 judgments targeted the effect of adherence (per-protocol) assessment and were outcome-specific. The quality of evidence was tabulated using the Confidence in Network Meta-Analysis (CINeMA) software (http://cinema.ispm.unibe.ch, CINeMA 2.0.0, accessed on 22 May 2025) [28]. An OR lower than 0.7 (or higher than 1.43) across primary outcome endpoints was judged clinically significant.

In a further attempt to reduce the influence of subjective evaluation, the methodological quality attributed to each trial was judged separately by three reviewers (G.T., A.N., C.P.), while any disagreements that arose following the evidence evaluations were handled by consensus.

2.7. Statistical Synthesis

We conducted a network meta-analysis for each outcome using R software (version 4.5.1, http://www.r-project.org, accessed on 17 August 2025) using "meta" and "netmeta" packages.

Initially, a pairwise meta-analysis was conducted for each pair of interventions using a random-effects model to yield odds ratios (ORs) with 95% confidence intervals (CIs) of the relative treatment effects. The restricted maximum likelihood (REML) method was used to estimate heterogeneity for each pairwise comparison [29]. We then conducted a network meta-analysis using the REML method in sensitivity analyses in addition to the DerSimonian–Laird estimator (Tau^2) for heterogeneity assessment across all comparisons, though this estimator can underestimate Tau^2 in small and sparse networks. The node-splitting approach was used in each closed loop to assess the disparities between direct and indirect evidence [30].

The ranking probability for all AEDs of being at each possible rank for each intervention was also assessed. The relative plots (rankograms) and *p-scores* were utilized to create a hierarchy of competing interventions, with a higher ranking representing superior efficacy [31].

A funnel plot was constructed to detect small-study effects, and tests for funnel plot asymmetry determination were planned if at least ten studies were included in the meta-analysis. In an attempt to disentangle publication bias from small-study effects, contour-enhanced funnel plots were created.

3. Results

3.1. Search Process

The primary database search returned a total of 4976 citations. Thirteen additional publications were detected from registries or hand-searching through reference lists of the included trials. Among them, 5 were promptly discarded for involving early-terminated or ongoing studies. After removing all duplicates and screening titles/abstracts, the full-text versions of the remaining 26 publications were examined for possible eligibility. A single paper was excluded from consideration on the basis that a full-text version could not be acquired, leaving 25 papers for further assessment. At this point, 13 full-text articles were discarded due to methodological constraints, namely the inclusion of patients with pre-existing seizure activity in >50% of patients, prior use of anticonvulsant medication, no craniotomy procedures, irrelevant study design, or non-full-text publications. Thus, 12 RCTs examining the effectiveness of AEDs on post-craniotomy seizures (PCS) involving a total of 2011 participants were selected for inclusion in the final qualitative appraisal [32–43]. A flowchart describing the literature search process is presented in Figure A1.

3.2. Description of Included Trials

All included studies but two [34,42] employed a two-arm study design. Phenytoin constituted the main anticonvulsant medication being used, while the tested arms involved an active comparator [32–38], a no-prophylaxis control group [34,39–41], or the combination of an active comparator and a no-prophylaxis control group [34,42]. Valproate [32,33], carbamazepine [34], levetiracetam [35–37], gabapentin [38], and phenobarbital [42,43] served as active controls. A two-arm study assessed the comparable use of zonisamide to phenobarbital [43]. It should be pointed out that a single study [42] reported a pooled analysis of the efficacy and safety of either phenytoin or phenobarbital.

The duration of anti-seizure treatment varied considerably among studies, ranging from 3 days up to 24 months, while in one trial, the treatment period was not clearly identified [42]. Regarding the follow-up determination, early seizures were consistently defined as seizures occurring within 3 to 7 days post-surgery, while late seizure assessment demonstrated a considerable variation among the included studies, ranging from 1 month to 4 years. Early seizures were evaluated as a primary point of interest in 11 studies [32,33,35–43], while complete data on both primary outcome parameters were provided by 7 trials [32,37–43]. The occurrence of late seizures constituted the single endpoint of the efficacy of seizure prophylaxis in only a three-arm RCT [34]. Two RCTs used either tolerability and safety of the administered AEDs [35] or postoperative pain control [38] as the primary study endpoints, while seizure control served as a secondary study outcome.

It should be noted that no uniformity in drug administration route and dosing regimen could be detected among the selected RCTs. In more than 50% of the studies, anti-seizure prophylaxis was implemented perioperatively [33–35,37,41–43]. In three RCTs, anticonvulsants were administered only postoperatively [32,39,40], in one, only preoperatively [38], while in the remaining one, the tested drugs were commenced intraoperatively and continued thereafter [36].

The study group consisted of seizure-naïve participants in nine trials [32–34,37–41,43]. Although Franceschetti et al. [42] included both seizure-naïve patients as well as those with preoperative seizures, they analyzed separately the seizure-naïve group compared to the control one in order to conform to our inclusion criteria. Similarly, Iuchi et al. [36] included people who had preoperative seizures, but the trial authors provided the results of

subgroup analysis for participants with no preoperative seizures. Finally, a single trial [35] also incorporated patients with seizure activity before randomization, but the percentage in both treatment arms was considerably low (5% in each group). Study characteristics and individual study outcomes are detailed in Appendix A (Tables A1 and A2).

3.3. Network Plots

The network plots showing the evidence for assessing the impact of anti-seizure prophylaxis on primary and secondary outcomes are presented in Figure 1. No closed loop between treatment arms existed in early seizure control and major adverse effects plots.

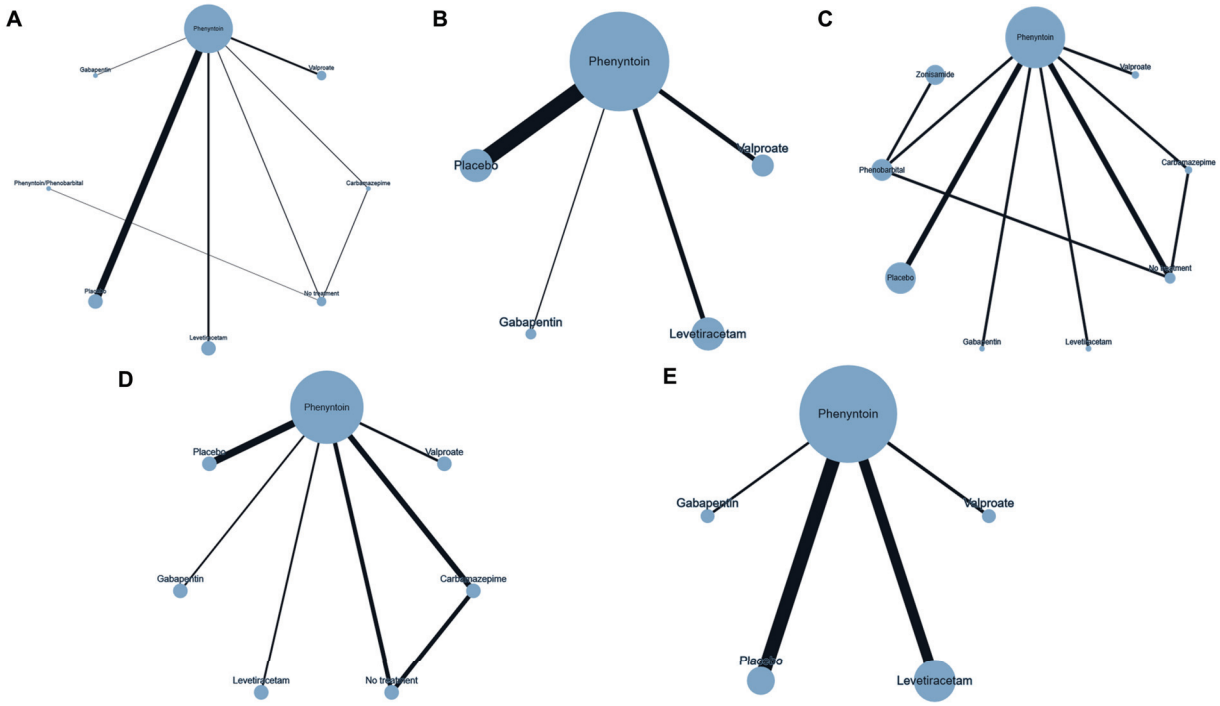

Figure 1. Network plot of the efficacy and safety of the assessed anti-epileptic drugs (AEDs). Total (**A**), early (**B**), and late (**C**) seizure control as well as mortality (**D**), (**E**), and adverse events imposing the discontinuation of AEDs. The width of each edge is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants (sample size).

