Open and endovascular surgical techniques in oncovascular and vascular surgery

Habilitationsschrift

zur Erlangung des akademischen Grades

eines habilitierten Doktors der Medizin (Dr. med. habil.)

für das Fachgebiet Chirurgie

vorgelegt

der Medizinischen Fakultät

der Martin-Luther-Universität Halle-Wittenberg

von Dr. med. Artur Rebelo

Gutachter*in:

Prof. Dr. Michael Ghadimi, Göttingen
Prof. Dr. Jürgen Weitz, Dresden

Datum der Verteidigung: 07.05.2024

Abstract

The main goal of oncovascular surgery is to significantly reduce the risk of postoperative complications and improve patient outcomes, by combining the surgical expertise from vascular and surgical oncology surgeons. Both open surgery and endovascular surgery have their own advantages and disadvantages, and the choice of surgery depends on the specific condition being treated. The conducted research program was designed to evaluate open questions regarding patient outcomes, surgical techniques, and diagnostic methods regarding A) oncovascular and B) endovascular and open vascular surgery.

A1) The current evidence suggests that patients undergoing surgery for hilar cholangiocarcinoma with arterial resections show higher morbidity and mortality rates and shorter long-term survival when compared to standard resections. This demands new multimodal treatment strategies for these patients. A2) Concerning cervical paraganglioma, tumor volume can be used as additional information in a risk-benefit analysis and discussions with patients prior to cervical paraganglioma resection.

B1) Regarding patients with mesenteric ischemia, morbidity and in-hospital mortality are low when treating chronic mesenteric ischemia and high for acute mesenteric ischemia. B2) Patients undergoing endovascular treatment for popliteal artery aneurysms show higher rates on major amputation and loss of secondary patency when compared to open surgery. B3) On the other hand, endovascular repair should be considered as first line treatment for patients with visceral artery aneurysms in the elective and emergency setting in the light of comparable mortality and technical success and lower morbidity and length of stay when compared to open surgery. B4) Regarding the occlusive processes of the femoral artery bifurcation, thrombendarterectomy can continue to be considered the gold standard. B5) Finally, the percutaneous technique for vessel access in endovascular aortic repair is safe and can be quickly performed. Nevertheless, this technique reached no superiority in terms of minor complications when compared to cutdown access.

Dr. med. Rebelo, Artur: Open and endovascular surgical techniques in vascular and oncovascular surgery, Halle (Saale), Univ., Med. Fak., Habil., 136 Seiten, 0 Tabellen, 0 Abbildungen, 2023

Table of Contents

List of Abbreviations

AD – aggregated data

AMI – acute mesenteric ischemia

AR – arterial resection

ASA – American society of Anesthesiologists

cEVAR – cutdown endovascular aortic repair

CI – confidence interval

CMI – chronic mesenteric ischemia

COPD - chronic obstructive pulmonary disease

CRP - c-reactive protein

CT – computer tomography

ER – endovascular repair

HR – hazard ratios

IPD – individual patient data

MRI - magnetic resonance imaging

OR – odds ratio

OS – open surgery

PAA – popliteal artery aneurysms

pEVAR – percutaneous endovascular aortic repair

R0 – no residual tumor

SDHD - succinate dehydrogenase complex subunit

T/EVAR – thoracic / endovascular aortic repair

VAA – visceral artery aneurysms

1 Introduction

2.1 General Background

Cancer has remained a major cause of morbidity and mortality worldwide, and it continues to pose a significant challenge to healthcare systems globally. The treatment of cancer has seen tremendous progress over the past decade, with advancements in therapies, diagnostics, and surgical techniques. Among these advancements, oncovascular surgery stands out as a critical innovation in the treatment of cancer. This surgical concept involves the removal of tumor tissues while preserving the blood supply to vital organs. The goal of oncovascular surgery is to significantly reduce the risk of postoperative complications and improve patient outcomes, by combining the surgical expertise from vascular and surgical oncology surgeons. Despite significant advancements, oncological surgery remains challenging, with many patients requiring multiple surgeries. As such, there is a growing emphasis on developing innovative surgical techniques, diagnostic methods that are both effective and minimally invasive.

This work seeks to expand the current knowledge on oncovascular surgery, providing insights into the pertinent issues, challenges, and opportunities associated with oncovascular surgery. It sheds light on the latest techniques, best practices, and research findings in the field, showcasing the potential of oncovascular surgery. In this thesis, research regarding a meta-analysis on cholangiocarcinoma with arterial resections and a multicentric study on tumor volumetry for predicting complications on resection of paragangliomas were included. Ultimately, this research aims to provide a solid foundation for further research in this field, paving the way for more effective and innovative cancer treatment techniques.

The treatment of vascular diseases has also evolved significantly in recent decades, with the advent of both open vascular surgery and endovascular surgery techniques. While open surgery has been the traditional approach for many years, endovascular surgery has gained popularity due to its minimally invasive nature and potential for quicker recovery times. Despite these advantages, there remains an ongoing debate about which approach is superior for different types of vascular conditions. In this research project, open vascular surgery and endovascular surgery in terms of their efficacy and outcomes for the treatment of mesenteric ischemia, popliteal aneurysms, visceral artery aneurysms and femoral artery occlusion disease were compared. Furthermore, the outcome of cutdown or a percutaneous technique for the treatment of aortic aneurysms was assessed. Through systematic review and meta-analysis of the available evidence and analysis of patient outcomes, a comprehensive understanding of the strengths and weaknesses of each approach is provided, that ultimately will shed light on the optimal treatment strategy for different vascular conditions.

2.2 Oncovascular surgery

As previously stated, oncovascular surgery is specialized on the treatment of cancer that is localized in or around the blood vessels. This technique involves the removal of the cancerous tissue along with the affected blood vessels. The goal of oncovascular surgery is to remove the cancerous tissue while preserving the blood supply to the affected area. This type of surgery is typically performed by a team of surgeons, including a vascular surgeon and a surgical oncologist. The procedure can be performed using open surgery or minimally invasive techniques like laparoscopy or robotic-assisted surgery. Oncovascular surgery is commonly used to treat cancers that are in the liver, pancreas,

kidney, and other organs that are rich in blood vessels. It is also used to treat tumors that have spread to the blood vessels from other parts of the body. The success of oncovascular surgery depends on several factors, including the size and location of the tumor, the extent of the cancerous tissue, and the overall health of the patient. In some cases, additional treatments like chemotherapy or radiation therapy may be required to ensure the complete removal of the cancerous tissue. Overall, oncovascular surgery is a complex and specialized surgical technique that requires a high level of expertise and skill. However, it can be an effective treatment option for many types of cancers that involve the blood vessels.

2.2.1 Cholangiocarcinoma

Cholangiocarcinoma has an estimated incidence of 1-2 per 100,000 persons per year (1) and constitutes the second most common primary hepatic malignancy (2). The effect of systemic treatment is limited in most patients and surgery with complete removal of the tumor is the only option offering a chance of cure or at least of long-term freedom from tumor with 20-30% 5-year overall survival (3,4). Most cholangiocarcinomas arise in the bile duct bifurcation. They are commonly referred to as hilar cholangiocarcinomas or Klatskin tumors (5). Due to the proximity of vascular structures to the bile duct bifurcation, tumor invasion of the portal vein, the proper hepatic artery or the contralateral hepatic artery (i.e. a tumor arising from the left bile duct invading the right hepatic artery) occur in a relevant proportion of cases. Vascular and especially arterial resection (AR) and reconstruction during surgical removal of hilar cholangiocarcinoma is a debated issue (6). Although it is the only way of facilitating complete resection if the vessels are invaded, there are concerns of high postoperative morbidity and mortality rates following

vascular reconstruction, including hemorrhage and liver failure, which might offset the potential survival advantage gained from complete removal of the tumor. However, thanks to technical improvements in microvascular anastomoses and to a growing experience with liver transplants in many centers, the surgical approaches for hilar cholangiocarcinoma have generally become more aggressive in recent years and concurrently the number of studies assessing feasibility, safety and oncological effectiveness of AR and arterial reconstruction has been growing (7-11).

2.2.2 Cervical paraganglioma

Paragangliomas are vascularized neoplasms that derive from the neural crest and occur sporadically or due to a hereditary predisposition (12-15). They commonly occur in the cervical region (16). Carotid body tumors are paragangliomas located in the carotid bifurcation (17). Their incidence is estimated at 1/100,000 persons per year. Most of them have a benign biological behavior, but 5–16% of these tumors show malignant transformation and metastasis. Lymphatic as well as distant metastases can occur (18). The risk of metastasis, multilocular appearance and recurrences represent challenging aspects in the care of these patients (19). A definite differentiation between benign and malignant lesions can only be made by a histopathological assessment of the specimen, and resection is therefore generally recommended (20). Preoperative imaging of cervical paraganglioma allows to confirm the diagnosis, identify multifocal disease, and determine the extent of the tumor. MRI including magnetic resonance angiography is considered the non-invasive imaging modality of choice, but CT angiography is an appropriate alternative (21-23). Because of the proximity to vascular and nerval structures, surgical resection of cervical paraganglioma can be challenging. There is a

relevant risk of resection-related neurological complications, such as cranial nerve injury in 27–53.8% of patients (24-25). Based on preoperative imaging, cervical paraganglioma is commonly described using the Shamblin classification. This system stratifies tumors according to the extent of their anatomic contact with the carotid vessels in three groups: I = minimal contact to III = full encasement (26). This classification shows a good correlation with postoperative morbidity and cranial nerve injury (20). However, it remains unclear if other features, which can be assessed on preoperative imaging, such as tumor volume and tumor location, also correlate with postoperative morbidity.

2.3 Open and endovascular techniques in vascular surgery

Open surgery and endovascular surgery are two different surgical techniques used to treat a variety of medical conditions. Each technique has its own advantages and disadvantages, and the choice of surgery depends on the specific condition being treated, as well as the patient's overall health and medical history. Open surgery is a traditional surgical technique in which an incision is made in the skin, and the surgeon operates directly on the affected area. This technique is used to treat a variety of conditions, including cancer, heart disease, and trauma. Open surgery allows the surgeon to have direct access to the affected area, making it easier to remove tumors or repair damaged tissues. However, open surgery is a more invasive procedure, requiring a longer recovery time and a higher risk of complications. Endovascular surgery, on the other hand, is a minimally invasive surgical technique that involves the use of catheters and tiny instruments to access the affected area. This technique is used to treat a variety of conditions, including aneurysms, arteriosclerosis, and varicose veins. Endovascular surgery is less invasive than open surgery, with smaller

incisions and a shorter recovery time. However, endovascular surgery may not be suitable for all patients, and it may not be as effective as open surgery for certain conditions. Both open surgery and endovascular surgery have their own advantages and disadvantages, and the choice of surgery depends on the specific condition being treated. In general, open surgery is more invasive but may be more effective for certain conditions, while endovascular surgery is less invasive but may not be suitable for all patients.

2.3.1 Mesenteric ischemia

The first descriptions of mesenteric ischemia were published before 1950 (27,28). Shaw et al. performed the first open atherectomy of the superior mesenteric artery in 1958 (29). Crawford, DeBakey et al. published a report on open revascularization of the celiac trunk and superior mesenteric artery in 1962 (30). However, even nowadays mesenteric ischemia has a high mortality rate. In recent years, endovascular and hybrid approaches have been developed to reduce periprocedural morbidity and mortality of mesenteric interventions (Figure 1) (31). Chronic mesenteric ischemia (CMI) is defined as symptomatic ischemia without irreversible tissue damage caused by insufficient blood supply to the gastrointestinal tract. The most common cause is atherosclerosis of the celiac trunk, the superior mesenteric artery, or the inferior mesenteric artery (32,33). CMI is the cause of abdominal pain in only 0.1% of hospital admissions for abdominal symptoms (34). Symptoms are mostly postprandial abdominal pain (stage II), "food anxiety", rest pain (stage III) and weight loss. CMI remains an underdiagnosed disease (35). Therefore, most patients present in late stages with weight loss, chronic malnutrition, or intestinal infarction, which is then termed acute or acute on chronic

mesenteric ischemia (AMI, stage IV) (36,37). In addition, AMI can also be caused by arterial embolism and non-occlusive mesenteric ischemia. The mortality of AMI is between 30% and 65% (38). CT angiography should be performed if AMI or CMI is suspected and is also the gold standard for follow-up after open and endovascular procedures (35,39). Early diagnosis and intervention are critical to AMI. ER and OS in asymptomatic patients with CMI is rarely indicated. On the other hand, symptomatic CMI should be treated to prevent AMI, bowel infarction, and death. It is still controversial which patients should undergo open or endovascular interventions.

2.3.2 Popliteal aneuryms

Since 1994 (40) endovascular repair (ER) has been used as an alternative to "the gold standard" open repair/surgery (OR/OS) on the treatment of popliteal aneuryms (PAA). When symptomatic, PAA should undergo repair no matter its size. The risk factors associated with growth of popliteal aneurysms are >20 mm in diameter, presence of luminal thrombus, or atrial fibrillation (41). There is no unique approach for OR. It is not clear if vein or prosthetic graft and posterior or medial approach have better outcomes (42). ER represents an attractive alternative approach due to its lower invasiveness and thus presumed lower morbidity and length of hospital stay (43). Several meta-analyses have been performed to evaluate the outcomes of OR and ER in the treatment of PAA (44,45). Moreover, studies reporting on the use of fibrinolysis in the acute treatment of PAA have been published (46). Only one randomized controlled trial comparing OR with ER exists (47). In Germany (48) and the registries such as the German POPART registry or the Swedvasc (49) and Vascunet collaboration (50) represent a unique approach, making it possible to analyze the modern treatment of PAA. Recently, a meta-analysis

also addressed the natural history of popliteal artery aneurysms (51). However, no meta-analyses on the acute treatment of PAA with OR and ER have been published.

2.3.3 Aortic pathologies

Treatment of aortic pathologies changed fundamentally during the last two decades: endovascular treatments and especially the use of stentgrafts have become more and more frequent. Treatment of the abdominal aorta is commonly referred to as EVAR, and that of the thoracic aorta as thoracic endovascular aortic repair TEVAR (52). With the establishment of T/EVAR, during which stentgrafts are deployed minimally invasive through an arterial access vessel, risky OR can mostly be circumvented (53). Potential benefits of T/EVAR versus OR include reduced perioperative and 1-year mortality, shortening of hospital stay and fewer periprocedural complications (54-56).

To establish large-bore vessel access in T/EVAR, either cutdown or a percutaneous technique may be performed. cEVAR consists of a skin incision and surgical preparation of the access vessel. In percutaneous pEVAR, the access vessel is punctured through the skin. After puncture, a suture mediated closure device is used to prepare the sutures for closure of the puncture site (57,58).

Both access techniques have been compared to a limited extent regarding different parameters. A meta-analysis from 2017 comparing both techniques analyzed two randomized controlled trials with 181 patients and suggested equivalence of pEVAR and cEVAR. Analyzed parameters included bleeding complications, wound infections, and major vessel complications (59). Especially access-related major complications like thrombosis and access-vessel injury were rarely observed in either technique throughout different studies (60,61).

Current evidence clearly shows a reduction of operation time in pEVAR. Technical success rates of more than 90% imply good feasibility of the percutaneous technique (62-66). Achieving high success rates presupposes preoperative evaluation of the access vessel, usually the common femoral artery. Particularly diameter, anterior calcification and possible kinking of the vessel are relevant (67,68). The impact of the calcification level remains uncertain. Starnes et al. postulate safe feasibility of pEVAR even in calcified vessels (69), other studies suggest different results (70,71). Furthermore, routine ultrasound guidance for pEVAR access seems to reduce incidence of access-site complications, especially hematomas and injuries of the femoral nerve (72,73).

Complications of both techniques frequently have been recorded only for short term outcomes. A randomized controlled trial from 2019 showed no superiority for either approach with wound infection rates between 0% or 1.5% but a reduction of postoperative pain after pEVAR (74). Other studies also included access-related complications, however only until one month after surgery or without comparing them to cEVAR (62-66,75).