3.4. Primary Outcomes

3.4.1. Total Seizures

Eleven RCTs comprising 13 pairwise comparisons were assessed in the meta-analysis model. Only levetiracetam (OR 6.62; 95%CI 1.36–32.21) demonstrated a notable superiority compared with placebo in terms of total PTS occurrence and was ranked as the most effective intervention (Figures 2A and A2a). In line with previous findings, NMA showed that levetiracetam was more likely to reduce total PCS compared with phenytoin [OR 5.21; 95%CI 1.19–22.91], valproate [OR 6.19; 95%CI 1.13–33.77], no treatment [OR 6.20; 95%CI 1.13–34.09], as well as placebo [OR 6.62; 95%CI 1.36–32.21]. No other significant differences were found; yet, estimates were very imprecise (Table 1). No particular heterogeneity (τ^2 = 0.038; I^2 = 9.1%) or asymmetry due to publication bias (Bias estimate = 0.056; SE = 0.462; p = 0.905) was encountered in the NMA model (Figure A3).

3.4.2. Early Seizures

All included RCTs but one [34] assessed the impact of anticonvulsant prophylaxis on early postoperative seizure occurrence. Although the early-seizure network contained no closed loops, we conducted an NMA anchored on common comparators ($\tau^2 = 0$); however, local inconsistency could not be assessed. Levetiracetam (OR 12.08; 95%CI 2.34–62.43) and phenytoin (OR 2.31; 95% CI 1.09–4.88) showed superior efficacy over placebo on early seizure control, while the favorable effect registered for gabapentin and valproate was not statistically significant (Figure A2b). Although local inconsistency could not be assessed, gabapentin was ranked as a second choice after levetiracetam, yet the probability was quite low (<0.4) (Figure A2b). According to the league table (Table 2) levetiracetam was superior to phenytoin [OR 5.23; 95%CI 1.21–22.57], valproate [OR 8.23; 95%CI 1.53–44.29], or placebo [OR 12.08; 95%CI 2.34–62.43] for early seizure control, while phenytoin presented higher efficacy only compared to placebo (OR 2.31; 95%CI 1.09–4.88). Model heterogeneity was negligible ($\tau^2 = 0$; $I^2 = 0\%$). Because the network plot did not form a closed loop, inconsistency was not evaluated.

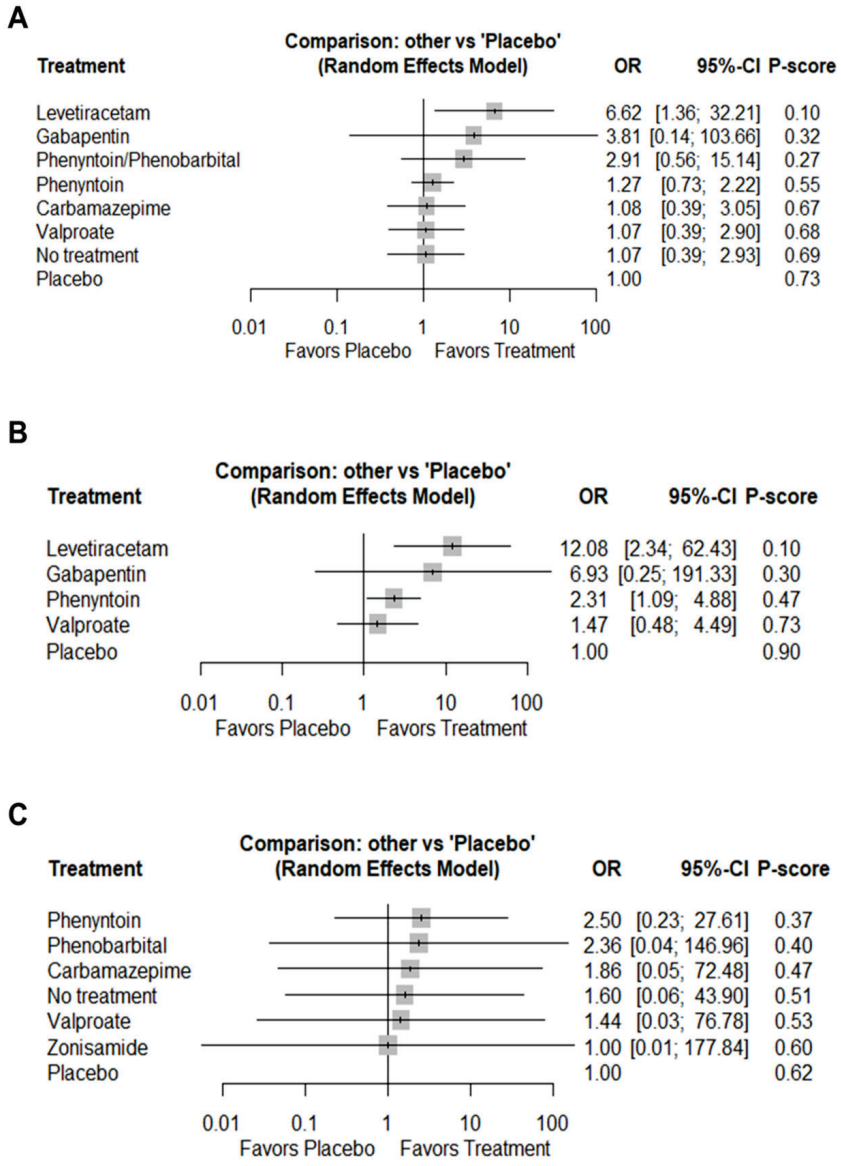

Figure 2. Forest plot of each treatment modality versus placebo for total (**A**), early (**B**) and late (**C**) seizure control.

Table 1. League table demonstrating the relative effectiveness of each pair of comparisons for total seizures. Odds ratios greater than 1 favor interventions in the column; forest plots use the conventional orientation (values < 1 favor the intervention versus placebo). Treatment modalities and statistically significant findings are highlighted using bold font.

CBZ							
0.28 (0.01; 8.27)	**GAB**						
0.16 (0.03; 0.91)	0.58 (0.02; 20.58)	**LEV**					
1.02 (0.43; 2.39)	3.57 (0.12; 103.11)	**6.20 (1.13; 34.09)**	**No treatment**				
0.85 (0.36; 2.04)	3.00 (0.12; 77.79)	**5.21 (1.19; 22.91)**	0.84 (0.36; 1.95)	**PHT**			
0.37 (0.08; 1.78)	1.31 (0.04; 48.36)	2.28 (0.27; 19.49)	0.37 (0.10; 1.35)	0.44 (0.09; 2.07)	**PHT/PB**		
1.08 (0.39; 3.05)	3.81 (0.14; 103.66)	**6.62 (1.36; 32.21)**	1.07 (0.39; 2.93)	1.27 (0.73; 2.22)	2.91 (0.56; 15.14)	**PBO**	
1.01 (0.30; 3.37)	3.56 (0.12; 102.51)	**6.19 (1.13; 33.77)**	1.00 (0.31; 3.26)	1.19 (0.52; 2.72)	2.72 (0.47; 15.81)	0.93 (0.34; 2.54)	**VAL**

Table 2. League table demonstrating the relative effectiveness of each pair of comparisons for early seizure control. Odds ratios greater than 1 favor interventions in the column; forest plots use the conventional orientation (values < 1 favor the intervention versus placebo). Treatment modalities and statistically significant findings are highlighted using bold font.

GAB				
0.57 (0.02; 19.93)	**LEV**			
3.00 (0.12; 76.03)	**5.23 (1.21; 22.57)**	**PHT**		
6.93 (0.25; 191.33)	**12.08 (2.34; 62.43)**	**2.31 (1.09; 4.88)**	**PBO**	
4.72 (0.17; 133.01)	**8.23 (1.53; 44.29)**	1.57 (0.68; 3.62)	0.68 (0.22; 2.09)	**VAL**

3.4.3. Late Seizures

Importantly, no difference in late seizure occurrence between treatment arms was reported [32,34,35,37,38,40–43], a finding further confirmed by the synthesis of relevant data from 8 RCTs and 10 pairwise comparisons, which showed that none of the tested treatment regimens demonstrated any notable superiority in terms of late PCS occurrence (Figure A2c). Similarly, when we assessed the relative effectiveness of each pair of comparisons, we failed to detect any notable difference between the tested AEDs in late seizure control (Table 3). Between-study heterogeneity was substantial ($\tau^2 = 2.04$; $I^2 = 67.3\%$). The direct/indirect effect for both loops (phenytoin, carbamazepine, no treatment, and phenytoin, no treatment, phenobarbital) did not show any evidence of inconsistency (χ^2 statistic = 0.003; $p = 0.961$) (Figure A4). Of importance, in the majority of comparisons, data were provided by a single trial, a small number of participants, or both.

Table 3. League table demonstrating the relative effectiveness of each pair of comparisons for late seizures. Odds ratios greater than 1 favor interventions in the column; forest plots use the conventional orientation (values < 1 favor the intervention versus placebo). Treatment modalities are highlighted using bold font.

CBZ						
1.02 (0.07; 14.99)	**No treatment**					
1.89 (0.04; 92.78)	1.85 (0.08; 43.16)	**PB**				
2.80 (0.19; 42.00)	2.75 (0.29; 25.85)	1.48 (0.05; 40.24)	**PHT**			
1.14 (0.03; 41.19)	1.12 (0.04; 28.84)	0.60 (0.01; 34.78)	0.41 (0.04; 4.28)	**PBO**		
1.61 (0.03; 98.49)	1.58 (0.03; 72.28)	0.85 (0.01; 78.78)	0.57 (0.03; 12.73)	1.41 (0.03; 68.75)	**VAL**	
0.80 (0.01; 112.65)	0.79 (0.01; 62.92)	0.43 (0.02; 8.94)	0.29 (0.00; 25.64)	0.70 (0.00; 111.9)	0.50 (0.00; 117.12)	**ZNS**

Finally, a single study [43] comparing zonisamide and phenobarbital failed to detect any notable effect regarding total, early, and late PCS control.

3.5. Secondary Outcomes

3.5.1. Mortality

From the limited number of studies (4 RCTs, 6 pairwise comparisons) [32,34,35,40], carbamazepine presented a higher tendency compared to the other tested AEDs for mortality aggravation (OR 3.30; 95%CI 1.22–8.91). Surprisingly, the no-treatment arm presented a two-fold higher odds ratio than placebo for an adverse effect on mortality (Figure A5A). The ranking of the tested interventions identified placebo as the intervention with the most favorable effect on mortality (Figure A6A). Nonetheless, the league table revealed that none of the tested AEDs exerted any notable effect compared to placebo or to other active drugs (Table A3), while the heterogeneity/inconsistency of this model could not be estimated.

3.5.2. Major Adverse Effects

All included studies but one [39] assessed the impact of anticonvulsant treatment on adverse effects. The most common adverse effects related to phenytoin implementation were liver dysfunction, skin rashes, allergic reactions, postoperative nausea and vomiting, or drug intoxication [32,34–36,40,41]. The use of valproate elicited thrombocytopenia or liver dysfunction [32], while levetiracetam induced limited adverse effects involving mainly delirium, headache, and mood disturbances [35].

Major adverse effects necessitating the discontinuation of the applied anticonvulsant were reported in 7 trials [32,35–38,40,41], while one study reported the development of adverse effects in the whole study population [34]. The incidence of major adverse effects ranged from 0 to 10%, while up to 47% of the patients treated by AEDs suffered from minimal adverse events. Of importance, none of the applied AEDs exerted a statistically significant unfavorable effect on the occurrence of serious adverse effects, imposing the discontinuation of AEDs (Figure A5B). As anticipated, placebo (p-score = 0.880) ranked as the safest practice concerning the occurrence of major adverse effects leading to drug discontinuation, yet the local inconsistency could not be assessed in the model (Figure A6B).

Using the league table (Table A4) to demonstrate the relative contribution of each pair of comparisons, we failed to detect any notable effect of the tested AEDs on major adverse effects, with the model estimates being considerably imprecise. Because the network plot did not form a closed loop, inconsistency was not evaluated.

3.6. Risk of Bias Assessment and Confidence in Evidence

The estimation of the overall risk bias being assessed by the RoB 2 tool revealed that seven out of 12 RCTs (58%) were rated as having "some concerns", while the remaining ones were classified as "high risk" of bias (Figures 3 and A7). Approximately 35% of the studies were graded with a high risk of bias in the component of adherence to study protocol, while all included studies failed to provide clear data regarding the selectivity of the reported outcomes.

The final estimation of the confidence rating regarding primary outcomes with CINeMA revealed that the relevant models were predominantly of moderate to low quality, with main concerns involving within-study bias and incoherence. Evidence of imprecision was noted, likely due to the limited number of trials available for comparison (Table A5). The comparisons relevant to secondary outcomes were graded with low to very low confidence ratings, with within-study bias, imprecision, and incoherence being the domains

presenting the major quality issues (Table A6). Of note, incoherence in both primary and secondary outcomes could not be evaluated due to the failure of closed-loops formation.

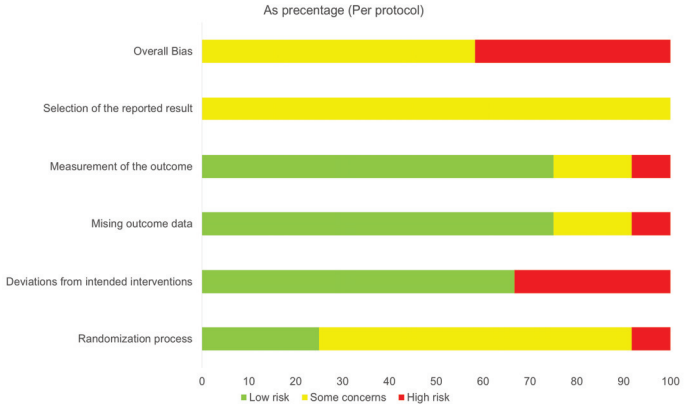

Figure 3. Risk of bias assessment of the included studies according to the RoB-2 Cochrane Bias Tool.

4. Discussion

This network meta-analysis showed that levetiracetam constituted the only AED demonstrating obvious superiority in total and early seizure control after brain tumor excision over no prophylaxis or other established AEDs. However, phenytoin exerted a positive effect on early seizure activity compared only with the no prophylaxis group. None of the commonly applied AEDs presented any notable advantage in terms of post-operative seizure occurrence, mortality, or adverse effects compared to placebo. Of note, levetiracetam ranked as the top choice for total and early seizure control as well as mortality reduction compared to other anticonvulsant regimens.

Experts in neuroscience have been intensively investigating the safety and effectiveness of different AEDs in preventing post-craniotomy epilepsy [14,19,44,45]. Considering that epilepsy might develop later in the course after craniotomy surgery, prophylactic AEDs have been increasingly prescribed for newly diagnosed primary or metastatic brain tumors, even in the absence of a seizure, to reduce the risk of developing seizure activity following craniotomy surgery. However, this practice remains controversial, as shown by relevant meta-analyses [5,12,14,23,45–47]. A plausible explanation for the failure of earlier studies to demonstrate the efficacy of prophylactic AEDs is that the investigators assessed the use of phenytoin, a traditional AED, for craniotomy-related epilepsy prevention rather than more recent AEDs, such as levetiracetam [47].

Taking into account the inconclusive existing evidence, the current practice seems to be determined by the recommendations of the Society for Neuro-Oncology (SNO) and the European Association of Neuro-Oncology (EANO) [48], and the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) [49], as well as the clinical experience or subjective judgments of the doctor. Preventive administration of AEDs is still often practiced by neurosurgeons—even in the absence of Class I evidence—a practice guided by tumor size, histology, and location as well as the extent of peritumoral edema [3,4,14].

A relevant survey conducted in 2005 demonstrated that approximately 70% of neurosurgeons prescribed prophylactic AEDs; a practice more frequently applied for intra-axial tumors (70%) and less frequently for stereotactic biopsies (21.4%) [50]. A decade later, Dewan et al. [49] showed that levetiracetam is the medicine of choice for more than 63% of neurosurgeons who treat seizure-naïve patients being administered from one week to six weeks following tumor excision. Nonetheless, a recently conducted UK survey [8] reported

that seizure prophylaxis is less commonly applied by neurosurgeons, with 59% and 79% of them not prescribing prophylactic AEDs for glioma and meningioma resections, respectively. In particular, the implementation of seizure prophylaxis in patients undergoing craniotomy who have not yet experienced a seizure could not be substantiated as routine practice by current research, based on the claim that the postoperative seizure rate is not high enough to compensate for any potential negative effects of AEDs [5].

Our NMA confirmed current evidence on this topic, as the prophylactic use of the commonly used AEDs in seizure-naïve patients failed to exert any beneficial effect on post-craniotomy epilepsy occurrence. The single exception was levetiracetam, which exhibited a statistically significant reduction in both early and total seizures compared not only to no prophylaxis but also to phenytoin or valproate and emerged as a potential first-line monotherapy according to its efficacy ranking. Phenytoin was shown to be beneficial for early seizure control only compared with no prophylaxis. Nonetheless, the impact of levetiracetam on late seizure occurrence could not be ascertained. It should be underlined that the early seizures model demonstrated an enhanced quality in the analysis of late seizure control.