2.3.4 Visceral aneurysms

Visceral arterial aneurysms (VAA) are rare (prevalence 1-2%). Most VAA originate from the splenic artery (60%), followed by the hepatic artery (20–50%). An origin from the superior mesenteric artery (6%), the celiac trunk (4%) or other, smaller visceral arteries is considerably less common. (76-78) The natural history of VAA is not entirely clear, and they are mostly asymptomatic.(79) The incidental detection of VAA has increased with evolving and more frequently used imaging modalities. (80) Risk factors associated with rupture are pancreatitis, rapid growth, size >2 cm, and pregnancy. The mortality

associated with splenic artery aneurysm rupture has been reported at around 30%. (81) In pregnancy, these rates are higher, with maternal mortality of up to 75% and fetal mortality of up to 95%. (82-85) Nowadays, conservative therapy, endovascular, and open or laparoscopic surgery are the treatment options for these patients. During the last decade, endovascular repair of VAA has been increasingly done with several types of vascular implants. (86-91)

2.3.5 Occlusive processes of the femoral artery bifurcation

Two modalities are available for the revascularization of occlusive processes in the region of the femoral artery bifurcation in the setting of peripheral arterial disease. To date, OS has represented the gold standard (92-98). However, ER are increasingly being proposed as alternative treatment forms (99).

OS refers to the surgical removal of atherosclerotic plaques. It has high technical success rates of almost 100% with very good short- and long-term outcomes (97). However, OS carries a relevant risk of morbidity of up to 20%.This includes local complications such as impaired wound healing, hematomas, and hemorrhage. The post- operative mortality rate is 1–2 % (92-98).

ER is performed via a percutaneous access. Removal of the occlusive process is carried out using transluminal angioplasty and, where necessary, stent implantation. The fact that the femoral artery bifurcation is in the segment of motion poses problems such as mechanical alterations to the stent. In addition, there is the risk of covering outflow vessels, and thus the risk of obstruction of important collateral circulation, as well as renewed occlusive processes because of neointimal hyperplasia. Subsequent interventions may also be hampered by stent material (99-106).

3 Research questions and objectives

The conducted research program was designed to evaluate open questions regarding patient outcomes and surgical techniques and diagnostic methods regarding oncovascular, endovascular and open vascular surgery. The addressed research questions are presented in the following sections.

3.1 Oncovascular surgery

3.1.1 Evaluation of the patient outcomes

I. What are the outcomes of patients undergoing arterial resection when compared to patients undergoing standard resection for the treatment of cholangiocarcinoma?

3.1.2 Evaluation of surgical techniques and diagnostic methods

II. Is there an association between tumor volume and tumor location determined on preoperative imaging and postoperative outcomes for the resection of cervical paraganglioma?

3.2 Open and endovascular surgery

3.2.1 Evaluation of patient outcomes

III. What are the outcomes of open surgical, endovascular, and hybrid interventions in the treatment of acute and chronic mesenteric ischemia?

IV. What are the outcomes of patients undergoing OS or ER for the emergency treatment of PAA?

V. What are the outcomes of patients undergoing OS or ER for the treatment of VAA?

VI. What are the outcomes of patients undergoing OS or ER for the treatment of femoral artery occlusion disease?

3.2.2 Evaluation of surgical techniques and diagnostic methods

VII. What are the outcomes of vessel access during T/EVAR regarding in-hospital and post-hospital complications?

4 Methods

4.1 Meta-analysis

Meta-analysis is a statistical technique that involves combining data from multiple studies to draw a more accurate conclusion. It is commonly used in scientific research to evaluate the effectiveness of various treatments or interventions. The process of conducting a meta-analysis involves identifying relevant studies, extracting data from those studies,

and analyzing the data using statistical methods. The goal is to identify patterns or trends across the studies and draw a conclusion that is based on the collective evidence. Meta-analysis is especially useful when individual studies produce conflicting results, as it provides a way to synthesize the available evidence and arrive at a more definitive conclusion. It can also help to identify areas where further research is needed. Overall, meta-analysis is a powerful tool for researchers and practitioners alike, as it provides a way to make more informed decisions based on the best available evidence.

In this research program we conducted meta-analysis to address the research questions I, IV, V and VI.

The literature search and data analysis were conducted in accordance with the PRISMA or MOOSE guidelines (107,108). The studies were prospectively registered in the PROSPERO database (109).

Databases were searched through their respective online search engines. Furthermore, the reference lists of the included studies were manually searched to find relevant articles. Abstracts and full-text reviews were evaluated independently in an unblinded standardized manner by two authors to assess eligibility for inclusion. Disagreements between reviewers was resolved by consensus; if no agreement could be reached, a third author decided if the respective study was included.

Risk of bias was assessed using the risk of bias in non-randomized studies of interventions tool or the Newcastle-Ottawa Scale (110,111)

A more detailed description of the used methods for each research question are described in the ***original publications 1, 4, 5, 7 and 8.***

4.2 Retrospective observational studies

Observational retrospective studies are a type of observational study that involves analyzing data that has already been collected in the past. These studies are often used in medical research to explore the relationship between various risk factors and health outcomes. In a retrospective study, researchers identify a group of individuals who have already experienced an outcome of interest (such as a particular disease) and then look back in time to see if there were any common factors or exposures that may have contributed to the outcome. This can involve analyzing medical records, surveys, or other forms of data that were collected at an earlier point in time. One major advantage of retrospective studies is that they can be conducted more quickly and at lower cost than prospective studies, which involve following a group of individuals forward in time. Retrospective studies can also provide a wealth of data on a particular population, as they can draw on existing data sources such as medical records or administrative data. However, retrospective studies also have some limitations. Because the data has already been collected, researchers cannot control the types of data that are available, which may limit the scope of the study. Retrospective studies may also be subject to biases, such as recall bias (where participants may not remember certain information accurately) or selection bias (where the group of individuals studied may not be representative of the broader population). Despite these limitations, observational retrospective studies can provide valuable insights into the relationships between different risk factors and health outcomes and can help to guide future research and interventions.

In this research program we conducted meta-analysis to address the research questions II, III, IV, VI and VII.

Demographic and clinical data as well as follow-up data were collected retrospectively from patient charts, hospital information systems, and picture archiving and communication systems (PACS). The studies were approved by the responsible ethics committees.

A more detailed description of the used methods for each research question are described in the ***original publications 2, 3, 4, 6 and 8.***

5 Results

In this section the main results of the research program are presented. A more detailed description of the results is available on the ***"List of publications for this thesis"*** section.

I. What are the outcomes of patients undergoing arterial resection when compared to patients undergoing standard resection for the treatment of cholangiocarcinoma?

To address this research question, we performed a meta-analysis ***(original publication 1)***. Concerning in-hospital mortality, the meta-analysis showed higher mortality rates in the AR group compared to the control group (6.8% vs 3.3%, OR 2.65, 95% CI [1.27; 5.32], p=0.009). In the meta-analysis regarding morbidity, higher rates were observed in the AR group (55% vs 46%, OR 1.44, 95% CI [0.67; 3.09], p=0.003). In the meta-analysis regarding morbidity defined as Clavien-Dindo classification > 3, statically significant higher rates could be verified in the AR group (52% vs 47%, OR 1.44, 95% CI [1.02; 1.75], p=0.04). Six studies reported on vascular complications, with lower rates in the control group (13% vs 5%, OR 3.53, 95% CI [2.26; 5.53, p<0.00001). Liver failure rates were higher in the AR group, but the difference was not statically significant (26% vs

16%, OR 2.50, 95% CI [0.95; 6.54, p=0.06). Postoperative bleeding was more frequent in the AR group (4% vs 2%, OR 2.19, 95% CI [1.06; 4.52, p=0.03). Concerning actuarial survival, 1-year, 3-year and 5-year survival rates were lower in the AR group compared to the control group, respectively (54% vs 69%, OR 0.55, 95% CI [0.34; 0.91 p=0.02), (34% vs 38%, OR 0.74, 95% CI [0.55; 0.98, p=0.03) , (18% vs 29%, OR 0.54, 95% CI [0.39; 0.75, p=0.0002). R0 resection rates were slightly higher in the control group, but the difference was not statistically significant (68% vs 75%, OR 0.70, 95% CI [0.46; 1.07, p=0.10).

II. Is there an association between tumor volume and tumor location determined on preoperative imaging and postoperative outcomes for the resection of cervical paraganglioma?

To analyse this research question one multicentric observational study was performed ***(original publication 2)***. The study included 47 patients (mean age 49 years, range 17–77 years, 63.8% female). All patients had carotid body paraganglioma. Three patients (6.4%) showed preoperative symptoms, such as local pain, dysphagia, and hoarseness. The Shamblin classification was ascertained in 97.9% of patients (n = 46): most patients (n = 19, 40.4%) had a type I tumor followed by type III (n = 14, 29.8%) and type II (n = 13, 27.6%). Five patients (10.6%) underwent successful preoperative embolization. In one patient (2.1%), preoperative angiography with unsuccessful embolization was performed; the patient suffered from an intraprocedural stroke. Six (12.7%) patients had a prior cervical surgical intervention. In five (10.6%) of these patients, this was a prior paraganglioma resection. In one patient, only cervical lymph nodes had been removed before without a resection of the paraganglioma. In all patients, a complete tumor

resection was technically successful. Two tumors showed criteria of malignancy on histopathology (4.3%). In a seventeen-year-old patient, systemic metastasis was observed; this patient underwent postoperative chemoradiotherapy because of pulmonary and bone metastases. Two patients had bilateral tumors (4.3%), and in one patient with a family history of paragangliomas, an SDHD-gene mutation was found. In 17% (n = 8) of patients, surgery was performed in an interdisciplinary team. The mean procedural time was 132 min. In four patients (8.5%), a vascular reconstruction of the internal carotid artery was necessary. Three patients (6.4%) received an alloplastic carotid interposition graft and one patient an autologous interposition graft. In one patient with preoperative embolization and endovascular occlusion of the internal carotid artery, a resection of the internal carotid artery with reconstruction of the external carotid artery was performed.

Thirty-day mortality was 0%. The overall perioperative complication rate was 27.6% (n = 13). Fifteen cranial nerve lesions in eleven patients (23.4%) were observed: four hypoglossal nerve, seven vagal nerve, three glossopharyngeal nerve and one facial nerve lesion. Three patients (6.4%) suffered from postoperative Horner syndrome. In eight patients, the cranial nerve lesion was permanent at 30-day follow-up. Three patients with a perioperative cranial nerve lesion were lost to follow-up. Thirty-day stroke incidence was 4.2% (n = 2). One patient had an infiltrative tumor requiring an autologous interposition graft; in addition, internal carotid artery stenting at the skull base was necessary. Postoperatively, the patient developed hemiparesis and aphasia. The second patient had an uneventful intraoperative course and developed immediate postoperative sensory aphasia. Both patients still showed neurological symptoms at 30-day follow-up.

Duplex imaging was performed in all patients. Among the 47 included patients, preoperative MRI (63.8%, n = 30) and/or CT (55.3%, n = 26) was conducted. The volume measurement was successful in 78.8% (n = 37/47): eight CT and twenty-nine MRI. The

mean horizontal tumor extension was 2.9 cm (range 1.1–5.5 cm), and the mean vertical extension was 2.2 cm (range 0.8–3.9 cm). The degree of encasement of the carotid vessels (Shamblin classification) showed no significant correlation with cranial nerve injury (p = 0.44) but did so with overall postoperative morbidity (cranial nerve injury, Horner syndrome, and stroke) (p = 0.037). There was a significant difference in tumor volume, as ascertained by volumetry, between patients with and without overall postoperative complications. Patients without complications had a mean tumor volume of 6.92 cm3, while patients with complications had one of 15.89 cm3 (p = 0.035). The mean tumor volume was 7.64 cm3 in patients with no cranial nerve injury and 16.28 cm3 in patients with cranial nerve injury (p = 0.05). Most tumors projected to the fourth cervical vertebra (n = 18; 38.3%) and were located at the lower third of the vertebra. There was no significant correlation between the tumor location in relation to the vertebra and the occurrence of cranial nerve lesions (p = 0.42). The degree of encasement of the carotid vessels showed no significant correlation with cranial nerve injury (p = 0.44).

III. What are the outcomes of open surgical, endovascular, and hybrid interventions in the treatment of acute and chronic mesenteric ischemia?

To answer this research question a retrospective observational study ***(original publication 3)*** was conducted including a total of 64 patients, 20 with CMI and 44 with AMI, underwent open, endovascular or hybrid surgery. In the CMI and AMI groups, 60% and 64.6% of patients were male, respectively. Mean age was 66.9 and 70.7 years in the CMI and AMI groups, respectively. Patients in the CMI group had higher prevalence of obesity and COPD and lower prevalence of diabetes mellitus, cardiac comorbidities, renal insufficiency, and history of malignancy. All patients were classified as ASA score 3 or

4. Patients in the AMI group were classified as higher ASA score when compared to the CMI group. There were no statistically significant differences between both groups. In the AMI group, 27.3% had an embolic and 72.7% a thrombotic occlusion. Bowel resection was performed in 45.5% of the patients with AMI (29.5% small intestine, 2.3% colon and 13.6% both). Second-look laparotomy was performed in 27.3% of the patients. Regarding the CMI group, 25% of the patients were classified as stadium II and 75% as stadium III. The most often revascularized artery was the superior mesenteric artery in both groups. On the CMI group, all patients underwent revascularization. On the AMI group, 15.9% of the patients underwent bowel resection alone. In the CMI group only one patient underwent open surgery, 19 received endovascular treatment. 80% of the patients received treatment for stenosis/occlusion of the superior mesenteric artery and 20% for stenosis/occlusion of the celiac trunk. In the AMI group, of a total of 44 patients, 27 underwent open surgery and 17 endovascular treatments. The superior mesenteric artery was treated in 52.3 % of the patients, TC in 13.6% and both in 23.5% of the patients. Regarding the preoperative laboratory values, leukocytosis and elevated lactate were more frequent in the AMI group when compared to the CMI group (10.95 (± 1.69) Gpt/l vs 18.3 (±1.9) Gpt/l, p= 0.011 and 1.45 (±0.27) mmol/l vs 4.42 (±0.79) mmol/l, p=0.016). No statistically significant differences in CRP levels were observed between groups. Concerning in-hospital mortality, no CMI patient died. In contrast, a mortality rate of 29.5%was observed in the AMI group, with no differences regarding endovascular and open surgery (29.6% vs 29.4% mortality). Severe morbidity (Dindo-Clavien $\geq$3) was also significantly more frequent in the AMI group when compared to the CMI group (77.3% vs 20%, p<0.001). Endovascular surgery was associated with fewer postoperative complications when compared to open surgery (64.7% vs 85.2 %, p <0.001). The length of intensive care stay, and hospital stay were different between the CMI and AMI groups

(0.5 (±0.45) vs 7.2 (±1.9) days, p<0.001 and 5.8 (±1.2) vs 22.7 (±3.3), p=0.003). The ASA classification was found to be associated with postoperative mortality in the AMI group. Patients who died had a longer intensive care stay (10 (±12.9) vs 6 (±12) days, p=0.05), and more often bowel resections (61.5% vs 38.7%, p=0.14) than those who survived. Severe postoperative morbidity (Dindo-Clavien ≥3) was associated with bowel resections (55.8% vs 10%, p=0.065) and inversely associated with second-look laparotomy (20.5% vs 50%, p=0.066).

IV. What are the outcomes of patients undergoing OS or ER for the emergency treatment of PAA?

Regarding this topic we performed a meta-analysis and a retrospective observational study analysis ***(original publication 4)***. In the meta-analysis, among the 354 articles, one retrospective study and one registry from two countries were included in the meta-analysis. Our retrospective patient collective of 26 patients was also included. Publication year varied from 2014 to 2021. Inclusion period varied from 2005 to 2021. Within these 2 studies and our patient collective, a total of 199 patients underwent emergent surgery (39 ER and 160 OR) and 543 an elective procedure (102 ER and 441 OR). In the risk of bias assessment, no study was classified as low risk. Median age range was 68 to 86 years and 97% of the patients were male. There were no relevant differences concerning comorbidities between the groups. Concerning major amputation (30 days), our meta-analysis showed lower rates (30 days) in the elective group (OR 6.64, 95% CI [2.25; 19.62], p<0.05), both for the ER subgroup (OR 12.1, 95% CI [2.35; 62.18], p<0.05) and OR subgroup (OR 4.16, 95% CI [0.98; 17.66], p<0.05). Major amputation (30 days) rates in emergency treatment were higher in the ER group when compared to the OR group.