The beneficial effect of levetiracetam on early seizure activity has important clinical implications, considering that the highest risk of postoperative seizures occurs within the first week of surgery [12,51]. However, two recently published meta-analyses on the prophylactic role of levetiracetam in post-craniotomy epilepsy in seizure-naïve patients provided conflicting evidence. In detail, Wang et al. [15] failed to demonstrate the efficacy of levetiracetam for early seizure prophylaxis in seizure-naïve glioma patients, while Lee et al. [47] showed that levetiracetam yielded a superior impact on seizure prevention for nontraumatic pathology compared to phenytoin with a concomitant reduction in serious adverse effects that led to drug discontinuation. It should be noted that both of these meta-analyses incorporated a limited number of RCTs; thus, the majority of evidence was extracted from observational retrospective studies.

Another important finding of our NMA was that phenytoin exhibited a positive effect only on early seizure activity over no prophylaxis. Although this anticonvulsant drug has long been considered the prototype AED for mitigating seizure activity, it failed to demonstrate any profound superiority in terms of efficacy over other tested AEDs or no-prophylaxis in our clinical setting.

Phenytoin has historically been preferred in neurosurgery, as it presents a well-established therapeutic serum concentration range, does not impair the level of consciousness, and can be monitored easily [14,52]. Nonetheless, phenytoin presents numerous drawbacks, including its unpredictable nonlinear pharmacokinetics, risk of adverse reactions, drug interactions, and reported negative influence on outcome in stroke and trauma cases [52,53].

It should be emphasized that determining whether seizure prophylaxis succeeds in preventing postoperative seizures in patients with brain tumors is challenging due to the intricate pathologic processes and the existence of several predisposing factors, such as the tumor size and type, the craniotomy location, as well as the extent of resection [15].

Based on a systematic literature review, the majority of documented adverse effects associated with AED prophylaxis range from 15% to 24% and are not considered serious [14]. The implementation of novel antiepileptic medications like levetiracetam can reduce this risk even further. A recently published meta-analysis [13] registered an augmented risk of adverse effects in phenytoin-treated patients compared to those receiving levetiracetam (15.5% versus 7.5%, respectively). Over and above, levetiracetam has been reported to enhance the sensitivity of glioblastoma to chemotherapy, with some investigators suggesting

that levetiracetam should be used as a first-line treatment for individuals suffering from brain tumors [13,47].

Levetiracetam is a pyrridoline derivative with greater potency and an attractive pharmacokinetic profile. It has limited plasma protein binding, great bioavailability, linear kinetics, a rapid rate of reaching steady-state concentrations, and a comparatively wide therapeutic window that does not require slow titration or serological monitoring at standard doses [47]. There have been fewer drug–drug interactions since levetiracetam is predominantly metabolized in the kidneys, where CYP enzymes are not engaged [13].

Our findings seem to reinforce existing evidence, considering the low ranking of phenytoin in safety outcomes assessment, namely, mortality and adverse effects. On the other hand, levetiracetam demonstrated enhanced safety performance in terms of mortality, ranking second after placebo, and improved tolerability compared to phenytoin, indicating its considerable potential. Discontinuation due to adverse effects was more common with phenytoin than with levetiracetam. Nonetheless, none of the safety-relevant outcomes in our analysis exhibited any statistical significance.

It should be emphasized that the frequency and magnitude of AED-related side effects should be interpreted in light of their potential clinical efficacy. A significant therapeutic or preventive benefit may warrant adverse effects, while a negligible or uncertain benefit does not warrant any degree of risk. A risk-benefit analysis from the included studies would have been largely out of date even if network outcomes for safety were more consistently reported because the included studies used first-generation AEDs (phenytoin, carbamazepine, valproic acid, and phenobarbital) for seizure prophylaxis rather than second-generation AEDs like levetiracetam, which are known to be more tolerable. Determining whether a newer generation AED will be beneficial for a population of seizure-naïve patients, given the possible risk reduction, is the next step towards definitively ending this lengthy but significant controversy. The estimation of the benefits of AEDs may vary if side effects occur less frequently or if a specific high-risk category is targeted [13].

It should be emphasized that rankings for early seizures and major AEs are descriptive, given the absence of closed loops; mortality comparisons showed no significant differences with sparse data.

Several limitations should be acknowledged and addressed in this network meta-analysis. First, the sample sizes for our pooled analyses are fairly limited since there are very few RCTs of AED prophylaxis with extractable data from patients undergoing craniotomy for various brain pathologies. Second, the implementation of seizure prophylaxis differed in timing, routes or dosing, duration of treatment, and the administration of AEDs either as monotherapy or as a mixture of anticonvulsants. Third, there was a notable variability in the time frame of outcomes assessment, with the interventions relevant to short-term analysis being more consistent compared to those included in the analysis of long-term outcomes. Fourth, the included studies are heterogeneous in terms of the type and location of the primary brain tumor, the complexity of the surgical intervention, as well as the incorporation of either seizure-naive individuals or individuals who experience seizures. Notably, only five RCTs included exclusively brain tumor populations, with the remaining incorporating other surgically treated brain pathologies. Lastly, the uncertainty in the risk of bias in the included trials, as well as the moderate to low-quality network analysis of study endpoints, might have attenuated the validity of the reported finding.

5. Conclusions

The findings of our network meta-analysis indicate that, in individuals without a history of seizures undergoing craniotomy for brain tumor excision, levetiracetam effec-

tively prevents postoperative total and short-term seizure activity and emerges as a more advantageous anticonvulsant drug than phenytoin and valproate, while phenytoin seems to be superior only to placebo. Nonetheless, none of the tested AEDs modulated late seizure development. Moreover, levetiracetam presents an enhanced safety profile in terms of unfavorable outcomes, yet no statistical superiority over other AEDs could be demonstrated. Nonetheless, the limited current evidence precludes any definite recommendation based on the routine use of AEDs in clinical practice for post-craniotomy seizure prophylaxis.

Thus, there is an urgent need for more well-designed, high-quality, and head-to-head comparisons with other control group trials to comprehensively evaluate the effectiveness of AEDs for seizure prevention following cranial surgery and to generate enough data to identify the most appropriate AED if prophylactic treatment is needed. The top priorities of future trials should be to overcome the methodological inconsistencies encountered in this analysis and to define the timing of AED administration (pre- or post-surgery), as well as the adequate length of treatment or follow-up period.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jcm14217854/s1. Table S1: PRISMA Checklist; Table S2: PUBMED Search strategy; Table S3: CENTRAL Search strategy; Figure S1: Web of Science Search strategy.

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Abbreviations

The following abbreviations are used in this manuscript:

RCT	Randomized Controlled Trial
AED	Anticonvulsant Drug
NMA	Network Meta Analysis
CINeMA	Confidence in Network Meta-Analysis
CI	Confidence Interval
OR	Odds Ratio

Appendix A

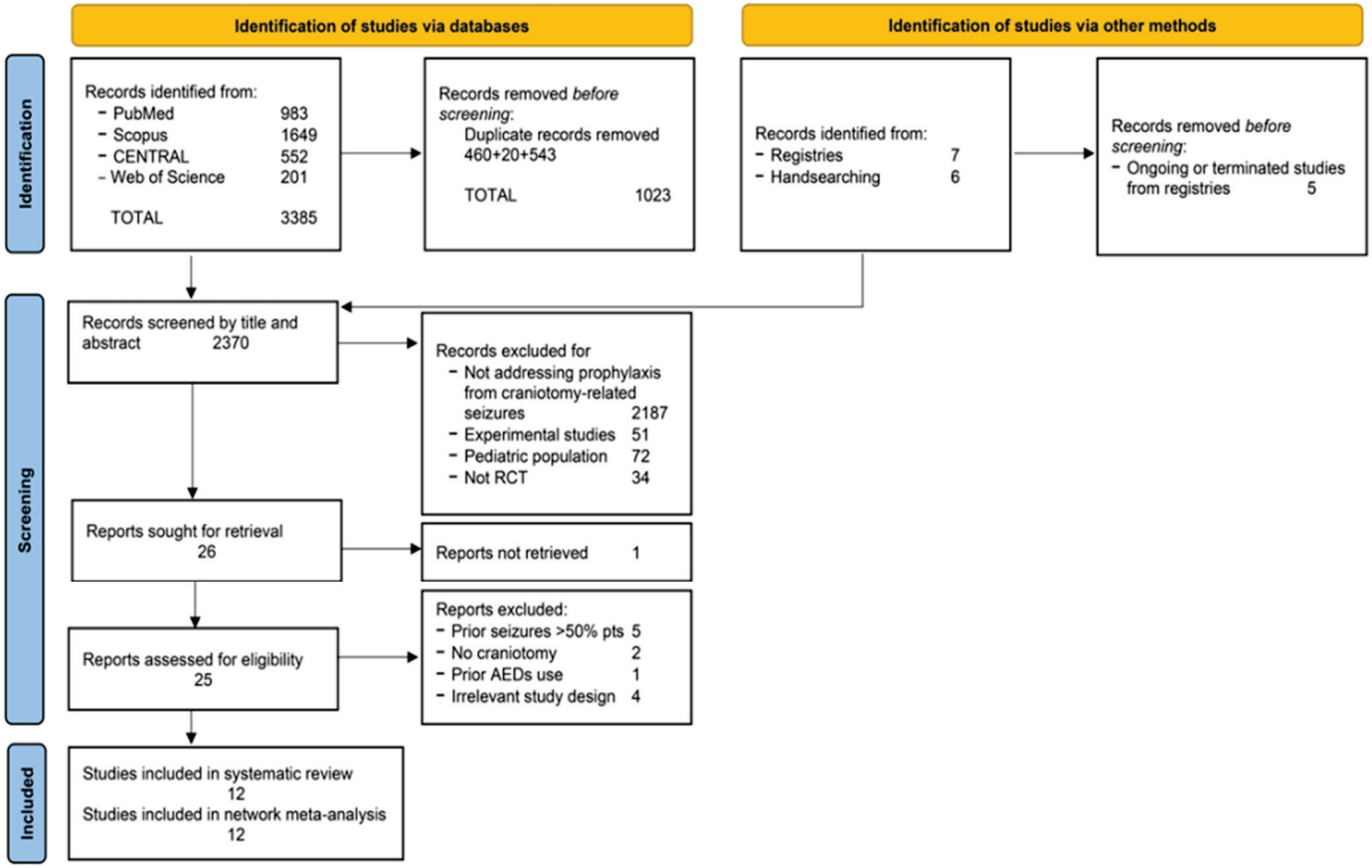

Figure A1. PRISMA flow chart of the study selection process.

Table A1. Characteristics of the included studies.

Study ID	Study Design	No of pts	Study Arms	Brain Pathology	Treatment Duration	Follow-Up	
						Early	Late
Beenen et al., 1999 [32]	Double-blind RCT	100	PHT 300 mg/d (iv) vs. VAL 1500 mg/d (iv) post-op	Vascular lesions, tumor, trauma	12 mo	1 wk	2 wks–12 mo
Zhang et al., 2000 [33]	RCT	152	PHT 10 mg/kg × 3 daily (oral) for 7 d pre-op & 5 mg/kg × 3 daily (iv) for 2 d & 5 mg/kg × 3 daily (oral) for 1 mo post-op vs. VAL 30 mg/kg × 3 daily (oral) for 7 d pre-op & 20 mg/kg × 3 daily (iv) for 2 d & 20 mg/kg × 2 daily (oral) for 1 mo post-op	Vascular lesions, tumor, trauma	1 mo	1 wk	>3 mo
Foy et al., 1992 [34]	Open-label, controlled RCT	276	PHT (15 mg/kg for 24 h pre-op & 300 mg/d post-op) vs. CBZ (800 mg for 24 h pre-op & 600 mg/d post-op) vs. NT	Vascular lesions, abscess, tumor	6 & 24 mo	NR	4 yrs (median)
Fuller et al., 2013 [35]	Single-blind RCT	81	PHT 300 mg × 3/d to 1 gr/d (iv) preop & 300 mg (oral) postop vs. LEV 500 mg–1 g/d (iv or oral) Preop (3 d) & post-op (3 mo)	Vascular lesions tumor, hematoma, abscess	3 mo	3 d & hospital discharge	3 mo
Iuchi et al., 2015 [36]	Open-cohort RCT	146	PHT 15–18 mg/kg & 5–7.5 mg/kg/d iv & 250 mg/d (oral) vs. LEV 500 mg iv & 1 g/d (sup or oral) intra-op & post-op	Tumors	7 d	1 wk	NA
Faghihjouibari et al., 2023 [37]	Double-blind, RCT	80	PHT 300 mg/d (iv or oral) vs. LEV 1 g/d (oral) preop (5 d) & post-op	Tumor	3 mo	1 wk	1 mo & 3 mo
Türe et al., 2009 [38]	RCT	80	PHT 300 mg/d (oral) vs. GAB 1200 mg/d (oral) 7 d pre-op	Tumor	6–12 mo	1 wk	1 mo
Lee et al., 1989 [39]	RCT	374	PHT (15 mg/kg end surgery & 5–6 mg/kg/d for 3 d post-op iv) vs. PBO	Vascular lesions tumor, hematoma, trauma	3 d	3 d	NA
North et al., 1983 [40]	Double-blind, RCT	281	PHT 500 mg/d (iv) & 300 mg/d (oral) post-op vs. PBO	Vascular lesions, tumor, trauma	12 mo	1 wk	12 mo
Wu et al., 2013 [41]	RCT	123	PHT 15 mg/kg (iv) pre-op & 300 mg/d (iv or peros) post-op for 7 d vs. PBO	Tumor	7 d	1 wk	>30 d
Franceschetti et al., 1990 [42]	RCT	63	PHT 10 mg/kg (iv for 5 d) & then 5 mg/kg (oral) vs. PB 4 mg/kg (iv for 5 d) & then 2 mg/kg (oral) vs. NT	Tumor	Unclear	1 wk	Unclear
Nakamura et al., 1999 [43]	Double-blind RCT	255	ZNS 200 mg/d (iv) vs. PB 80 mg/d (oral) for 1 mo pre-op & post-op	Vascular lesions, tumor, trauma	12 mo	NA	1–12 mo

ABBREVIATIONS. RCT, randomized controlled trial; PHT, phenytoin; VAL, valproic acid; CBZ, carbamazepine; LEV, levetiracetam; PB, phenobarbital; GAB, gabapentin; ZNS, zonisamide; NT, no-treatment; PBO, placebo; mo, month; wk, week; d, days; h, hours; iv, intravenous; pre-op, preoperatively; post-op, postoperatively; pts, patients; NA, not assessed.

Table A2. Outcome parameters of the included studies.

Study ID	Primary Outcome					Secondary Outcomes	
	All Seizures		Early Seizures	Late Seizures	Mortality	Discontinuation Due to AEs	Other Adverse Events
	NT or PBO	Control AED					
Beenen et al., 1999 [32]	-	PHT (7/50, 14%) vs. VAL (7/50, 14%) [NS]	PHT (4/50, 8%) vs. VAL (2/50, 4%) [NS]	PHT (3/50, 6%) vs. VAL (5/50, 10%) [NS]	PHT (13/50%, 26%) vs. VAL (10/50, 20%)	Skin rashes, PONV in PHT (5/50, 10%) vs. liver dysfunction, thrombopenia in VAL (2/50, 4%)	Anemia, PONV in PHT (4/50, 8%) vs. weight gain, PONV in VAL (2/50, 4%) [NS]
Zhang et al., 2000 [33]	-	PHT (6/72, 8%) vs. VAL (9/80, 11%)	PHT (6/72, 8%) vs. VAL (9/80, 11%)	NA	NA	NA	PHT (11/52, 15%) vs. VAL (2/80, 3%) [$p < 0.05$]
Foy et al., 1992 [34]	NT (25/59, 42%) 6-mo NT (20/59, 42%) 24 mo	PHT (21/55, 38%) vs. CBZ (21/50, 42%) 6-mo PHT (16/56, 29%) vs. CBZ (20/56, 36%) 24 mo	NA	PHT (21/55, 38%) vs. CBZ (21/50, 42%) vs. NT (25/59, 42%) 6-mo PHT (16/56, 29%) vs. CBZ (20/56, 36%) vs. NT (20/59, 42%) 24 mo	CBZ (19/106) vs. PHT (32/111) & vs. NT (13/59) [NS]	Skin rashes (28/217, 13%) Drug intoxication (6/217, 3%)	
Fuller et al., 2013 [35]	-	PHT (6/42, 14%) vs. LEV (0/30, 0%) up to 6 d [$p = 0.01$]	PHT (6/42, 14%) vs. LEV (0/30, 0%) up to 6 d [$p = 0.01$]	NA	PHT (5/42, 12%) vs. LEV (3/39, 8%)	Allergic reactions PHE iv (2/38, 5%) vs. skin rash LEV iv (1/36, 3%) Intoxication, rash, ataxia, nausea PHE oral (3/38, 8%) vs. delirium, pruritus, & headache LEV oral (3/36, 8%) [NS]	Thrombophlebitis PHT (3/38, 8%) Mood disturbance PHT (3/38, 8%) vs. LEV (7/36, 19%) PHT AEs (18/42, 43%) vs. LEV (22/39, 56%)
Iuchi et al., 2015 [36]	-	PHT (8/53, 14%) vs. LEV (1/53, 1.9%) [$p = 0.034$]	PHT (8/53, 14%) vs. LEV (1/53, 1.9%) [$p = 0.034$]	NA	NA	PHT 5/73, 6.8%) due to liver dysfunction, skin eruption & AF vs. LEV 0 [$p = 0.058$]	PHT (8/73, 11%) vs. LEV (3/73, 4%) [NS]
Faghihjouibari et al., 2023 [37]	-	PHT (1/40, 2.5%) vs. LEV (1/39, 2.6%) [NS]	PHE (1/40, 2.5%) 6 d vs. LEV (1/39, 2.6%) intra-op	None in either group	NA	None in either group	Skin rash PHT (3/40, 7.5%) vs. LEV 0% [NS] Thrombocytopenia PHT (1/40, 2.5%) vs. LEV 0%