(OR 5.46, 95% CI [1.65; 18], p<0.05). In all included studies, mortality was higher in the emergency group (OR 9.72, 95% CI [2.21; 42.71], p<0.05, ER subgroup OR 15.52, 95% CI [2.13; 113.15], p<0.05), OR subgroup OR 5.41 95% CI [0.59; 49.87], p<0.05). Our analysis reported slightly lower mortality rates in the OR group compared to the ER group on emergency surgery (OR 6.20, 95% CI [1.15; 33.60], p=0.03). Also regarding 1 year amputation rates in both subgroups, ER (OR 12.46, 95% CI [1.87; 82.88], p=0.009) and OR (OR 2.26, 95% CI [0.93; 5.48], p=0.07), higher rates were reported in the emergency group (OR 3.07, 95% CI [1.37; 6.86], p=0.006). Higher rates were observed on the ER group compared to OR in emergency surgery (OR 3.61, 95% CI [1.18; 11.09], p=0.02). A higher loss of primary patency (1 year) was observed for the emergency compared to the elective groups (OR 2.26, 95% CI [1.52; 3.38], p<0.05) and in the ER (OR 3.13, 95% CI [1.45; 6.75], p<0.05) and OR (OR 2.01, 95% CI [1.26; 3.21], p<0.05) subgroups. When comparing ER and OR in emergency surgery, no statically significant result was obtained (OR 3.38, 95% CI [0.87; 13.09], p=0.08). Loss of secondary patency (1 year) was not statistically different between both groups (OR 1.58, 95% CI [0.63; 3.95], p=0.33) and on subgroup analysis (OR 2.33, 95% CI [0.45; 12.16], p=0.31; OR 1.33, 95% CI [0.74; 2.39], p=0.34)). In the meta-analysis from ER vs OR in emergency treatment, higher rates of loss of secondary patency (1 year) were observed in the ER group (OR 7.08, 95% CI [3.10; 16.20], p<0.05).

V. What are the outcomes of patients undergoing OS or ER for the treatment of VAA?

To address this research question a meta-analysis and a retrospective observational study were performed ***(original publications 5 and 6)***. In the meta-analysis 25 cohort studies

from ten countries published between 2004 and 2022 were included in the meta-analysis (table 1).[22-46] The enrolment period of these studies ranged from 1975 to 2020. 4,447 patients (2,469 patients in the OS group and 1,978 in the ER group) were included. Regarding 1-year mortality, no meta-analysis could be performed as all three studies reporting on this outcome did not report any mortality in this period. Regarding in-hospital and 30-day mortality, slightly lower rates were observed in the ER group when compared to the OR group (1.8% vs 2.1%, OR 0.77, 95% CI [0.51; 1.17], p=0.23). ER had lower mortality compared to OS in three VAA location subgroups (GDA/PDA, HA, and SA: 0% vs 7%, OR 0.07 95% CI [0.01; 10.81], p=0.03; 0% vs 26%, OR 0.18 95% CI [0.02; 1.62], p=0.13; 2.3% vs 3.2%, OR 0.6 95% CI [0.21; 1.69], p=0.33). For VAA originating from the RA, higher mortality rates were observed for ER compared to OS (1.7% vs 0.9%, OR 1.72, 95% CI [0.93; 3.17], p=0.08). In the subgroup analysis of rupture vs. no rupture, mortality was only observed in one study in the no rupture subgroup. In the rupture subgroup lower mortality rates were observed in the ER group when compared to the OR group (4.1% vs 31 %, OR 0.43 95% CI [0.13; 1.43], p=0.17) . Regarding morbidity (defined as Clavien-Dindo grade $\geq$ 3), lower rates were observed in the ER group (5.6% vs 8.4%, OR 0.61 95% CI [0.21; 1.77], p=0.02). Technical success rates were comparable between both groups (97% vs 98%, OR 0.50 95% CI [0.21; 1.16], p=0.11). Length of stay was shorter in the ER group (mean difference -4.25 days, 95% CI [-5.52; -2.98], p<0.00001). 1-year reintervention rates were higher in the ER group (9% vs 5%, OR 1.55 95% CI [0.58; 4.12], p=0.38).

In the observational study, from 2014 to 2022, twelve patients with VAA, eleven females and one male, were treated at the University Hospital Halle (Saale). The median age was 59 years (range 40 to 87 years). Only one patient was male, and all were diagnosed by a CT-scan. There were eight patients with an aneurysm of the splenic artery, two patients

with aneurysms of the superior mesenteric artery, one patient with an aneurysm of the HA and one patient with an aneurysm of the celiac trunk. Only one patient was symptomatic and presented with signs of bleeding. All patients received a contrast-enhanced CT-scan. The median aneurysm diameter was 2 cm (range 1.5 cm to 5 cm) for all aneurysms, 3.75 cm for aneurysms of the superior mesenteric artery, 2 cm for aneurysms of the splenic artery and for aneurysms of the celiac trunk and 1.5 for the aneurysm of the hepatic artery. Six aneurysms of the splenic artery, one aneurysm of the celiac trunk and one aneurysm of the hepatic artery were treated with ER (eight patients). Seven patients were treated with covered stents and one with coiling embolization. In total, eight covered stents were implanted. Two patients with splenic artery aneurysms and two patients with superior mesenteric artery aneurysms underwent OS. No allogeneic grafts were required. Three patients needed direct suture only and one a vein graft. There was no in-hospital mortality and no major postoperative complications (Clavien-Dindo grade ≥3). Technical success was achieved in all patients. The median postoperative stay was 4 days for all procedures and significantly longer after OS when compared to ER (7 days vs 3 days).

VI. What are the outcomes of patients undergoing OS or ER for the treatment of femoral artery occlusion disease?

We performed a meta-analysis with AD and IPD to access this question ***(original publication 7)***. The literature search identified 671 studies, 42 of which met the inclusion criteria and were included in the meta- analysis. The meta-analysis of IPD and AD revealed no significant difference in primary patency following OS and ER at the 6-month, 12-month, and 5-year time points. For the time point at 12 months post

intervention, data from 13 studies were available. Here, as for the 6-month, 2-, 3-, and 5-year time points, higher freedom from interventions was seen for OS compared to ER. At 6- and 12-months post intervention, no significant differences were seen in secondary patency rates, with patency rates of 87–93% for ER and 97–100% for OS. The same was true at the 2-, 3-, and 5-year time points post intervention, whereby no data were available for secondary patency at 3 years. The analysis on the endpoint of limb preservation was carried out using AD for the 12-month, 1-, 2-, 3-, and 5-year time points post intervention. At 12 months, limb preservation rates of 97% for OS and 95% for ER were seen. No differences were seen at 2-, 3-, and 5-years post intervention, with values of 95–96% for OS and 97–100% for ER. The meta-analysis of the two RCTs with AD and IPD found a weighted mean difference in the duration of inpatient hospital stay of 4.2 days (95% confidence interval [CI]: [2.5; 6.0]) in favor of ER. In the meta- analysis of IPD and AD, a mean length of stay of 2.5 days (95% CI: [1.45; 3.6]) was seen for ER and 6.4 days (95% CI: [4.0; 8.8]) for OS. The meta-analysis of AD and IPD found a complication rate of 16% (95% CI: [12; 20]) following OS and 9% (95% CI: [5; 15]) following ER. A meta-analysis of AD and IPD revealed a cumulative perioperative mortality rate of 2% for both procedures (OS: 95% CI: [2; 2], ER: 95% CI: [1; 2]). The meta-analysis of AD and IPD found a need for-revision frequency of 5% (95% CI: [3; 10]) for ER and 6% (95% CI: [4; 10]) for OS. Univariate Cox regression revealed an association between overall survival following TEA and age, Rutherford classification, length of lesion, ASA score, renal failure, and cardiac comorbidities. A multivariable analysis was carried out with these variables; all factors were negatively associated with overall survival. In the meta-analysis of AD and IPD, an overall survival after OS of 80–96% was seen for the 6-month, 12-month, 2-year, and 3-year time points. Overall survival at 5 years was 70%.

For ER, the meta-analysis yielded a cumulative overall survival of 80–93% for the 12-month, 2-year, and 3-year post intervention time points.

VII. What are the outcomes of vessel access during T/EVAR regarding in-hospital and post-hospital minor-complications?

Concerning this research question, we conducted a retrospective observational study ***(original publication 8)***. Indications for T/EVAR included abdominal, thoracic and thoracoabdominal aortic aneurysms as well as penetrating aortic ulcers and aortic dissections. Emergency indication for surgery made up a remarkable part in both groups (pEVAR: 22,6%, cEVAR: 16%). However, no significant correlation between emergent procedures and complications could be observed in a subgroup analysis. Patients receiving pEVAR got local anesthesia in 64.5% of cases compared to 25% of patients in the cEVAR-group (p=<0.01). After cEVAR, a significantly more frequent use of local hemostyptic agents could be observed. Mean duration of surgery differed by 24.7 minutes in favor of pEVAR (79.7 versus 104.4 minutes, p=0.03). Regarding minor complications until postoperative hospital discharge no significant overall difference could be observed between both techniques. The overall incidence of complications was at a similar level (11,4% versus 9%, p=0,78). Only conservatively treatable bleedings occurred significantly more often after pEVAR (6,8% versus <1%, p=0,02). Likewise, complications recorded during follow-up had a similar incidence (10% versus 13,7%, p=0,77) with no significant difference in any complication. Regarding secondary endpoints, subjective pain levels were different among the two groups with mean values of 0,9 (pEVAR) and 1,3 (cEVAR) (p=0,02). Furthermore, hematomas needing invasive

revision occurred significantly more often in the pEVAR-group (pEVAR: 4,5%, cEVAR: 1%, p=0,03).

6 Discussion and Outlook

6.1 Oncovascular surgery

Oncovascular surgery is a highly specialized surgical approach that can be used to treat certain types of cancer. The surgery involves the removal of cancerous tumors located near major blood vessels, which can be challenging due to the potential for damage to the vessels. Although the surgery is complex and carries a high risk of complications, it can be a lifesaving treatment option for some patients. In this research project we addressed two research questions on this topic, one regarding cholangiocarcinoma and one regarding cervical paraganglioma.

Firstly, we addressed the impact of arterial resection in surgery for cholangiocarcinoma by performing a meta-analysis on the topic ***(original publication 1)***. Most patients with perihilar cholangiocarcinoma present with unresectable disease and have a poor survival. Adjuvant chemotherapy provides significant improvement in overall survival with any adjuvant therapy compared with surgery only (HR 0.74; 95% CI, 0.67 to 0.83; P < 0.001) (112). Nevertheless, sensitivity and response to chemotherapy are generally rather poor. In most patients, liver transplantation is not a viable option due to the highly selective criteria. Therefore, complete surgical resection offers the only chance of cure or at least longer-term survival. In a previous meta-analysis on the topic published in 2013, resection of the hepatic artery in surgery for cholangiocarcinoma was shown to have higher morbidity and mortality rates than operations without arterial resection (113). The authors

concluded that arterial resection has no proven benefit. Since the publication of the mentioned meta-analysis, several larger studies on the topic have been published, which was the motivation for us to conduct the present systematic review with meta-analysis. In contrast to the previous study, we only performed an analysis on arterial resections and only included studies reporting exclusively on cholangiocarcinoma. We also provide an extended analysis on multiple outcomes specifically regarding arterial resection. Furthermore, only studies with a control group were included. Our results mostly corroborate those of the previous meta-analysis. Morbidity and mortality rates, although deemed acceptable in absolute terms, were shown to be substantially higher for AR while AR did not result in a higher probability of microscopically complete resection and long-term survival was shorter. Given the non-randomized design of all included studies, which implies a considerable selection bias, these findings do not necessarily mean that AR is detrimental to long-term survival in patients which would otherwise not be resected at all but only receive palliative treatment. To provide a valid information on the value of AR in such patients, a randomized controlled trial would be necessary. It needs to be noted that in the included studies, there was no clear differentiation if AR was planned a priori or performed due to intraoperative injury of the hepatic artery. An indication for the latter could be that histological arterial invasion was shown in only 28% of patients in the AR group in the studies where it was reported (114,115).

Neoadjuvant chemotherapy might improve resectability and outcomes for patients with locally advanced cholangiocarcinoma and several clinical trials are currently evaluating its role for the treatment of cholangiocarcinoma However, results will be available only in several years from now. In our analysis, only the study by Schimizzi et al. (116) reported on neoadjuvant chemotherapy with a higher proportion of patients who underwent neoadjuvant chemotherapy in the AR group. Interestingly, a higher median

survival was observed in the AR group when compared to patients who underwent combined arterial and venous resection or venous resection alone (33, 21 and 24 months, respectively).

In addition to neoadjuvant or perioperative chemotherapy alone, chemotherapy combined with transplantation may be an alternative for patients with arterial invasion. According to the guidelines of the British Society of Gastroenterology, a liver transplantation may be considered in highly selected patients in specialized centers after neoadjuvant chemotherapy (117). Similarly, the guidelines of the European Association for the Study of the Liver (EASL) state that in patients with neoadjuvant therapy concepts, liver transplantation may be considered (118). In a study involving patients from 10 US hospitals that compared transplantation with resection for hilar cholangiocarcinoma, among all patients who underwent curative-intent surgery, transplantation was associated with improved 5-year survival (64% vs 18%). Of note, many of the transplant cases in the study were relatively early stage cholangiocarcinomas, and many of them were cases of sclerosing cholangitis, making a direct comparison to the patient collective in our meta-analysis not possible (119). A meta-analysis from 2012, which included 14 studies, addressed the efficacy and safety of liver transplantation in patients with cholangiocarcinoma. Neoadjuvant therapies provided better outcomes with ORs for 1-, 3- and 5-year pooled survival of 0.83 (95% CI = 0.57-0.98), 0.57 (95% CI = 0.18-0.92) and 0.65 (95% CI = 0.40-0.87) (120). Evidence from non-randomized studies shows higher morbidity and mortality rates and shorter long-term survival in patients with cholangiocarcinoma undergoing AR. However, the results are prone to selection bias, and only randomized trials comparing AR with and without neoadjuvant therapy and palliative treatment in patients with cholangiocarcinoma and arterial invasion might reveal a possible benefit of arterial resection.

Concerning cervical paraganglioma, we addressed the association of tumor volumetry with postoperative outcomes ***(original publication 2)***. We can confirm that the resection of cervical paraganglioma bears a relevant risk of morbidity and of cranial nerve injury and stroke. Resection is recommended for all tumors of the carotid bifurcation region considering their potentially malignant behavior. However, given that most cervical paragangliomas are asymptomatic and of benign histology, a thorough risk-benefit assessment needs to be performed, and procedural risks need to be well discussed with patients prior to surgery. The findings of our study show that, in addition to the established Shamblin classification, which was also significantly associated with the study outcome perioperative complications, tumor volume measured with a dedicated software based on preoperative cross-sectional imaging can be used to predict the risk of perioperative complications, with larger tumors bearing a higher risk of complications. This information can be used in shared decision-making with patients.

6.2 Open and endovascular techniques in vascular surgery

Open and endovascular surgeries are two different approaches in vascular surgery. Each approach has its own unique benefits and drawbacks, and the choice of which method to use will depend on a variety of factors, including the patient's medical history, the nature of the condition being treated, and the preferences of the surgeon. Most of these decisions are based on poor evidence and are mostly based on the surgical expertise of the team treating these patients. Concerning this topic, we performed several studies comparing open and endovascular approaches. The outcome of patients with mesenteric ischemia, popliteal artery aneurysms, visceral artery aneurysms and femoral artery occlusion

disease undergoing OS and ER was analyzed and compared. Furthermore, the outcomes of vessel access during T/EVAR were accessed.

Concerning mesenteric ischemia, in a retrospective study ***(original publication 3)***, a single center experience regarding the treatment of CMI and AMI, both with endovascular and open surgery was reported. The major finding from this study concerns the zero in-hospital mortality in CMI patients and the elevated in-hospital mortality in the AMI group. Severe postoperative morbidity (Dindo-Clavien $\geq$3) was also significantly more frequent in the AMI group when compared to the CMI group (77.3% vs 20%, $p<0.001$). Endovascular surgery had fewer postoperative complications in AMI patients when compared to open surgery (64.7% vs 85.2 %), not affecting mortality rates (29.6% vs 29.4). An elevated leukocyte count and lactate levels were present in the AMI group when compared to the CMI group. Finally, ASA classification and longer intensive care stay were identified as factors associated with mortality in the AMI group. Our results regarding outcomes of AMI are comparable with a 12-year retrospective analysis in which 72 patients with AMI were analyzed. Perioperative morbidity and 30-day mortality rates were 39% and 31%, respectively, and second-look surgery was performed in 53% of the patients (121). In another retrospective study, data from a 20-year period revealed a 30-day mortality rate of 27% in the 1990s and 17% during the 2000s. As in our study, no significant differences in outcomes between open and endovascular revascularization were observed (122). In another retrospective analysis, summarizing a 12-year experience with endovascular treatment of AMI due to embolic occlusion of the SMA, the total in-hospital mortality was 27.0%. Laparotomy was performed in 73.0% and bowel resection in 40.5% of the patients (123). In a meta-analysis of 30-day mortality after open and endovascular therapy of AMI, five non- randomized studies were included. Endovascular therapy had lower bowel resection rates (OR 0.37, p=0.03) and lower 30-day mortality

rates (OR 0.50; p=0.002) when compared to open surgery. The pooled overall 30-day mortality rate after endovascular therapy was 17.2% compared with 38.5% after open surgery (32). Concerning patients with CMI, we observed no mortality or severe (Clavien-Dindo ≥3) morbidity. These findings could be related to the small patient collective. Nevertheless, in another retrospective analysis, similarly low mortality rates were observed. In a retrospective study from the Mayo Clinic (Rochester, Minnesota, USA), 343 patients showed a procedure-related mortality of 2.6% (124). In our analysis, no significant difference in terms of mortality between endovascular and open treatment for AMI was observed, despite higher morbidity rates in the open surgery group. In an analysis of register data from the Johns Hopkins Hospital, Baltimore, USA, 679 patients underwent vascular intervention for AMI. Mortality was significantly higher after open revascularization compared with endovascular intervention (39.3% vs 24.9%; P=0.01) (125). A meta-analysis regarding mortality after open and endovascular revascularization for CMI was published within the ESVS guidelines. In single center cohorts from highly specialized centers, no difference in mortality was identified (OR 1.12). In administrative data from the *Nationwide Inpatient Sample* from the USA, the mortality was lower after endovascular compared to open revascularization (OR 0.20) (32).

We observed a higher leukocyte count and elevated lactate levels in the AMI group when compared to the CMI group. According to the recent ESVS guidelines, in patients with acute abdominal pain, D-dimer measurement is recommended to exclude AMI. In contrast, lactate measurement is not recommended to diagnose AMI (32). In our study, no data on preoperative D-dimer was available, as it is not commonly used at our center in this context. In our analysis, ASA classification and length of intensive care stay were associated with mortality. Some small single center studies showed comparable results (126-130). In another retrospective study, congestive heart failure and chronic kidney

disease predicted postoperative mortality, and bowel resection and cerebrovascular disease predicted postoperative morbidity (131). Mesenteric ischemia remains a challenge. Morbidity and in-hospital mortality are low when treating CMI and high for AMI. Early diagnosis and open or endovascular treatment may be decisive for the outcome of these patients.

Regarding the emergency treatment of PAA, our analysis ***(original publication 4)*** achieved two major findings. The first concerns the higher postoperative major amputation rates for ER in emergency treatment. The second refers to lower rates on 1-year secondary patency for endovascular repair in emergency surgery. Our analysis is the first comparing OR and ER in emergency surgery. Regarding asymptomatic patients, in a Cochrane Systematic Review on endovascular versus open repair of asymptomatic popliteal artery aneurysms, only one single RCT was identified (132). In this study from Antonello et al., 15 patients underwent ER and 15 patients OR. The primary patency rate was 100% at 12 months for OR and 86.7% at 12 months for ER (47). In another study involving 390 patients with asymptomatic popliteal aneurysms, no mortality was observed. OR showed lower primary patency loss (HR 0.25; 95% CI, 0.10-0.58; P< .05) (133). In a Study from Germany involving 206 OR, overall mortality was 2% with no differences in 5-year primary patency between the emergent and elective repair groups. 88.1 (134). Concerning endovascular surgery, 1-year primary patency rates are described between 82% and 87% (135-137). In another study, Speziale et al. analyzed 53 patients who underwent ER. At a mean follow-up of 37.4 ± 29.3 months, primary patency, secondary patency, and limb salvage were 73.6%, 92.4%, and 100%, respectively. (138) In the present analysis, major amputation (30 days) rates in emergence treatment were higher in the ER group, when compared to the OR group. (OR 5.46, 95% CI [1.65; 18], p<0.05). In a study from Vascunet, involving data from 1471 popliteal aneurysm repairs

from 10 countries, the overall major amputation rate was 2.0%, and 6.5% after emergency surgery. Major amputation was higher for ER (1.0%) compared to OR (1.8%) and hybrid repair (26.3%, p < .0001) (139). In another study from Italy, involving 234 open procedures, 30-day major amputation rates were 3.8% (140). In our meta-analysis, a more frequent loss of secondary patency (1 year) was observed in the ER group (OR 7.08, 95% CI [3.10; 16.20], p<0.05). In a retrospective study, Saunders et al. reported primary and secondary patency for ER of 88% and 90%, respectively (141). In a 2016 meta-analysis, 14 studies with 4880 popliteal artery aneurysm repairs were identified (OR, 3915 and ER, 1210). 1-year primary patency was higher for OR (0.607 [P=.01) and no difference in 1-year secondary patency (0.770 [P=.458]) was observed (142). Another meta-analysis from 2015 reported outcomes for 514 PAA. Pooled primary and secondary patency rates were 69.4% (95% CI 63.3% to 76.2%) and 77.4% (95% CI 70.1% to 85.3%), respectively, at 5 years. No difference in primary patency on evidence synthesis (hazard ratio 1.30, 95% CI 0.79 to 12.14, p=0.189) was described. (143) There were very few data on long-term results of ER after emergency surgery. Although, the current data is scarce, long-term results of OR are better than ER. Better patient selection regarding suitable anatomy for ER and improvement of endovascular stent grafts could improve results. There is no evidence to support ER during emergency treatment of PAA. New studies are needed to generate new evidence in the endovascular era of vascular surgery.

Concerning VAA, we performed a meta-analysis and a retrospective observational study ***(original publications 5 and 6)***. In the systematic review and meta-analysis, mortality was comparable between ER and OS (1.8% vs 2.1%). Lower mortality for ER prevailed in the subgroup analysis of ruptured aneurysms. Considerable mortality is a known problem of this pathology in an emergency setting. (144) Our results are comparable to large cohort studies. In a retrospective study from the Mayo Clinic, reporting on

endovascular management of VAA between 1999 and 2009, 185 aneurysms were identified in 176 patients. 46% of the patients were symptomatic with aneurysm rupture. While a 98% technical success rate was reported after the initial intervention, the 30-day overall and aneurysm-related mortality was 6.2% and 3.4%, respectively, in these patients. In contrast, no deaths were observed in patients undergoing elective treatment. (145) In another report from the same institution comprising 217 splenic artery aneurysms, operative mortality was 5% in the elective group and 20% in the emergency group (146). These data suggest that, in terms of mortality, ER should be considered as first line treatment for VAA, especially in the emergency setting, if it is technically possible and the necessary experience in endovascular procedures is present. Length of stay was shorter in the ER group (mean difference -4.25 days, 95% CI [-5.52; -2.98], $p<0.00001$). Comparable results regarding the length of stay were reported in a previous meta-analysis. (147) In the present meta-analysis, technical success rates were comparable between ER and OS (97% vs 98%). In a previous meta-analysis involving 1,321 patients with true splenic artery aneurysms, endovascular surgery required more reinterventions (3.2%) compared with open surgery (0.5%). (148) Despite the higher reintervention rates, endovascular repair is reported as the most cost-effective treatment when compared to open surgery, independent of the risk profile in the treatment of splenic artery aneurysms. (149) Contemporary evidence shows that ER is superior in terms of length of stay and morbidity. With comparable technical success, but higher reintervention rates, follow-up remains mandatory in these patients to avoid secondary problems such as stent occlusion, endoleaks or secondary growth and rupture of the aneurysm. The data suggest that ER should be considered as first line treatment for patients with VAA in the elective and emergency setting in the light of comparable mortality and technical success and lower morbidity and length of stay when compared

to OR. Due to the higher re-intervention rates, a structured follow-up must be offered to patients treated with ER.

Concerning the occlusive process of the femoral artery bifurcation ***(original publication 7)***, we performed a meta-analysis to compare the outcomes between OS and ER. The study demonstrated that OS is the more effective procedure compared to ER in terms of patency, re-intervention, and limb preservation, albeit with a higher probability of peri-operative complications. Due to the study design and available data, it was not possible to generate formal statistical proof of superiority. Nevertheless, at present, OS can continue to be considered the gold standard in the treatment of occlusive processes of the femoral artery bifurcation. Endovascular procedures should only be used in exceptional cases and following critical interdisciplinary evaluation. To generate broader evidence to inform the treatment decision between OS and ER, randomized controlled studies meeting quality standards and with sufficient statistical power (case number) and follow-up duration need to be conducted.

Finally, the presented research program included an observational comparative study on the percutaneous and cutdown access related minor complications after endovascular aortic repair ***(original publication 8)***. The study suggests equivalence of percutaneous and cutdown techniques for vessel access in T/EVAR regarding minor complications after surgery. Neither early nor late postoperative complications occurred significantly more often in either group. Nevertheless, the results of the study suggest that despite ongoing development of closure systems, the percutaneous access technique does not reach superiority over cutdown access concerning minor complications. As complications during follow-up emerge in approximately the same number of cases as during hospital stay, clinical examination of the access site should always be conducted and properly documented on follow-up appointments. Future studies might quantify the period in

which access-related complications most likely appear after T/EVAR. For patients being dependent on or wishing for local anesthesia for T/EVAR, the percutaneous technique should be the first choice for groin access if anatomical suitability is given. Future studies and guidelines should aim for investigation and definition of more precise criteria for selection of the individually best fitting access technique.

7. Conclusion and Outlook

Oncovascular surgery is an emerging field in the treatment of tumor patients. The current evidence suggests that patients undergoing surgery for hilar cholangiocarcinoma with arterial resections show higher morbidity and mortality rates and shorter long-term survival when compared to standard resections. This demands new multimodal treatment strategies for these patients. Concerning cervical paraganglioma, we showed that tumor volume can be used as additional information in a risk-benefit analysis and discussions with patients prior to cervical paraganglioma resection.

Endovascular techniques are also in more widespread use, but a multidisciplinary evidence-based approach in using these tools is essential. Regarding patients with mesenteric ischemia, morbidity and in-hospital mortality are low when treating chronic mesenteric ischemia and high for acute mesenteric ischemia. Early diagnosis and open or endovascular treatment may be decisive for the outcome of these patients. Patients undergoing endovascular treatment for popliteal artery aneurysms show higher rates on major amputation and loss of secondary patency when compared to open surgery. Currently, there is no evidence to support endovascular surgery during emergency treatment of popliteal artery aneurysms. On the other hand, endovascular repair should be considered as first line treatment for patients with visceral artery aneurysms in the

elective and emergency setting in the light of comparable mortality and technical success and lower morbidity and length of stay when compared to open surgery. Regarding the occlusive processes of the femoral artery bifurcation, thrombendarterectomy can continue to be considered the gold standard. Finally, the percutaneous technique for vessel access in endovascular aortic repair is safe and can be quickly executable. Nevertheless, this technique reached no superiority in terms of minor complications when compared to cutdown access.

8. References

1. Young, A. L., Prasad, K. R., Toogood, G. J., & Lodge, J. P. (2010). Surgical treatment of hilar cholangiocarcinoma in a new era: comparison among leading Eastern and Western centers, Leeds. J Hepatobiliary Pancreat Sci, 17(4), 497–504.
2. Khan, S. A., Thomas, H. C., Davidson, B. R., & Taylor-Robinson, S. D. (2005). Cholangiocarcinoma. Lancet (London, England), 366(9493), 1303–1314.
3. Ito, F., Cho, C. S., Rikkers, L. F., & Weber, S. M. (2009). Hilar cholangiocarcinoma: current management. Ann Surg, 250(2), 210–218.
4. Hidalgo, E., Asthana, S., Nishio, H., Wyatt, J., Toogood, G. J., Prasad, K. R., & Lodge, J. P. (2008). Surgery for hilar cholangiocarcinoma: the Leeds experience. Eur J Surg Oncol, 34(7), 787–794.
5. Klatskin, G. (1965). Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis. An unusual tumor with distinctive clinical and pathological features. The american journal of medicine, 38, 241–256.
6. Serrablo, A.; Serrablo, L.; Alikhanov, R.; Tejedor, L. Vascular Resection in Perihilar Cholangiocarcinoma. Cancers 2021, 13, 5278. https://doi.org/10.3390/cancers13215278
7. She W, Cheung TT, Ma KW, Tsang SHY, Dai WC, Chan ACY, et al. Vascular resection and reconstruction in hilar cholangiocarcinoma. ANZ J Surg 2020 Sep;90(9):1653-1659.
8. Matsuyama R, Mori R, Ota Y, Homma Y, Kumamoto T, Takeda K, et al. Significance of vascular resection and reconstruction in surgery for hilar cholangiocarcinoma: with

special reference to hepatic arterial resection and reconstruction. Ann Surg Oncol 2016 Aug;23(Suppl 4):475-484.
9. Heinrich S, Baumgart J, Mittler J, Lang H. [Vascular reconstruction in hepatic surgery]. Chirurg 2016 Feb;87(2):100-107.
10. Mizuno T, Ebata T, Yokoyama Y, Igami T, Yamaguchi J, Onoe S, et al. Combined vascular resection for locally advanced perihilar cholangiocarcinoma. Ann Surg 2020 Sep 24:1.
11. Govil S, Reddy MS, Rela M. Surgical resection techniques for locally advanced hilar cholangiocarcinoma. Langenbecks Arch Surg 2014 Aug;399(6):707-716.
12. Rangwala, A.F.; Sylvia, L.C.; Becker, S.M. Soft tissue metastases of a chemodectoma: A case report and review of the literature. Cancer 1978, 42, 2865–2869.
13. Schipper, J.; Boedeker, C.C.; Maier,W.; Neumann, H.P.H. Paragangliomas in the head-/neck region. I: Classification and diagnosis. HNO 2004, 52, 569–574, quiz 575.
14. Lee, J.H.; Barich, F.; Karnell, L.H.; Robinson, R.A.; Zhen, W.K.; Gantz, B.J. National Cancer Data Base report on malignant paragangliomas of the head and neck. Cancer 2002, 94, 730–737.
15. Fathalla, A.E.; Elalfy, M.A. Clinical Outcome of Carotid Body Paraganglioma Management: A Review of 10-Year Experience. J. Oncol. 2020, 2020, 6081273.
16. Persky, M.; Tran, T. Acquired Vascular Tumors of the Head and Neck. Otolaryngol. Clin. N. Am. 2018, 51, 255–274.
17. Pelliteri, P.; Rinaldo, A.; Myssiorek, D.; Jackson, C.; Bradley, P.; Devaney, K. Paragangliomas of the head and neck. Oral Oncol. 2004, 40, 563–575.
18. Manolidis, S.; Shohet, J.A.; Jackson, C.G.; Glasscock, M.E. Malignant glomus tumors. Laryngoscope 1999, 109, 30–34.
19. Erhart, P.; Körfer, D.; Hoffmann-Wieker, C.; Gieldon, L.; Dikow, N.; Wielpütz, M.O.; Plinkert, P.K.; Kender, Z.; Szendrödi, J.; Schaaf, C.P.; et al. Paraganglioma of the carotid artery. An interdisciplinary and heterogeneous pathology. Gefässchirurgie 2022, 27, 517–523.
20. Sajid, M.; Hamilton, G.; Baker, D. A Multicenter Review of Carotid Body Tumour Management. Eur. J. Vasc. Endovasc. Surg. 2007, 34, 127–130.
21. Guichard, J.-P.; Fakhry, N.; Franc, J.; Herman, P.; Righini, C.-A.; Taieb, D. Morphological and functional imaging of neck paragangliomas. Eur. Ann. Otorhinolaryngol. Head Neck Dis. 2017, 134, 243–248.