Table A2. *Cont.*

Study ID	Primary Outcome					Secondary Outcomes	
	All Seizures		Early Seizures	Late Seizures	Mortality	Discontinuation Due to AEs	Other Adverse Events
	NT or PBO	Control AED					
Türe et al., 2009 [38]	-	PHT (1/38, 3%) vs. GAB 0%	PHT (1/38, 3%) vs. GAB 0% [NS]	PHE 0% vs. GAB 0%	PHT 0% vs. GAB 0%	Fatigue & dizziness GAB (2/37, 5%) vs. PHT (0/37, 0%)	Fatigue & dizziness GAB (10/37, 27%) vs. PHT 0% Ataxia, myalgia, PONV in GAB (12/37, 32%) vs. ataxia, PONV in PHT (18/38, 47%)
Lee et al., 1989 [39]	PHT (2/189, 1%) vs. PBO (9/285, 5%)	-	PHT (2/189, 1%) vs. PBO (9/285, 5%)	NA	NA	NA	NA
North et al., 1983 [40]	PHT (18/140, 13%) vs. PBO (26/141, 18%)	-	PHT (4/140, 3%) vs. PBO (14/141, 20%) [$p < 0.05$]	PHT (14/140, 10%) vs. PBO (12/141, 8.5%)	PHT (20/140, 14%) vs. PBO (12/140, 9%) [NS]	Rashes (8/140, 6%) Involuntary movements, hirsutism, headache, discomfort of the face (1 pt/effect) in PHT vs. Rash, dizziness & nausea (1 pt/effect) in PBO	
Wu et al., 2013 [41]	PHT (15/62, 24%) vs. PBO (11/61, 18%)	-	PHT (5/62, 8%) vs. PBO (5/61, 8%) [NS]	PHT (9/62, 14%) vs. PBO (6/61, 10%) [NS]	NA	Major AEs PHT (3/62, 5%) vs. PBO (0/61, 0%)	Minor AEs PHT (9/62, 15%) vs. PBO 0% [$p < 0.01$]
Franceschetti et al., 1990 [42]	PHT or PB (6/41, 15%) vs. NT (7/22, 32%)		Total PHT or PB (3/41, 7%) vs. NT (4/22, 18%)	PHT (1/10, 10%) vs. PB (2/15, 13%) vs. NT (3/14, 21%) [NS]	NA	NA	Neurological AEs PHT (3/16, 19%) vs. PB (1/25, 4%) within 7 d
Nakamura et al., 1999 [43]	-	ZNS (13/129, 10%) vs. PB (11/126, 9%)	ZNS (6/129, 5%) vs. PB (3/126, 2%)	ZNS (7/129, 5%) vs. PB (8/126, 6%)	ZNS (8/112, 7%) vs. PB (13/107, 12%)	NA	ZNS (28/129, 22%) vs. PB (30/126, 24%)

ABBREVIATIONS. RCT, randomized controlled trial; GAB, gabapentin; PHT, phenytoin; VAL, valproic acid; CBZ, carbamazepine; LEV, levetiracetam; PB, phenobarbital; ZNS, zonisamide; NT, no-treatment; PBO, placebo; PONV, postoperative nausea and vomiting; AEs, adverse events; mo, month; wk, week; d, days; h, hours; iv, intravenous; pre-op, preoperatively; post-op, postoperatively; pts, patients; NA, not assessed; NS, non-significant.

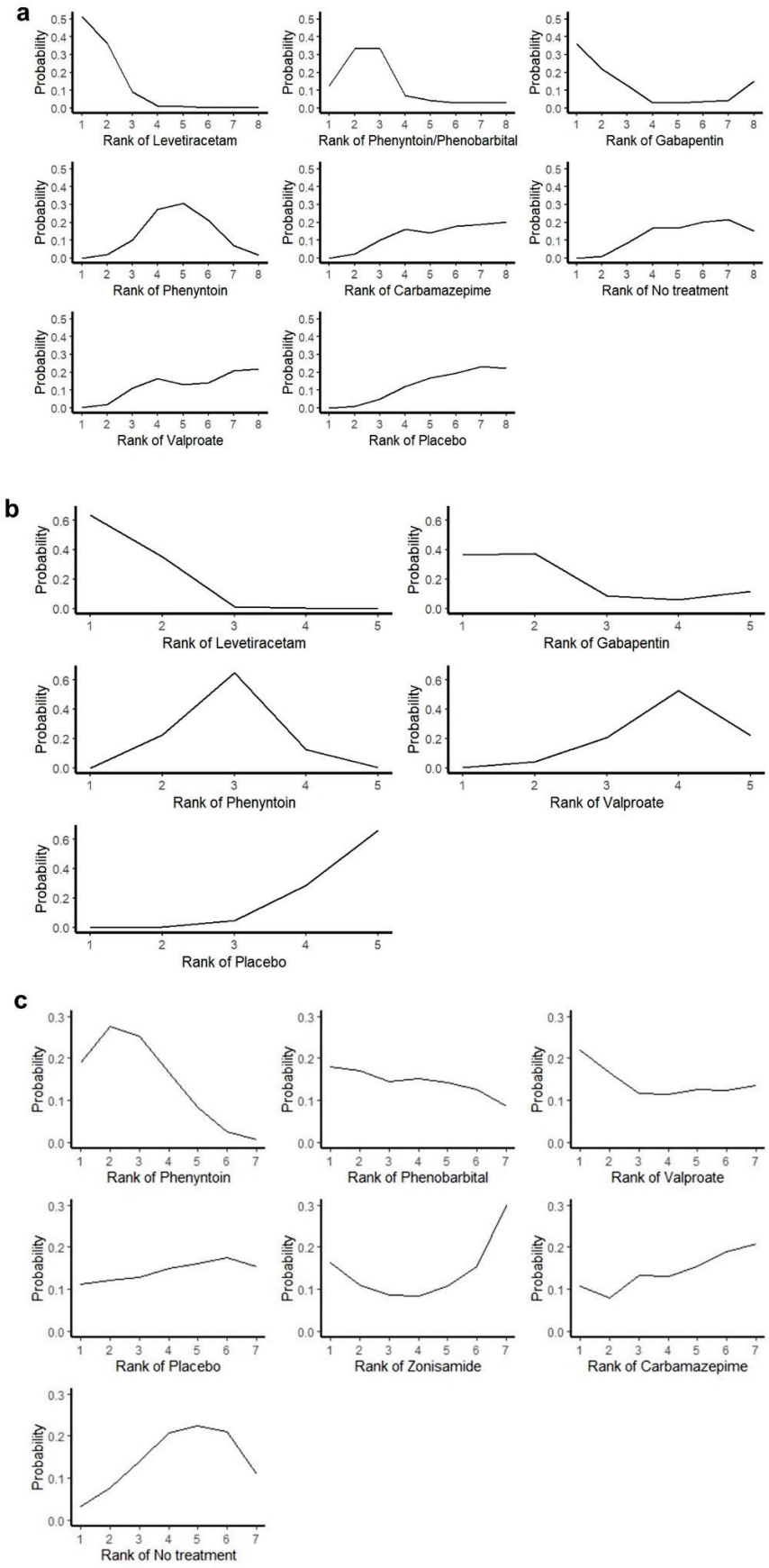

Figure A2. Rankograms illustrating the relative ranking of each treatment modality for the control of (**a**) total, (**b**) early, and (**c**) late seizures.

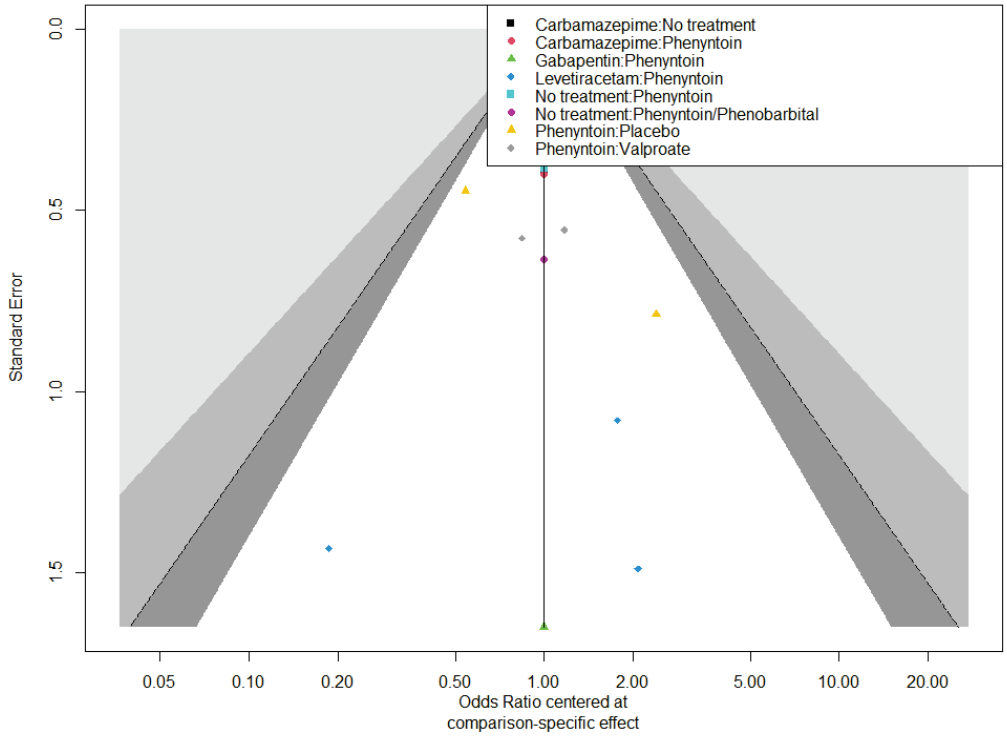

Figure A3. Contour-enhanced funnel plot for total seizures. Different shades indicate *p*-value ranges (white for >0.10, gray for 0.05–0.10, dark gray for 0.01–0.05, and black for <0.01).

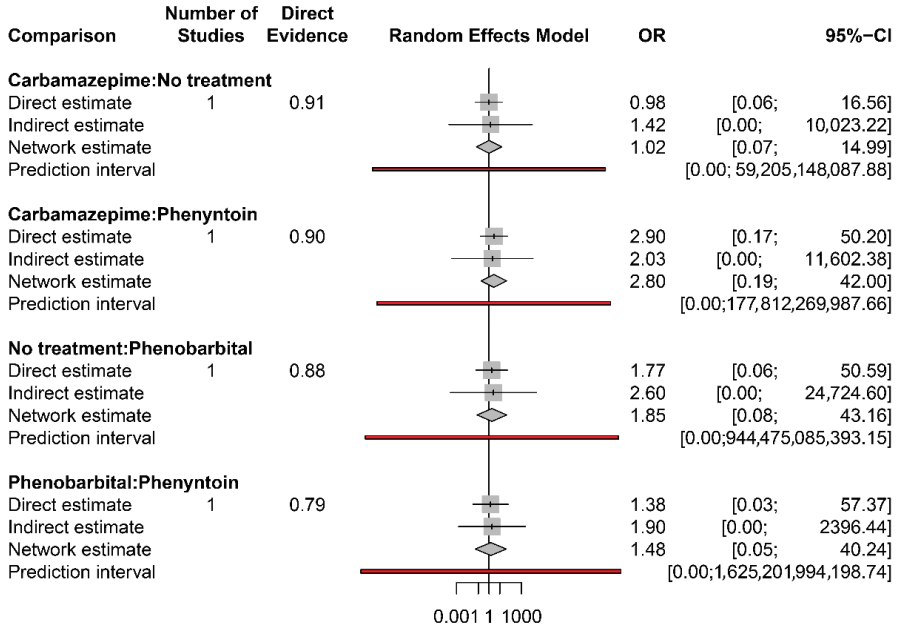

Figure A4. Forest plot for direct and indirect estimates for each pair of comparisons for late seizures, using separate indirect from direct evidence (SIDE) and back-calculation methods. Red lines represent prediction intervals.

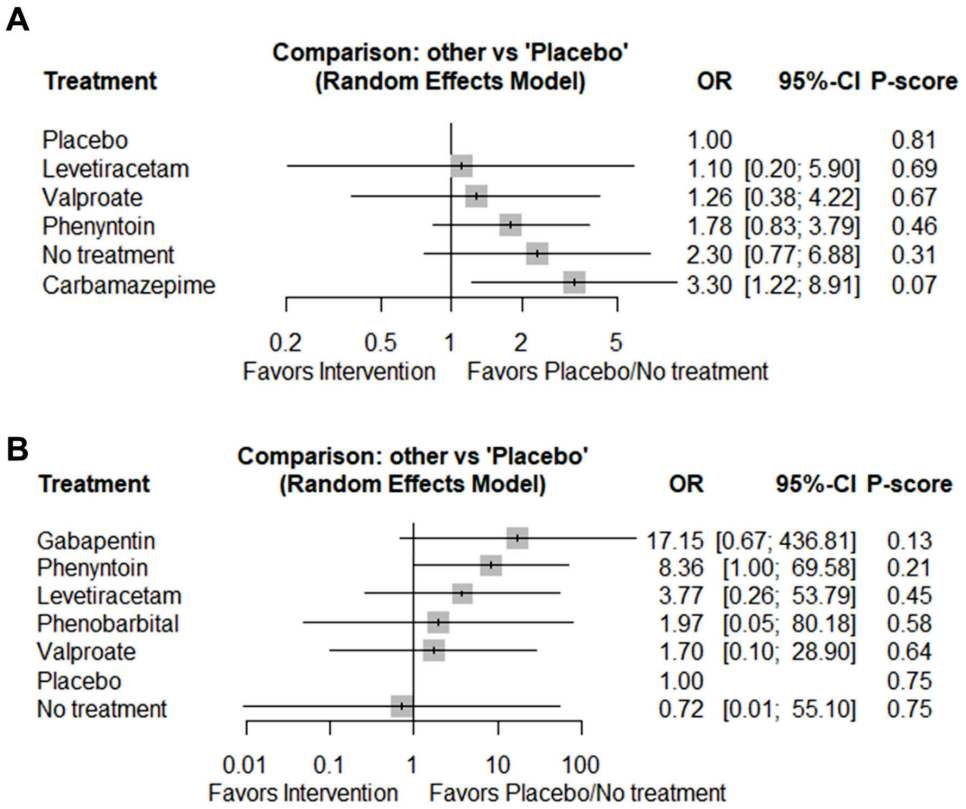

Figure A5. Forest plot of each treatment modality versus placebo for mortality (**A**) and major adverse events leading to drug discontinuation (**B**).

Table A3. League table demonstrating the relative effectiveness of each pair of comparisons for mortality. Odds ratios greater than 1 favor interventions in the column; forest plots use the conventional orientation (values < 1 favor the intervention versus placebo). Treatment modalities are highlighted using bold font.

CBZ					
3.01 (0.59; 15.43)	**LEV**	.			
1.43 (0.68; 3.00)	0.48 (0.09; 2.60)	**No treatment**			
1.85 (0.97; 3.53)	0.62 (0.14; 2.77)	1.29 (0.59; 2.85)	**PHT**		
3.30 (1.22; 8.91)	1.10 (0.20; 5.90)	2.30 (0.77; 6.88)	1.78 (0.83; 3.79)	**PBO**	
2.61 (0.84; 8.13)	0.87 (0.15; 5.10)	1.82 (0.53; 6.20)	1.41 (0.55; 3.59)	0.79 (0.24; 2.64)	**VAL**

Table A4. League table demonstrating the relative contribution of each pair of comparisons to major adverse effects. Odds ratios greater than 1 favor interventions in the column; forest plots use the conventional orientation (values < 1 favor the intervention versus placebo). Treatment modalities are highlighted using bold font.