22. van den Berg, R. Imaging and management of head and neck paragangliomas. Eur. Radiol. 2005, 15, 1310–1318.
23. Berger, G.; Łukasiewicz, A.; Grinievych, V.; Tarasów, E. Carotid Body Tumor—Radiological imaging and genetic assessment. Pol. J. Surg. 2020, 92, 39–44.
24. Kruger, A.J.; Walker, P.J.; Foster, W.J.; Jenkins, J.S.; Boyne, N.S.; Jenkins, J. Important observations made managing carotid body tumors during a 25-year experience. J. Vasc. Surg. 2010, 52, 1518–1523.
25. Antonitsis, P.; Saratzis, N.; Velissaris, I.; Lazaridis, I.; Melas, N.; Ginis, G. Management of cervical paragangliomas: Review of a 15-year experience. Langenbeck's Arch. Surg. 2006, 391, 396–402.
26. Shamblin,W.R.; ReMine, W.H.; Sheps, S.G.; Harrison, E.G. Carotid body tumor (chemodectoma): Clinicopathologic analysis of ninety cases. Am. J. Surg. 1971, 122, 732–739.
27. Tiedemann, Friedrich. Von der Verengung und Schliessung der Pulsadern in Krankheiten. Groos, 1843.
28. Dunphy JE. Abdominal pain of vascular origin. Am J Med Sci 1936;192:109-12.
29. Shaw RS, Maynard EP 3rd. Acute and chronic thrombosis of the mesenteric arteries associated with malabsorption; a report of two cases successfully treated by throm - boendarterectomy . N Engl J Med 1958; 258: 874-8.
30. Morris GC, Crawford ES, Cooley DA, DeBakey ME. Revascularization of the celiac and superior mesenteric arteries. Arch Surg 1962; 84: 95-107.
31. Schermerhorn ML, Giles KA, Hamdan AD, Wyers MC, Pomposelli FB. Mesenteric revascularization: management and outcomes in the United States, 1988-2006. J Vasc Surg 2009; 50: 341-8 e1.
32. Bjorck M, Koelemay M, Acosta S, et al. Editor's choice — Management of the diseases of mesenteric arteries and veins: Clinical practice guidelines of the European society of vascular surgery (ESVS). Eur J Vasc Endovasc Surg 2017; 53: 460-510.
33. Mensink PB, Moons LM, Kuipers EJ. Chronic gastrointestinal ischaemia : shifting paradigms. Gut 2011; 60: 722-37.
34. Clair DG, Beach JM. Mesenteric ischemia . N Engl J Med 2016; 374: 959-68.
35. Terlouw LG, Moelker A, Abrahamsen J, Acosta S, Bakker OJ, Baumgartner I, Bruno MJ. European guidelines on chronic mesenteric ischaemia -owned joint United European gastroenterology, European association for gastroenterology, endoscopy and nutrition European society of gastrointestinal and abdominal radiology, Nether- lands association

of, hepatogastroenterologists , Hellenic Society of gastroenterology , cardiovascular and interventional radiological society of Europe, and Dutch Mesenteric ischemia study group clinical guidelines on the diagnosis and treatment of patients with chronic mesenteric ischaemia . United Eur Gastroenterol J 2020.

36. Biolato M, Miele L, Gasbarrini G, et al. Abdominal angina. Am J Med Sci 2009; 338: 389-95.

37. Pecoraro F, Rancic Z, Lachat M, et al. Chronic mesenteric ischemia: critical review and guidelines for management. Ann Vasc Surg 2013; 27: 113-22.

38. Kougias P, Lau D, El Sayed HF, Zhou W, Huynh TT, Lin PH. Determinants of tomorrow mortality and treatment outcome Following surgical interventions for acute mesenteric ischemia. J Vasc Surg 2007; 46: 467-74 .

39. Cudnik MT, Darbha S, Jones J, et al. The diagnosis of acute mesenteric ischemia: a systematic review and meta-analysis. Acad Emerg Med 2013; 20: 1087-100.

40. Marin ML, Veith FJ, Panetta TF, Cynamon J, Bakal CW, Suggs WD, et al. Transfemoral endoluminal stented graft repair of a popliteal artery aneurysm. J Vasc Surg 1994;19: 754-7.

41. Cousins, R. S., Dexter, D. J., Ahanchi, S. S., Cain, B. C., Powell, O. M., Ongstad, S. B., … Panneton, J. M. (n.d.). Determining patient risk factors associated with accelerated growth of popliteal artery aneurysms. J Vasc Surg, 67, 838–847.

42. Kropman, R. H. J., van Santvoort, H. C., Teijink, J., van de Pavoordt, H. D. W. M., Belgers, H. J., Moll, F. L., & de Vries, J.-P. P. M. (2007). The medial versus the posterior approach in the repair of popliteal artery aneurysms: A multicenter case-matched study. Journal of Vascular Surgery, 46(1), 24–30.

43. Ghotbi R, Sotiriou A, Schönhofer S, Zikos D, Schips K, Westermeier W. Stent-graft placement in popliteal artery aneurysms: midterm results. *Vascular Disease Management*2007;4(4):123-127.

44. Leake, A. E., Segal, M. A., & Chaer, R. A. (n.d.). Meta-analysis of open and endovascular repair of popliteal artery aneurysms. J Vasc Surg, 65(1), 246–256.

45. Patel, S. R., Hughes, C. O., Jones, K. G., Holt, P. J. E., Thompson, M. M., Hinchliffe, R. J., & Karthikesalingam, A. (2015). A Systematic Review and Meta-analysis of Endovascular Popliteal Aneurysm Repair Using the Hemobahn/Viabahn Stent-Graft. Journal of Endovascular Therapy, 22(3), 330–337.

46. Gabrielli, R., Rosati, M. S., Carra, A., Vitale, S., & Siani, A. (n.d.). Outcome after preoperative or intraoperative use of intra-arterial urokinase thrombolysis for acute popliteal artery thrombosis and leg ischemia. Thorac Cardiovasc Surg, 63, 164–167.
47. Antonello, M., Frigatti, P., & Battocchio, P. (n.d.). Open repair versus endovascular treatment for asymptomatic popliteal artery aneurysm: results of a prospective randomized study. J Vasc Surg, 42(2), 185–193.
48. Schmitz-Rixen, T., Debus, E. S., Torsello, G., Stojanovic, T., Peter, J., Eckstein, H. H., & Grundmann, R. T. (2014). Poplitealarterienaneurysma. Was ist die beste Behandlungsoption? Gefässchirurgie, 19(5), 459–467.
49. Cervin, A., Tjärnström, J., Ravn, H., Acosta, S., Hultgren, R., Welander, M., & Björck, M. (2015). Treatment of Popliteal Aneurysm by Open and Endovascular Surgery: A Contemporary Study of 592 Procedures in Sweden. European Journal of Vascular and Endovascular Surgery, 50(3), 342–350.
50. Grip, O., Mani, K., Altreuther, M., Bastos Gonçalves, F., Beiles, B., Cassar, K., … Björck, M. (2020). Contemporary Treatment of Popliteal Artery Aneurysms in 14 Countries: A Vascunet Report. *European Journal of Vascular and Endovascular Surgery: The Official Journal of the European Society for Vascular Surgery*, *60*(5), 721–729.
51. Beuschel B, Nayfeh T, Kunbaz A, Haddad A, Alzuabi M, Vindhyal S, Farber A, Murad MH. A systematic review and meta-analysis of treatment and natural history of popliteal artery aneurysms. J Vasc Surg. 2021 May 29:S0741-5214(21)00833-8. doi: 10.1016/j.jvs.2021.05.023.
52. Calero A, Illig KA. Overview of aortic aneurysm management in the endovascular era. Semin Vasc Surg. 2016;29(1–2):3–17.
53. Brown LC, Powell JT, Thompson SG, et al. The UK endovascular aneurysm repair (EVAR) trials: Randomised trials of EVAR versus standard therapy. Heal Technol Assess. 2012;16(9):1–218.
54. Greenhalgh RM. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. Lancet. 2004;364(9437):843–8.
55. Patel R, Sweeting MJ, Powell JT, et al. Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. Lancet. 2016;388(10058):2366–74.

56. Hogg ME, Kibbe MR. Percutaneous Thoracic and Abdominal Aortic Aneurysm Repair: Techniques and Outcomes. Vascular. 2006;14(5):270–81.
57. Van Wiechen MP, Ligthart JM, Van Mieghem NM. Large-bore Vascular Closure: New devices and techniques. Interv Cardiol. 2019;14(1):17–21.
58. Gimzewska M, Air J, Se Y, et al. Totally percutaneous versus surgical cut-down femoral artery access for elective bifurcated abdominal endovascular aneurysm repair (Review) Summary of the findings for the main comaprison. Cochrane Database Syst Rev. 2017;(2).
59. Hajibandeh S, Hajibandeh S, Antoniou SA, et al. Percutaneous access for endovascular aortic aneurysm repair: A systematic review and meta-analysis. Vascular. 2016;24(6):638–48.
60. Yang L, Liu J, Li Y. Femoral artery closure versus surgical cutdown for endovascular aortic repair: A single-center experience. Med Sci Monit. 2018;24:92–9.
61. Lee W, Brown M, Nelson P. Total percutaneous access for endovascular aortic aneurysm repair („Preclose“ technique). J Vasc Surg. 2007;45(6):1095–101.
62. Nelson PR, Kracjer Z, Kansal N, et al. A multicenter, randomized, controlled trial of totally percutaneous access versus open femoral exposure for endovascular aortic aneurysm repair (the PEVAR trial). J Vasc Surg. 2014;59(5):1181–93.
63. Torsello GB, Kasprzak B, Klenk E, et al. Endovascular suture versus cutdown for endovascular aneurysm repair: A prospective randomized pilot study. J Vasc Surg. 2003;38(1):78–82.
64. Buck DB, Karthaus EG, Soden PA, et al. Percutaneous versus femoral cutdown access for endovascular aneurysm repair. J Vasc Surg. 2015;62(1):16–21.
65. Thomas RP, Kowald T, Schmuck B, et al. Retrospective Evaluation of Percutaneous Access for TEVAR and EVAR: Time to Make it the Standard Approach? Fortschr Röntgenstr. 2017;189(04):347–55.
66. Barbash IM, Barbanti M, Webb J, et al. Comparison of vascular closure devices for access site closure after transfemoral aortic valve implantation. Eur Heart J. 2015;36(47):3370–9.
67. Vatakencherry G, Molloy C, Sheth N, et al. Percutaneous access planning, techniques and considerations for endovascular aortic repair (EVAR). Cardiovasc Diagn Ther. 2018;8(Suppl 1):184-S190.

68. Starnes BW, O'Donnell SD, Gillespie DL, et al. Percutaneous arterial closure in peripheral vascular disease: A prospective randomized evaluation of the Perclose device. J Vasc Surg. 2003;38(2):263–71.
69. Manunga JM, Gloviczki P, Oderich GS, et al. Femoral artery calcification as a determinant of success for percutaneous access for endovascular abdominal aortic aneurysm repair. J Vasc Surg. 2013;58(5):1208–12.
70. Mousa AY, Campbell JE, Broce M, et al. Predictors of percutaneous access failure requiring open femoral surgical conversion during endovascular aortic aneurysm repair. J Vasc Surg. 2013;58(5):1213–9.
71. Kalish J, Eslami M, Gillespie D, et al. Routine use of ultrasound guidance in femoral arterial access for peripheral vascular intervention decreases groin hematoma rates. J Vasc Surg. 2015;61(5):1231–8.
72. Kuo F, Park J, Chow K, et al. Avoiding peripheral nerve injury in arterial interventions. Diagnostic Interv Radiol. 2019;25(5):380–91.
73. Vierhout BP, Pol RA, Ott MA, et al. Randomized multicenter trial on percutaneous versus open access in endovascular aneurysm repair (PiERO). J Vasc Surg. 2019;69(5):1429–36.
74. Dwivedi K, Regi JM, Cleveland TJ, et al. Long-Term Evaluation of Percutaneous Groin Access for EVAR. Cardiovasc Intervent Radiol. 2019;42(1):28–33.
75. Debus E, Heidemann F, Gross-Fengels W, et al. Screening, Diagnostik, Therapie und Nachsorge des Bauchaortenaneurysmas. AWMF online
76. Beaussier M. Sur un anervrisme de l'artere splenique dont les parois se sont ossifiées. J Med Clin Pharm Paris. 1770; 32:157.
77. MacLeod D, Maurice T. Rupture of branch of splenic artery associated with pregnancy. Lancet. 1940; 1:924
78. Meyer A, Uder M, Lang W, et al. Aneurysmen an viszeralen Arterien. Zentralbl Chir. 2010; 135: 416-20.
79. Abbas MA, Stone WM, Fowl RJ, et al. Splenic artery aneurysms: Two decades experience at Mayo Clinic. Ann Vasc Surg. 2002; 16:442-9.
80. Tulsyan N, Kashyap VS, Greenberg RK, et al. The endovascular management of visceral artery aneurysms and pseudoaneurysms. J Vasc Surg. 2007; 45:276-83.
81. Herbeck M, Horbach T, Putzenlechner C, et al. Ruptured splenic artery aneurysm during pregnancy: A rare case report with both maternal and fetal survival. Am J Obstet Gynecol. 1999; 181:763.

82. Barrett JM, Van Hooydonk JE, Boehm FH. Pregnancy related rupture of arterial aneurysms. Obstet Gynecol Surv. 1982; 37:557-66.
83. Lee PL, Rhee RY, Gordon RY, et al. Management of splenic artery aneurysms: the significance of portal and essential hypertension. J Am Coll Surg 1999; 5:483-90.
84. Berceli SA. Hepatic and splenic artery aneurysms. Semin Vasc Surg. 2005; 18:196-201.
85. Nanez L, Knowles M, Modrall JG, et al. Ruptured Splenic Artery Aneurysms Are Exceedingly Rare in Pregnant Women. J Vasc Surg. 2014; 60: 1520-3.
86. Iida A, Katayama K, Yamaguchi A. Laparoscopic resection for splenic artery aneurysm using the lateral approach: Report of two cases. Asian J Endosc Surg. 2014; 6: 147-50.
87. Kim Y, Johna S. Laparoscopic Excision of Splenic Artery Aneurysm. JSLS. 2014; 132-4.
88. Pietrabissa A, Ferrari M, Berchiolli, et al. Laparoscopic treatment of splenic artery aneurysms. J Vasc Surg. 2014; 50: 275-9.
89. Tiberio M, Bonardelli S, Gheza F, et al. Prospective randomized comparison of open versus laparoscopic management of splenic artery aneurysms: a 10-year study. Surg Endosc. 2012.
90. Balderi A, Antonietti A, Ferro L, et al. Trattamento endovascolare di aneurismi e pseudoaneurismi viscerali: la nostra esperienza. Rad Med. 2012; 117: 815-30.
91. Cappucci M, Zarco F, Orgera G, et al. Endovascular Treatment of Visceral Artery Aneurysms and Pseudoaneurysms with Stent-Graft: Analysis of Immediate and Long-Term Results. Cir. Esp. 2017; 95: 283-92.
92. Ballotta E, Gruppo M, Mazzalai F, Da Giau G: Common femoral artery endarterectomy for occlusive disease: an 8-year single-center prospective study. Surgery 2010; 147: 268–74.
93. Diehm C, Schuster A, Allenberg JR, et al.: High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. Atherosclerosis 2004; 172: 95–105.
94. Kang JL, Patel VI, Conrad MF, Lamuraglia GM, Chung TK, Cambria RP: Common femoral artery occlusive disease: contemporary results following surgical endarterectomy. J Vasc Surg 2008; 48: 872–7.
95. Kechagias A, Ylönen K, Biancari F: Long-term outcome after isolated endarterectomy of the femoral bifurcation. World J Surg 2008; 32: 51–4.

96. Lawall H, Huppert P, Espinola-Klein C, Rümenapf G: The diagnosis and treatment of peripheral arterial vascular disease. Dtsch Arztebl Int 2016; 113: 729–36.
97. Nasr B, Kaladji A, Vent PA, et al.: State-of-the-art treatment of common femoral artery disease. J Cardiovasc Surg (Torino) 2015; 56: 309–16.
98. Wieker CM, Schönefeld E, Osada N, et al.: Results of common femoral artery thromboendarterectomy evaluation of a traditional surgical management in the endovascular era. J Vasc Surg 2016; 64: 995–1001.
99. Andrews RT, Venbrux AC, Magee CA, Bova DA: Placement of a flexible endovascular stent across the femoral joint: an in vivo study in the swine model. J Vasc Interv Radiol 1999; 10: 1219–28.
100. Azéma L, Davaine JM, Guyomarch B, et al.: Endovascular repair of common femoral artery and concomitant arterial lesions. Eur J Vasc Endovasc Surg 2011; 41: 787–93.
101. Bonvini RF, Rastan A, Sixt S, et al.: Endovascular treatment of common femoral artery disease: medium-term outcomes of 360 consecutive procedures. J Am Coll Cardiol 2011; 58: 792–8.
102. Bucher HC, Guyatt GH, Griffith LE, Walter SD: The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997; 50: 683–91.
103. Changal KH, Syed MA, Dar T, Mangi MA, Sheikh MA: Systematic review and proportional meta-analysis of endarterectomy and endovascular therapy with routine or selective stenting for common femoral artery atherosclerotic disease. J Interv Cardiol 2019; 2019: 1593401:1–12.
104. Davaine JM, Quérat J, Guyomarch B, et al.: Incidence and the clinical impact of stent fractures after primary stenting for TASC C and D femoropopliteal lesions at 1 year. Eur J Vasc Endovasc Surg 2013; 46: 201–12.
105. McGovern PJ, Jr., Stark KR, Kaufman JL, Rosenberg N: Management of common femoral artery occlusion. A report of ten cases. J Cardiovasc Surg (Torino) 1987; 28: 38–41.
106. Siracuse JJ, Van Orden K, Kalish JA, et al.: Endovascular treatment of the common femoral artery in the Vascular Quality Initiative. J Vasc Surg 2017; 65: 1039–46.
107. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews.

108. Brooke BS, Schwartz TA, Pawlik TM. MOOSE Reporting Guidelines for Meta-analyses of Observational Studies. *JAMA Surg.* 2021;156(8):787–788.

109. https://www.crd.york.ac.uk/prospero/

110. Sterne JAC, Hernán MA, McAleenan A, Reeves BC, Higgins JPT. Assessing risk of bias in a non-randomized study. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editors. Cochrane Handbook for Systematic Reviews of Interventions. London: Cochrane; Feb 16, 2020.

111. Deeks J, Dinnes J, D'Amico R, Sowden A, Sakarovitch C. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7(27).

112. Rangarajan K, Simmons G, Manas D, Malik H, Hamady ZZ. Systemic adjuvant chemotherapy for cholangiocarcinoma surgery: A systematic review and meta-analysis. Eur J Surg Oncol. 2020 Apr;46(4 Pt A):684-693. doi: 10.1016/j.ejso.2019.11.499.

113. Abbas S, Sandroussi C. Systematic review and meta-analysis of the role of vascular resection in the treatment of hilar cholangiocarcinoma. HPB (Oxford). 2013 Jul;15(7):492-503.

114. Noji, T., Tsuchikawa, T., Okamura, K., Tanaka, K., Nakanishi, Y., Asano, T., … Hirano, S. (2016). Concomitant hepatic artery resection for advanced perihilar cholangiocarcinoma: a case-control study with propensity score matching. J Hepatobiliary Pancreat Sci, 23(7), 442–448.

115. Matsuyama, R., Mori, R., Ota, Y., Homma, Y., Kumamoto, T., Takeda, K., … Endo, I. (2016). Significance of Vascular Resection and Reconstruction in Surgery for Hilar Cholangiocarcinoma: With Special Reference to Hepatic Arterial Resection and Reconstruction. Ann Surg Oncol, 23(Suppl 4), 475–484.

116. Schimizzi, G. V., Jin, L. X., Davidson, J. T., Krasnick, B. A., Ethun, C. G., Pawlik, T. M., … Fields, R. C. (2018). Outcomes after vascular resection during curative-intent resection for hilar cholangiocarcinoma: a multi-institution study from the US extrahepatic biliary malignancy consortium. Hpb, 20(4), 332–339.

117. European Association for the Study of the Liver (2016) EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol 64(2):433–485.

118. Mantel HT, Westerkamp AC, Adam R, Bennet WF, Seehofer D, Settmacher U, Sánchez-Bueno F, Fabregat Prous J, Boleslawski E, Friman S, Porte RJ; European Liver and Intestine Transplant Association (ELITA) (2016) Strict Selection Alone of Patients Undergoing Liver Transplantation for Hilar Cholangiocarcinoma Is Associated with Improved Survival. PLoS One 11(6):e0156127.

119. Ethun CG, Lopez-Aguiar AG, Anderson DJ, Adams AB, Fields RC, Doyle MB, Chapman WC, Krasnick BA, Weber SM, Mezrich JD, Salem A, Pawlik TM, Poultsides G, Tran TB, Idrees K, Isom CA, Martin RCG, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Cardona K, Maithel SK (2018) Transplantation Versus Resection for Hilar Cholangiocarcinoma: An Argument for Shifting Treatment Paradigms for Resectable Disease. Ann Surg 267(5):797–805.

120. Gu J, Bai J, Shi X, Zhou J, Qiu Y, Wu Y, Jiang C, Sun X, Xu F, Zhang Y, Ding Y (2012) Efficacy and safety of liver transplantation in patients with cholangiocarcinoma: a systematic review and meta-analysis. Int J Cancer 130(9):2155–63.

121. Kougias P, Lau D, El Sayed HF, Zhou W, Huynh TT, Lin PH. Determinants of tomorrow tality and treatment outcome Following surgical interventions for acute mesenteric ischemia. J Vasc Surg 2007; 46: 467-74 .

122. Ryer, E. J., Kalra, M., Oderich, G. S., Duncan, A. A., Gloviczki, P., Cha, S., & Bower, T. C. (2012). Revascularization for acute mesenteric ischemia. Journal of Vascular Surgery, 55(6), 1682–1689.

123. Raupach, J., Lojik, M., Chovanec, V., Renc, O., Strýček, M., Dvořák, P., … Malý, R. (2016). Endovascular Management of Acute Embolic Occlusion of the Superior Mesenteric Artery: A 12-Year Single-Centre Experience. CardioVascular and Interventional Radiology, 39(2), 195–203.

124. llarita, T., Oderich, G. S., Gloviczki, P., Duncan, A. A., Kalra, M., Cha, S., … Bower, T. C. (2013). Patient survival after open and endovascular mesenteric revascularization for chronic mesenteric ischemia. Journal of Vascular Surgery, 57(3), 747–755.

125. Beaulieu, R. J., Arnaoutakis, K. D., Abularrage, C. J., Efron, D. T., Schneider, E., & Black, J. H. (2014). Comparison of open and endovascular treatment of acute mesenteric ischemia. Journal of Vascular Surgery, 59(1), 159–164.

126. Gagnière J, Favrolt G, Alfidja A, Kastler A, Chabrot P, Cassagnes L, Buc E, Pezet D, Boyer L. Acute thrombotic mesenteric ischemia: primary endovascular treatment in eight patients. Cardiovasc Intervent Radiol. 2011 Oct;34(5):942-8.

127. Ozturk S, Unver M, Ozdemir M, Bozbıyık O, Turk Y, Firat O, Calıskan C. Prognostic factors in acute mesenteric ischemia and evaluation with multiple logistic regression analysis effecting morbidity and mortality. Pol Przegl Chir. 2020 Dec 28;93(1):25-33.

128. Kassahun WT, Schulz T, Richter O, Hauss J. Unchanged high mortality rates from acute occlusive intestinal ischemia: six-year review. Langenbecks Arch Surg. 2008 Mar;393(2):163-71.
129. Gawenda M, Scherwitz P, Walter M, Erasmi H. Letalitätsfaktoren des Darminfarkts primär vaskulärer Genese [Fatal outcome factors of intestinal infarct of primary vascular origin]. Langenbecks Arch Chir. 1997;382(6):319-24.
130. Raupach, J., Lojik, M., Chovanec, V., Renc, O., Strýček, M., Dvořák, P., … Malý, R. (2016). Endovascular Management of Acute Embolic Occlusion of the Superior Mesenteric Artery: A 12-Year Single-Centre Experience. CardioVascular and Interventional Radiology, 39(2), 195–203.
131. Ryer, E. J., Kalra, M., Oderich, G. S., Duncan, A. A., Gloviczki, P., Cha, S., & Bower, T. C. (2012). Revascularization for acute mesenteric ischemia. Journal of Vascular Surgery, 55(6), 1682–1689.
132. Joshi D, Gupta Y, Ganai B, Mortensen C. Endovascular versus open repair of asymptomatic popliteal artery aneurysm. Cochrane Database Syst Rev. 2019 Dec 23;12(12):CD010149.
133. Eslami, M. H., Rybin, D., Doros, G., & Farber, A. (n.d.). Open repair of asymptomatic popliteal artery aneurysm is associated with better outcomes than endovascular repair. J Vasc Surg, 61(3), 663–669.
134. Dorweiler, B., Gemechu, A., Doemland, M., Neufang, A., Espinola-Klein, C., & Vahl, C. F. (n.d.). Durability of open popliteal artery aneurysm repair. J Vasc Surg, 60, 951–957.
135. Golchehr, B., Zeebregts, C. J., Reijnen, M. M. P. J., & Tielliu, I. F. J. (2018). Long-term outcome of endovascular popliteal artery aneurysm repair. Journal of Vascular Surgery, 67(6), 1797–1804.
136. Kumar, H. R., Rodriguez, H. E., & Eskandari, M. K. (2015). Mid-term outcomes of self-expanding covered stent grafts for repair of popliteal artery aneurysms. Surgery, 157(5), 874–880.
137. Piazza, M., Menegolo, M., Ferrari, A., Bonvini, S., Ricotta, J. J., Frigatti, P., … Antonello, M. (2014). Long-term Outcomes and Sac Volume Shrinkage after Endovascular Popliteal Artery Aneurysm Repair. European Journal of Vascular and Endovascular Surgery, 48(2), 161–168.
138. Speziale, F., Sirignano, P., Menna, D., Capoccia, L., Mansour, W., Serrao, E., … Mangialardi, N. (2015). Ten years' experience in endovascular repair of popliteal artery

aneurysm using the Viabahn endoprosthesis: a report from two Italian vascular centers. Annals of Vascular Surgery, 29(5), 941–949.

139. Björck, M., Beiles, B., Menyhei, G., Thomson, I., Wigger, P., Venermo, M., … Troëng, T. (2014). Editor's choice: Contemporary treatment of popliteal artery aneurysm in eight countries: A report from the vascunet collaboration of registries. European Journal of Vascular and Endovascular Surgery, 47(2), 164–171.

140. Dorigo, W., Pulli, R., Innocenti, A. A., & Azas, L. (2013). A 33-year experience with surgical management of popliteal artery aneurysms. Journal of Vascular Surgery, 62(5), 1176–1182.

141. Saunders, J. H., Abisi, S., Altaf, N., Yong, Y., MacSweeney, S. T., Whittaker, S., & Habib, S. (2014). Long-term outcome of endovascular repair of popliteal artery aneurysm presents a credible alternative to open surgery. Cardiovascular and Interventional Radiology, 37(4), 914–919.

142. Leake, A. E., Segal, M. A., & Chaer, R. A. (n.d.). Meta-analysis of open and endovascular repair of popliteal artery aneurysms. J Vasc Surg, 65(1), 246–256.

143. Patel, S. R., Hughes, C. O., Jones, K. G., Holt, P. J. E., Thompson, M. M., Hinchliffe, R. J., & Karthikesalingam, A. (2015). A Systematic Review and Meta-analysis of Endovascular Popliteal Aneurysm Repair Using the Hemobahn/Viabahn Stent-Graft. Journal of Endovascular Therapy, 22(3), 330–337.

144. Roberts KJ, McCulloch N, Forde C, et al. Emergency Treatment of Haemorrhaging Coeliac or Mesenteric Artery Aneurysms and Pseudoaneurysms in the Era of Endovascular Management. Eur J Vasc Endovasc Surg. 2015; 49: 382-9.

145. Fankhauser GT, Stone WM, Naidu SG, et al. The minimally invasive management of visceral artery aneurysms and pseudoaneurysms. J Vasc Surg. 2011; 53: 966-70.

146. Abbas MA, Stone WM, Fowl RJ, et al. Splenic artery aneurysms: two decades experience at Mayo clinic. Ann Vasc Surg. 2002; 16:442-9.

147. Barrionuevo P, Malas MB, Nejim B, et al. A systematic review and meta-analysis of the management of visceral artery aneurysms. J Vasc Surg. 2020; 72: 40-5.

148. Hogendoorn W, Lavida A, Hunink MG, et al. Open repair, endovascular repair, and conservative management of true splenic artery aneurysms. J Vasc Surg. 2014; 60:1667-76.

149. Hogendoorn W, Lavida, A, Hunink MG, et al. Cost-effectiveness of endovascular repair, open repair, and conservative management of splenic artery aneurysms. J Vasc Surg. 2015; 61: 1432-40.

9 List of publications for this thesis

ORIGINAL ARTICLE

Systematic review and meta-analysis of surgery for hilar cholangiocarcinoma with arterial resection

Artur Rebelo[1], Juliane Friedrichs[1], Maurizio Grilli[2], Nour Wahbeh[1], Jumber Partsakhashvili[1], Jörg Ukkat[1], Johannes Klose[1], Ulrich Ronellenfitsch[1] & Jörg Kleeff[1]

[1]Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle (Saale), Martin-Luther-University, Halle-Wittenberg, and [2]Professional Information Biomedicine and Health Profession, Karlsruhe, Germany

Abstract

Background: With the advances in multimodality treatment, an analysis of the outcome of arterial resections (AR) in surgery of cholangiocarcinoma is lacking. The aim of this meta-analysis was to summarize the currently available evidence onof AR for the treatment of cholangiocarcinoma.

Methods: A systematic literature search was carried out according to PRISMA guidelines.

Results: 10 retrospective cohort studies published from 2007 to 2020 with 2530 patients (408 AR group and 2122 control group) were identified. Higher in-hospital mortality rates (6.8% vs 3.3%, OR 2.65, 95% CI [1.27; 5.32], p = 0.009), higher morbidity rates (Clavien-Dindo classification $\geq$3) (52% vs 47%, OR 1.44, 95% CI [1.02; 1.75], p = 0.04) and lower 1-year, 3-year and 5-year survival rates (54% vs 69%, OR 0.55, 95% CI [0.34; 0.91 p = 0.02), (34% vs 38%, OR 0.74, 95% CI [0.55; 0.98, p = 0.03), (18% vs 29%, OR 0.54, 95% CI [0.39; 0.75, p = 0.0002) were observed in the AR group when compared to the control group.

Conclusion: Evidence from non-randomized studies shows a higher morbidity and mortality and shorter long-term survival in patients undergoing AR. However, the results are prone to selection bias, and only randomized trials comparing AR and palliative treatments AR might reveal a possible benefit of AR.

Systematic review registration: PROSPERO ID 223396.

Received 19 December 2021; accepted 7 April 2022

Correspondence

Artur Rebelo, Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle (Saale), Martin-Luther-University Halle-Wittenberg, Ernst-Grube-Str. 40, 06120 Halle (Saale), Germany. E-mail: artur.rebelo@uk-halle.de

Background

Cholangiocarcinoma has an estimated incidence of 1–2 per 100,000 persons per year[1] and constitutes the second most common primary hepatic malignancy.[2] The effect of systemic treatment is limited in most patients and surgery with complete removal of the tumor is the only option offering a chance of cure or at least of long-term freedom from tumor with 20–30% 5-year overall survival.[3,4] Most cholangiocarcinomas arise in the bile duct bifurcation. They are commonly referred to as hilar cholangiocarcinomas or Klatskin tumors.[5] Due to the proximity of vascular structures to the bile duct bifurcation, tumor invasion of the portal vein, the proper hepatic artery or the contralateral hepatic artery (i.e. a tumor arising from the left bile duct invading the right hepatic artery) occur in a relevant proportion of cases.

Vascular and especially arterial resection (AR) and reconstruction during surgical removal of hilar cholangiocarcinoma is a debated issue.[6] Although it is the only way of facilitating complete resection if the vessels are invaded, there are concerns of high postoperative morbidity and mortality rates following vascular reconstruction, including hemorrhage and liver failure, which might offset the potential survival advantage gained from complete removal of the tumor. However, thanks to technical improvements in microvascular anastomoses and to a growing experience with liver transplants in many centers, the surgical approaches for hilar cholangiocarcinoma have generally become more aggressive in recent years and concurrently the number of studies assessing feasibility, safety and oncological effectiveness of AR and arterial reconstruction has been growing.[7–11]

To summarize the currently available evidence on the topic, we conducted a systematic review with meta-analysis.