GAB				
10.08 (0.36; 279.10)	**LEV**			
5.42 (0.25; 116.90)	0.54 (0.15; 1.90)	**PHT**		
25.36 (0.94; 681.34)	2.52 (0.45; 14.20)	4.68 (1.43; 15.27)	**PBO**	
14.46 (0.43; 481.28)	1.43 (0.17; 11.83)	2.67 (0.49; 14.45)	0.57 (0.07; 4.49)	**VAL**

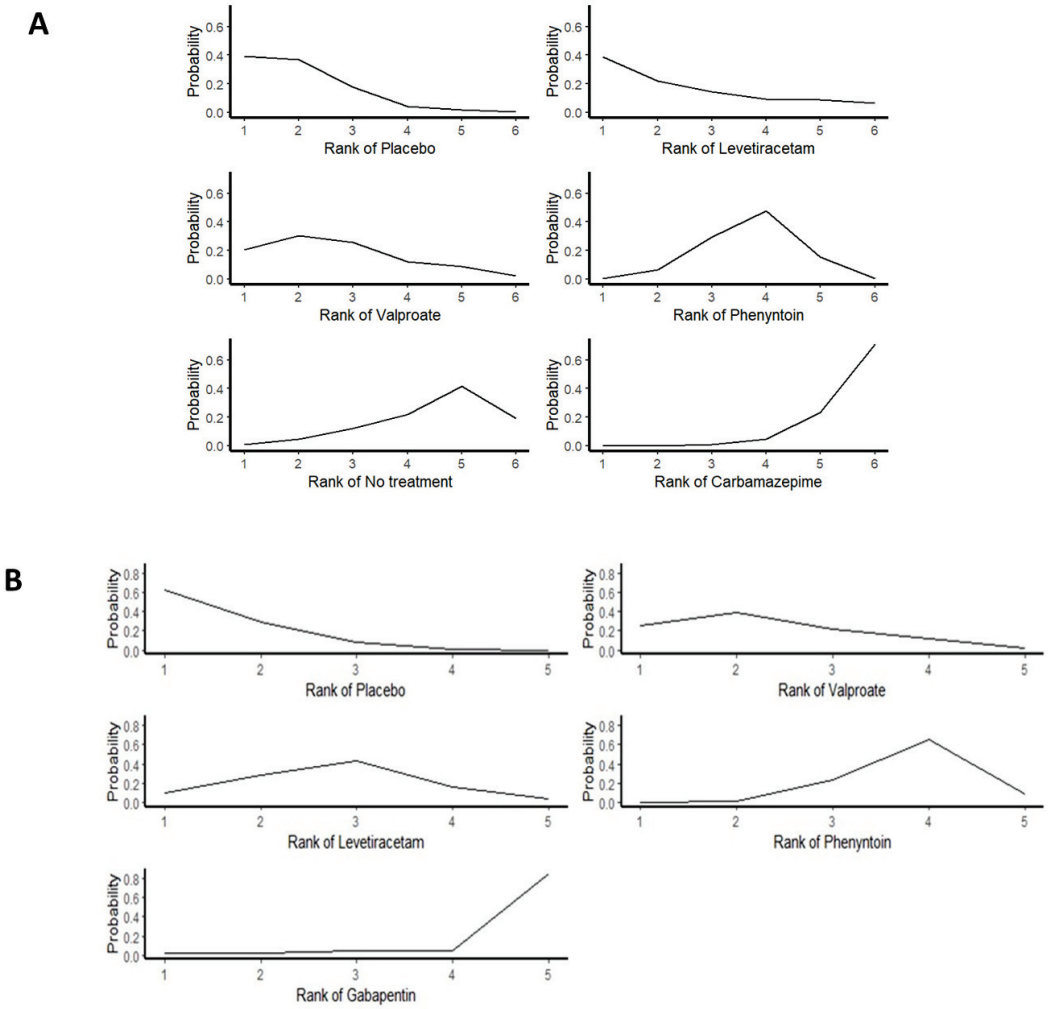

Figure A6. Rankograms demonstrating the relative ranking of each treatment modality regarding the mortality (**A**), and major adverse effects imposing drug discontinuation (**B**).

Figure A7. A traffic-light matrix plot of risk of bias assessment for each study according to the RoB-2 Cochrane Bias Tool.

Table A5. CINeMA summary tables for primary outcomes. CINeMA components are highlighted using bold font.

Comparison	N	Within-Study Bias	Reporting Bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence Rating
Carbamazepime: No treatment	1	Major concerns	Some concerns	Some concerns	Some concerns	Some concerns	Major concerns	Moderate
Carbamazepime: Phenyntoin	1	Major concerns	Some concerns	Some concerns	Some concerns	Some concerns	Major concerns	Moderate
Gabapentin: Phenyntoin	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Low
Levetiracetam: Phenyntoin	3	Some concerns	Some concerns	Some concerns	No concerns	Major concerns	Major concerns	Low
No treatment: Phenyntoin	1	Major concerns	Some concerns	Some concerns	Some concerns	Some concerns	Major concerns	Low
No treatment: Phenyntoin/Phenobarbital	1	Major concerns	Some concerns	Major concerns	Major concerns	Some concerns	Major concerns	Very low
Phenyntoin: Placebo	3	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	Major concerns	Moderate
Phenyntoin: Valproate	2	Some concerns	Some concerns	Some concerns	Major concerns	Some concerns	Major concerns	Moderate
Carbamazepime: Gabapentin	0	Major concerns	Some concerns	Some concerns	Major concerns	Major concerns	Major concerns	Very low
Carbamazepime: Levetiracetam	0	Major concerns	Some concerns	Some concerns	Major concerns	Major concerns	Major concerns	Very low
Carbamazepime: Phenyntoin/Phenobarbital	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Low
Carbamazepime: Placebo	0	Major concerns	Some concerns	Some concerns	Major concerns	Some concerns	Major concerns	Very low
Carbamazepime: Valproate	0	Major concerns	Some concerns	Some concerns	Major concerns	Some concerns	Major concerns	Very low
Gabapentin: Levetiracetam	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Moderate
Gabapentin: No treatment	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Low
Gabapentin: Phenyntoin/Phenobarbital	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Low
Gabapentin: Placebo	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Low
Gabapentin: Valporate	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Very low
Levetiracetam: No treatment	0	Major concerns	Some concerns	Some concerns	No concerns	Major concerns	Major concerns	Very low
Levetiracetam: Phenyntoin/Phenobarbital	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Low
Levetiracetam: Placebo	0	Major concerns	Some concerns	No concerns	No concerns	No concerns	Major concerns	Moderate
Levetiracetam: Valproate	0	Some concerns	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Low
No treatment: Placebo	0	Major concerns	Some concerns	Some concerns	Major concerns	Major concerns	Major concerns	Very low
No treatment: Valproate	0	Major concerns	Some concerns	Some concerns	Major concerns	Major concerns	Major concerns	Very low
Phenyntoin: : Phenyntoin/Phenobarbital	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Low
Phenyntoin/Phenobarbital: Placebo	0	Major concerns	Some concerns	Some concerns	Some concerns	No concerns	Major concerns	Moderate
Phenyntoin/Phenobarbital: Valproate	0	Major concerns	Some concerns	Some concerns	Some concerns	No concerns	Major concerns	Moderate
Placebo: Valproate	0	Some concerns	Some concerns	No concerns	Some concerns	No concerns	Major concerns	Moderate

Table A6. CINeMA summary tables for secondary outcomes. CINeMA components are highlighted using bold font.

Comparison	No	Within-Study bias	Reporting Bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence Rating
GAB:PHT	1	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Low
LEV:PHT	3	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
NT:PHE	1	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
NT:PHT	1	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
PBO:PHT	2	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	Very low
PHE:PHT	1	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
PHT:VAL	2	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Low
GAB:LEV	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
GAB:NT	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
GAB:PBO	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Very low
GAB:PHE	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
GAB:VAL	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Low
LEV:NT	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
LEV:PBO	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
LEV:PHE	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
LEV:VAL	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
NT:PBO	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
NT:VAL	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
PBO:PHE	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low
PBO:VAL	0	Some concerns	Some concerns	No concerns	Major concerns	No concerns	Major concerns	Low
PHE:VAL	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	Major concerns	Very low

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MDPI AG
Grosspeteranlage 5
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