Methods

The literature search and data analysis were conducted in accordance with the PRISMA Guidelines (support material 1).[12] The study has been prospectively registered in the PROSPERO database.[13] The study protocol was also published a priori.[14]

Search strategy

The PubMed/Medline, Cochrane Library, Cinahl, ClinicalTrials.gov (clinical trials registry) and Web of Science Core Collection databases were searched through their respective online search engines. The search was performed on studies published between database inception and the defined search date December 9, 2020. The search strategies used in the single databases are displayed in the support material 2. Furthermore, the reference lists of the included studies were manually searched to find relevant articles. Abstracts and full-text reviews were evaluated independently in an unblinded standardized manner by two authors (AR and NW) to assess eligibility for inclusion. Disagreements between reviewers was resolved by consensus; if no agreement could be reached, a third author (JU) decided if the respective study was included.

Inclusion and exclusion criteria

Articles in English, German, Spanish, Portuguese, and Italian language were considered. Studies reporting resection of cholangiocarcinoma, both primary and secondary, in curative intent including resection of a segment of the hepatic artery with a control group of patients undergoing resection without arterial resection were included. Studies with an irrelevant abstract or title or with less than five patients were excluded, as were reviews, case reports, comments, and letters. Details of the study selection process are summarized in a PRISMA flowchart (Fig. 1).

Data collection

Data were extracted separately by two authors (AR and UR) and presented in a tabular fashion. The following descriptive data were documented for each selected study: first author, year of publication, inclusion period, country where the study was conducted, sample size and median follow up time (Table 1). Patient and operation characteristics were documented: age, gender, ASA classification, ECOG performance status, preoperative chemotherapy, type of operation, type of vessel resection and reconstruction, duration of surgery and blood loss. The following predefined outcomes were also extracted (Table 2):

- Mortality (30-day, In-Hospital, 90-day, and 100-day).
- Morbidity (any type of complication, surgical and medical, as defined in the single studies, Clavien-Dindo classification ≥ 3 [15]).
- Vessel complications (thrombosis of the portal vein or hepatic artery, stenosis of these vessels, and formation of pseudoaneurysms).
- Liver failure (as defined in the single studies).
- Postoperative bleeding (within 48 h or as defined in the single studies), survival time, actuarial survival (2-, 3- and 5-year survival), complete resection rate, proportion of patients with no resection during surgery, rate of histologically confirmed arterial invasion and lymph node positivity (number of positive lymph nodes and lymph node ratio).
- Overall reoperation rate.
- Length of hospital stay.
- Survival time.
- Proportion of patients with no resection during surgery.
- Rate of histologic arterial invasion.
- Lymph node positivity (number of positive lymph nodes and lymph node ratio).

In addition, subgroup analysis for patients with concomitant portal vein resection and patients who had undergone neoadjuvant chemotherapy prior to resection was carried out. Risk of bias was assessed using the ROBINS-I tool (risk of bias in non-randomized studies of interventions).[16]

Statistical analysis

The Review Manager (RevMan) software, version 5.3 (Cochrane Collaboration, Oxford, UK) was used. If a given outcome was reported in two or more studies, meta-analysis was performed. The magnitude of the effect estimate was visualized by forest plots. Odds Ratios (OR) were calculated for binary data and weighted mean differences for continuous data. The 95% confidence interval (CI), heterogeneity and statistical significance are reported for each outcome. The X^2 and the Kruskal–Wallis tests were used for evaluation of statistical significance. $P < 0.05$ was considered statistically significant. When the studies did not report mean and standard deviation, these were calculated using the methods described by the guidelines of the Cochrane Collaboration[17] and Hozo *et al.*[18] As not all studies reported time-to-event data and hazard ratios, the survival analysis was performed with weighted rates.

Results

From the 7628 articles, 10 cohort studies[19–28] from three countries (Japan, China, USA) published between 2007 and 2020 were included in the meta-analysis. The enrolment period of these studies ranged from 1981 to 2018. In these studies, a total of 2530 patients (408 patients in the AR group and 2122 in the control group) were included. The study features, patient and operation characteristics are presented in Table 1 the risk of bias assessment is presented in Table 3. No meta-analysis of duration of surgery could be performed as only one study

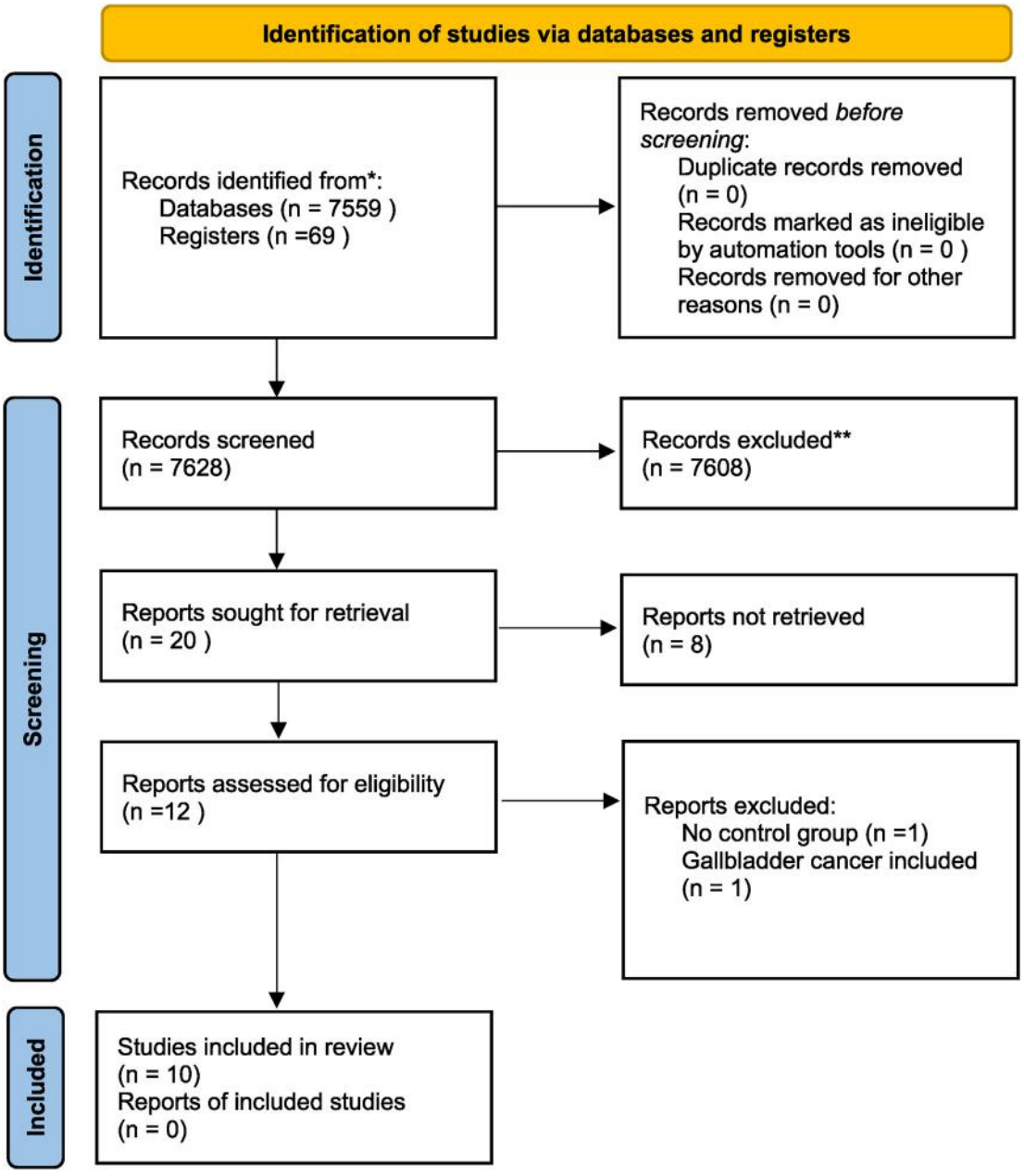


Figure 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

reported standard deviation of the mean. No meta-analysis was performed on 30-day mortality as only the study from Schimizzi *et al.*[27] reported on this outcome. Also, only the study Matsuyama *et al.*[24] reported on 90-day mortality, not allowing a meta-analysis on this outcome. No study reported on 100-day mortality. No subgroup analysis for patients with portal vein resection was performed as no data differentiating which patients in the AR group had a vein resection were provided. In addition, no subgroup analysis on patients who had undergone neoadjuvant chemotherapy prior to resection was performed, as only one study reported on this subject. Regarding adjuvant chemotherapy three studies did not report on this outcome.[20,21,23] Three studies reported that patients did not receive adjuvant chemotherapy.[19,22,25] From four studies that included patients undergoing adjuvant chemotherapy, only three reported on rates.[24,26–28] In these three studies, patients undergoing arterial resection received more frequently adjuvant treatment as compared to patients in the No AR group (AR: 98/202 patients, 49%, No AR: 242/981 patients, 25%, $p < 0.05$).

Weighted median survival was 30.4 months in the AR group and 42 months in the control group (data from five studies). Regarding blood loss, a favorable mean difference for the

Table 1 Descriptive data from the included studies

Study	Group/Sample Size	Inclusion Period	Country	Median follow up (months)
Miyazaki *et al*., 2007	AR n = 9	1981–2004	Japan	–
	No AVR n = 118			
	VR n = 34			
Igami *et al*., 2009	AR n = 53	2001–2008	Japan	–
	No AVR n = 176			
	VR n = 69			
Yu *et al*., 2014	AR n = 47	1998–2010	China	–
	No AVR n = 166			
	VR = 25			
Wang *et al*., 2015	AR = 24	2005–2012	China	–
	No AVR = 114			
	VR = 16			
Matsuyama *et al*., 2016	AR n = 44	1992–2014	Japan	38.2
	No AVR n = 74			
	VR n = 54			
Noji *et al*., 2016	AR n = 28	2000–2015	Japan	–
	No AR n = 181			
Peng *et al*., 2016	AR n = 26	2005–2012	China	18
	No AR n = 35			
Schimizzi *et al*., 2017	AR n = 12	1998–2015	USA	22
	No AVR = 170			
	VR n = 19			
Higuchi *et al*., 2018	AR n = 19	2000–2016	Japan	–
	No AVR n = 174			
	VR n = 56			
Mizuno *et al*., 2020	AR n = 146	2001–2018	Japan	59
	No AVR n = 484			
	VR n = 157			

AR: arterial resection; AVR: arterial and venous resection; VR: venous resection

control group could be verified, but the result was not statically significant (221.95, 95% CI [−229.77, 673.68], p = 0.34) (Fig. 2).

Concerning in-hospital mortality, this meta-analysis showed higher mortality rates in the AR group compared to the control group (6.8% vs 3.3%, OR 2.65, 95% CI [1.27; 5.32], p = 0.009) (Fig. 3). In this meta-analysis regarding morbidity, higher rates were observed in the AR group (55% vs 46%, OR 1.44, 95% CI [0.67; 3.09], p = 0.003) (Fig. 4a). In this meta-analysis regarding morbidity defined as Clavien-Dindo classification $\geq$ 3, statically significant higher rates could be verified in the AR group (52% vs 47%, OR 1.44, 95% CI [1.02; 1.75], p = 0.04) (Fig. 4b). Six studies reported on vascular complications, with lower rates in the control group (13% vs 5%, OR 3.53, 95% CI [2.26; 5.53, p < 0.00001) (Fig. 5). Liver failure rates were higher in the AR group, but the difference was not statically significant (26% vs 16%, OR 2.50, 95% CI [0.95; 6.54, p = 0.06) (Fig. 6). Post-operative bleeding was more frequent in the AR group (4% vs 2%, OR 2.19, 95% CI [1.06; 4.52, p = 0.03) (Fig. 7).

Concerning actuarial survival, 1-year, 3-year and 5-year survival rates were lower in the AR group compared to the control group, respectively (54% vs 69%, OR 0.55, 95% CI [0.34; 0.91 p = 0.02) (Fig. 8), (34% vs 38%, OR 0.74, 95% CI [0.55; 0.98, p = 0.03) (Fig. 9), (18% vs 29%, OR 0.54, 95% CI [0.39; 0.75, p = 0.0002) (Fig. 10).

R0 resection rates were slightly higher in the control group, but the difference was not statistically significant (68% vs 75%, OR 0.70, 95% CI [0.46; 1.07, p = 0.10) (Fig. 11).

Table 2 Patient and operation characteristics from the include studies

Study	Group	Age (Mean ± SD)	Gender (Male) (%)	ASA (3 and 4) %	ECOGPS	Preoperative chemotherapy (%)	Type of operation	Type of vessel resection and reconstruction	Duration of surgery (min)	Blood loss (mL)
Miyazaki et al., 2007	AR n = 9	59 ± 9	78	–	–	–	Hepatectomy	HA	–	1726 ± 1253
	No AVR n = 118	65 ± 11	63	–	–	–	Hepatectomy	–	–	1523 ± 1147
	VR n = 34	64 ± 9	53	–	–	–	Hepatectomy	PV, HV and IVC	–	1975 ± 1474
Igami et al., 2009	AR n = 53	–	–	–	–	–	Hepatectomy	HA	–	–
	No AVR n = 176	–	–	–	–	–	Hepatectomy	–	–	–
	VR n = 69	–	–	–	–	–	Hepatectomy	PV	–	–
Yu et al., 2014	AR n = 47	–	–	–	–	–	Hepatectomy	HA	–	–
	No AVR n = 166	–	–	–	–	–	Hepatectomy	–	–	–
	VR = 25	–	–	–	–	–	Hepatectomy	PV	–	–
Wang et al., 2015	AR = 24	60 ± 9	75	–	–	–	Hepatectomy	HA, Vein graft, E–E Anastomosis	–	1175 ± 713
	No AVR = 114	57 ± 12	61	–	–	–	Hepatectomy	–	–	527 ± 596
	VR = 16	53 ± 7	25	–	–	–	Hepatectomy	PV E–E Anastomosis	–	980 ± 511
Matsuyama et al., 2016	AR n = 44	69	61	–	–	–	Trisectionectomy, Hemihepatectomy, Caudate lobectomy, bile duct resection, Pancreatoduodenectomy	HA E–E Anastomosis	914 ± 148	2212 ± 2192
	No AVR n = 74	69	74	–	–	–	Trisectionectomy, Hemihepatectomy, Caudate lobectomy, bile duct resection, Pancreatoduodenectomy	–	703 ± 134	1929 ± 1387
	VR n = 54	70	72	–	–	–	Trisectionectomy, Hemihepatectomy, Caudate lobectomy, bile duct resection, Pancreatoduodenectomy	PV E–E Anastomosis, Interposition	773 ± 128	1981 ± 1926
Noji et al., 2016	AR n = 28	67	71	–	–	–	Hepatectomy	HA	771	1930
	No AR n = 181	69	71	–	–	–	Hepatectomy	–	638	1750
Peng et al., 2016	AR n = 26	59 ± 7	69	–	–	–	Left Hepatectomy	HA	–	327 ± 146
	No AR n = 35	63 ± 7	57	–	–	–	Left Hepatectomy	–	–	400 ± 209
Schimizzi et al., 2017	AR n = 12	52	50	67	–	25	Right and Left hepatectomy, Caudate resection	RHA, LHA, Vein Graft	–	2100
	No AVR = 170	66	40	71	–	4	Radical Cholecystectomy, Right and Left hepatectomy, Pancreaticoduodenectomy, Caudate resection	–	–	1011
	VR n = 19	62	53	89	–	5	Right and Left hepatectomy, Caudate resection	PV, Venous/ Prosthetic Patch/Conduit	–	1020
Higuchi et al., 2018	AR n = 19	67	63	–	–	–	Hepatectomy	HA	520	1580
	No AVR n = 174	70	72	–	–	–	Hepatectomy	–	389	1234
	VR n = 56	69.5	68	–	–	–	Hepatectomy	PV	415	1364

Table 2 (*continued*)

Study	Group	Age (Mean ± SD)	Gender (Male) (%)	ASA (3 and 4) %	ECOGPS	Preoperative chemotherapy (%)	Type of operation	Type of vessel resection and reconstruction	Duration of surgery (min)	Blood loss (mL)
Mizuno et al., 2020	AR n = 146	67	49	–	–	–	Hepatectomy, combined pancreatoduodenectomy	HA, E–E Anastomosis, Graft, rotating artery	685	1491
	No AVR n = 484	69	67	–	–	–	Hepatectomy, combined pancreatoduodenectomy	–	550	1078
	VR n = 157	67	68	–	–	–	Hepatectomy, combined pancreatoduodenectomy	PV,E–E Anastomosis, Graft, direct suture	610	1498

AR: arterial resection; No AVR: no arterial and venous resection; VR: venous resection; ASA: American Society of Anesthesiologists classification; ECOGPS: Eastern Cooperative Oncology Group performance status

Study	Group	Mortality in-hospital (%)	Mortality 30-day (%)	Mortality 90-day (%)	Mortality 100-day (%)	Morbidity (%)	Morbidity – Clavien Dindo III-V (%)	Vascular complications (%)	Liver failure (%)	Postoperative bleeding (%)	Reoperation rate (%)	Mean survival (Months)	Median survival (Months)
Miyazaki et al., 2007	AR = 9	33	–	–	–	78	–	11	–	11	–	–	7
	No AVR = 118	4	–	–	–	36	–	4	–	4	–	–	–
	VR = 34	9	–	–	–	38	–	3	–	3	–	–	11
Igami et al., 2009	AR n = 53	–	–	–	–	–	–	–	–	–	–	–	–
	No AVR n = 176	–	–	–	–	–	–	–	–	–	–	–	–
	VR n = 69	–	–	–	–	–	–	–	–	–	–	–	–
Yu et al., 2014	AR n = 47	–	–	–	–	40.4	–	–	–	–	–	–	–
	No AVR n = 166	–	–	–	–	12.1	–	–	–	–	–	–	–
	VR = 25	–				32	–	–	–	–	–	–	–
Wang et al., 2015	AR = 24	4	–	–	–	41.7	–	4	–	4	–	–	26
	No AVR = 114	4	–	–	–	35.1	–	2	–	2	–	–	32
	VR = 16	0	–	–	–	37.5	–	0	–	0	–	–	20
Matsuyama et al., 2016	AR n = 44	9	–	9	–	81.8	66	14	11	7	–	–	–
	No AVR n = 74	4	–	4	–	82.4	49	8	8	3	–	–	–
	VR n = 54	3.7	–	3.7	–	70.3	43	6	7	4	–	–	–
Noji et al., 2016	AR n = 28	3.6	–	–	–	–	57.1	–	31	9	–	–	–
	No AR n = 181	6.6	–	–	–	–	51.3	–	32	7	–	–	–
Peng et al., 2016	AR n = 26	7.7	–	–	–	42.9	19	0	12	0	–	–	49
	No AR n = 35	8.6	–	–	–	57.7	14	0	6	0	–	–	24
Schimizzi et al., 2017	AR n = 12	–	0	–	–	50	67	–	0	–	–	–	33
	No AVR = 170	–	7	–	–	69	61	–	4	–	–	–	21
	VR n = 19	–	16	–	–	68	47	–	16	–	–	–	24
Higuchi et al., 2018	AR n = 19	16	–	–	–	–	47	26	–	5.3	–	–	–
	No AVR n = 174	1.7	–	–	–	–	33	3	–	1.7	–	–	–
	VR n = 56	5.4	–	–	–	–	45	13	–	1.8	–	–	–
Mizuno et al., 2020	AR n = 146	4	–	–	–	–	51	16	34	1.4	–	–	29
	No AVR n = 484	1	–	–	–	–	48	3	22	0.4	–	–	61
	VR n = 157	3	–	–	–	–	48	10	34	1.3	–	–	34

AR: arterial resection; No AVR: no arterial and venous resection; VR: venous resection;

Study	Group	1-year survival (%)	2-year survival (%)	3-year survival (%)	5-year survival (%)	Adjuvant chemotherapy (Yes/No//%)	R0 (%)	R1 (%)	R2 (%)	No resection (%)	pTNM
Miyazaki et al., 2007	AR = 9	11	–	11	0	No	67	–	–	–	–
	No AVR = 118	–	–	–	–	No	65	–	–	–	–
	VR = 34	42	0	16	13	No	56	–	–	–	–
Igami et al., 2009	AR n = 53	66	–	15	4	No	–	–	–	–	–
	No AVR n = 176	74	–	34	14	No	–	–	–	–	–
	VR n = 69	62	–	17	7	No	–	–	–	–	–
Yu et al., 2014	AR n = 47	40	–	19.1	6.4	–	–	–	–	–	–
	No AVR n = 174	62.6	–	27.6	21.8	–	–	–	–	–	–
	VR = 25	48	–	20	0	–	–	–	–	–	–
Wang et al., 2015	AR = 24	–	–	–	25	–	–	–	–	–	–
	No AVR = 114	–	–	–	35.7	–	–	–	–	–	–
	VR = 16	–	–	–	25	–	–	–	–	–	–
Matsuyama et al., 2016	AR n = 44	–	–	–	22	45.4	80	20	0	–	–
	No AVR n = 74	–	–	–	46	12.1	74	26	0	–	–
	VR n = 54	–	–	–	51	51.8	80	20	0	–	–
Noji et al., 2016	AR n = 28	61	–	36	18	–	71	–	–	–	–
	No AR n = 181	80	–	54	27	–	81	–	–	–	–
Peng et al., 2016	AR n = 26	61.9	41.6	29.7	14.8	No	72.3	–	–	–	–
	No AR n = 35	58.2	50.7	44.3	23.6	No	80	–	–	–	–
Schimizzi et al., 2017	AR n = 12	–	–	–	–	53	67	33	0	–	–
	No AVR = 170	–	–	–	–	53	70	30	0	–	–
	VR n = 19	–	–	–	–	42	74	26	0	–	–
Higuchi et al., 2018	AR n = 19	–	–	–	14.5	Yes	63	37	0	0	–
	No AVR n = 174	–	–	–	45.8	Yes	66	34	0	0	–
	VR n = 56	–	–	–	21	Yes	63	37	0	0	–
Mizuno et al., 2020	AR n = 146	–	–	45	27	49	64	36	1	–	–
	No AVR n = 484	–	–	53	35	9	85	14	1	–	–
	VR n = 157	–	–	32	18	40	69	27	4	–	–

AR: arterial resection; No AVR: no arterial and venous resection; VR: venous resection; Proportion of macroscopically complete (R0), microscopically incomplete (R1), and macroscopically incomplete (R2) resection; histopathological tumor stage (pTNM)

Regarding adjuvant chemotherapy

Study	Group	Proportion of patients with histologically confirmed arterial tumor invasion (%)	Mean of tumor-positive lymph nodes and of retrieved lymph nodes	Median of tumor-positive lymph nodes and of retrieved lymph nodes
Miyazaki et al., 2007	AR = 9	–	–	–
	No AVR = 118	–	–	–
	VR = 34	–	–	–
Igami et al., 2009	AR n = 53	–	–	–
	No AVR n = 176	–	–	–
	VR n = 69	–	–	–
Yu et al., 2014	AR n = 47	–	–	–
	No AVR n = 174	–	–	–
	VR = n = 25	–	–	–
Wang et al., 2015	AR = 24	–	–	–
	No AVR = 114	–	–	–
	VR = 16	–	–	–

Table 2 (*continued*)

Study	Group	Proportion of patients with histologically confirmed arterial tumor invasion (%)	Mean of tumor-positive lymph nodes and of retrieved lymph nodes	Median of tumor-positive lymph nodes and of retrieved lymph nodes
Matsuyama et al., 2016	AR n = 44	32	–	–
	No AVR n = 74	7	–	–
	VR n = 54	9	–	–
Noji et al., 2016	AR n = 28	22	–	–
	No AR n = 181	12	–	–
Peng et al., 2016	AR n = 26	–	–	–
	No AVR n = 35	–	–	–
Schimizzi et al., 2017	AR n = 12	–	–	–
	No AVR = 170	–	–	–
	VR n = 19	–	–	–
Higuchi et al., 2018	AR n = 19	–	–	–
	No AVR n = 174	–	–	–
	VR n = 56	–	–	–
Mizuno et al., 2020	AR n = 146	–	–	–
	No AVR n = 484	–	–	–
	VR n = 157	–	–	–

AR: arterial resection; No AVR: no arterial and venous resection; VR: venous resection.

Table 3 Risk of bias assessed using the ROBINS-I tool (risk of bias in non-randomized studies of interventions)[8]

	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Miyazaki et al. 2007	Moderate: Difference between three resection groups analysed and reported	Low: Included eligible patients defined, baseline characteristics, intervention and follow up same	Low: Intervention (vascular resection) defined for all patient/ groups	Low: Single intervention of interest (vascular resection)	Low: Reasons for missing (not included) reported	Serious: Operative morbidity not defined, Survival stated and reported	Serious: Operative morbidity and mortality stated in analysis and reported, operative morbidity not defined before analysis (classification or something)- > several postop complications reported
Igami et al. 2009	Moderate: Patients have been divided into three groups (retrospective) and no differences between groups have been reported	Low: Included eligible patients defined, baseline characteristics, intervention and follow up same	Low: All surgery approaches for different groups stated and performed in the same hospital (assuming the same team/ surgeon)	Low: Intervention stated as surgical resection with curative intent - > single intervention	Low: Missings (death) stated and regression analysis accordingly	Serious: Morbidity and mortality reported (absolute and %), survival reported Both outcomes not defined beforehand Morbidity not defined beforehand	Moderate
Yu et al. 2014	Moderate: Difference among predefined groups analysed and stated (p511)	Moderate: in and exclusion criteria stated, predefined groups observed according to differences	Low: Intervention stated as vascular resection in surgical	Low: Single intervention of interest (vascular resection)	Low: missings stated (death during surgery) IPD and aggregated data pooled for	serious: Complications stated and reported as outcome but not defined	Moderate

(*continued on next page*)

Table 3 (*continued*)

	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
			management of HCCA for all participants		outcomes (complications and long-term survival)		
Wang et al. 2015	Moderate: Difference between three resection groups analysed and reported	Low: All patients with resectable hilar cholangiocarcinoma have been included	Low: Surgical intervention for all patients, stated and reported	Low: Resection and reconstruction approaches reported (Table 1)	Low: Missings/death reported and analysed via Kaplan-Maier	Low: Outcome measures defined and reported accordingly	Low: Outcomes predefined and reported
Matsuyama et al. 2016	Low: Patients divided into three groups - > characteristics compared (including p-Values) - > no differences between groups	Low: All eligible patients included	Low: Surgery with curative intent, procedures reported	Low: Intervention stated as surgical resection with curative intent - > single intervention	Low: Missings/death reported and analysed	Low: Outcome measurements defined and reported accordingly	Low: outcomes which have been reported have been beforehand
Noji et al. 2016	Low: Analysis for potential cofounders stated defined before analysis	Low: Eligible patient included, exclusion reported	Low: Surgical approach reported and the same with all patients	Low: Intervention stated as surgical resection with curative intent - > single intervention	Low: Missing reported, Potentially confounding analysed via binary logistic regression	Low: Survival, morbidity and mortality according to Calvien-Dindo pre-defined outcomes have been reported based on definition	Low: Survival, morbidity and mortality according to Calvien-Dindo pre-defined outcomes have been reported
Peng et al. 2016	Low: Patients divided into two groups - > characteristics compared (including p-Values) - > no differences between groups	Low: All patients undergoing radical left hepatectomy for hilar cholangiocarcinoma have been included in the study	Low: Intervtion the same for all patients	Low: Single intervention for all patients, surgical procedure reported, differences and reasons why are stated	Low: Missings/deaths reported and reported (Kapla-Maier)	Low: Outcome measurements defined and reported accordingly	Low: outcomes which have been reported have been beforehand
Schimizzi et al. 2018	Low: potential confounder stated and collected (age, race comorbidities); statistical analysis described but not specifically focused on confounding	Low: Included eligible patients defined, baseline characteristics, intervention and follow up same	Low: Intervention status stated (Table 2A)	Low: Single intervention of interest (Vascular resection)	Low: OS and RFS stated as outcome and reported	Moderate: OS defined and RFS defined	Low
Higuchi et al. 2018	Moderate: Patient groups have been analysed regarding differences before intervention (surgery), p-value have been reported too	Low: Included eligible patients defined, baseline characteristics, intervention and follow up same	Low: Surgical approach reported and all included patients	Low: Intervention same for all patients, HARs performed by general surgeon and changed to plastic surgeons due to more experience in microscopic surgery (calculations done and stated with and without patients undergoing intervention by general surgeon)	Low: uni and multivariate analysis of outcomes, all analysis reported	Moderate: Outcome measurement appropriate and could not be influenced by knowledge of intervention received	Moderate

Table 3 (*continued*)

	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Mizuno et al. 2020	Low: Patients divided into two groups and two subgroups (for patients with VR) - > characteristics compared (including p-Values) - > no differences between groups	Low: Eligible patient included, exclusion reported	Low: Surgical procedure stated and the same except intervention of VR	Low: intervention VR can be deviated ("control": no VR)	Low: Missings/deaths reported and reported (Kapla-Maier)	Moderate: OS defined beforehand and reported accordingly, all other outcomes stated (no definition e.g. TNM etc)	Moderate

Discussion

In this systematic review and meta-analysis, we have assessed the impact of arterial resection in surgery for cholangiocarcinoma. Most patients with perihilar cholangiocarcinoma present with unresectable disease and have a poor survival. Adjuvant chemotherapy provides significant improvement in overall survival with any adjuvant therapy after surgery compared with surgery only (HR 0.74; 95% CI, 0.67 to 0.83; P < 0.001).[29] Nevertheless, sensitivity and response to chemotherapy is generally rather poor. In most patients, liver transplantation is not a viable option due to the highly selective criteria. Therefore, complete surgical resection offers the only chance of cure or at least longer-term survival. In a previous meta-analysis on the topic published in 2013, resection of the hepatic artery in surgery for cholangiocarcinoma was shown to have higher morbidity and mortality rates.[30] The authors concluded that arterial resection has no proven benefit. Since the publication of the mentioned meta-analysis, several larger studies on the topic have been published, which was the motivation for us to conduct the present systematic review with meta-analysis. In contrast to the previous study, we only performed an analysis on arterial resections and only included studies reporting exclusively on cholangiocarcinoma. We also provide an extended analysis on multiple outcomes specifically regarding arterial resection. Furthermore, only studies with a control group were included.

Our results mostly corroborate those of the previous meta-analysis. Morbidity and mortality rates, although deemed acceptable in absolute terms, were shown to be substantially higher for AR while AR did not result in a higher probability of microscopically complete resection and long-term survival was shorter. Given the non-randomized design of all included studies, which implies a considerable selection bias, these findings do not necessarily mean that AR is detrimental to long-term survival in patients which would otherwise not be resected at all but only receive palliative treatment. To provide a valid information on the value of AR in such patients, a randomized controlled trial would be necessary. It needs to be noted that in the included studies, there was no clear differentiation if AR was planned a priori or performed due to intraoperative injury of the hepatic artery. An indication for the latter could be that histological arterial invasion was shown in only 28% of patients in the AR group in the studies where it was reported.[23,24]

Neoadjuvant chemotherapy might improve resectability and outcomes for patients with locally advanced cholangiocarcinoma and several clinical trials are currently evaluating its role for the treatment of cholangiocarcinoma However, results will be available only in several years from now. In our analysis, only the study by Schimizzi et al.[27] reported on neoadjuvant chemotherapy with a higher proportion of patients who underwent neoadjuvant chemotherapy in the AR group. Interestingly, a higher median survival was observed in the AR group when compared to patients who underwent combined arterial and venous resection or venous resection alone (33, 21 and 24 months, respectably).

In addition to neoadjuvant or perioperative chemotherapy alone, chemotherapy combined with transplantation may be an alternative for patients with arterial invasion. According to the guidelines of the British Society of Gastroenterology, a liver transplantation may be considered in highly selected patients in specialized centers after neoadjuvant chemotherapy.[31] Similarly, the guidelines of the European Association for the Study of the Liver (EASL) state that in patients with neoadjuvant therapy concepts, liver transplantation may be considered.[32] In a study involving patients from 10 US hospitals that compared transplantation with resection for hilar cholangiocarcinoma, among all patients who underwent curative-intent surgery, transplantation was associated with improved 5-year survival (64% vs 18%). Of note, many of the transplant cases in the aforementioned study were relatively early stage cholangiocarcinomas, and many of them were cases of sclerosing cholangitis, making a direct comparison to our patient collective not possible.[33] A meta-analysis from 2012, which included 14 studies, addressed the efficacy and safety of liver transplantation in patients with cholangiocarcinoma. Neoadjuvant therapies provided better outcomes with OR for 1-, 3- and 5-year pooled survival of OR 0.83 (95% CI = 0.57–0.98), OR 0.57 (95% CI = 0.18–0.92) and OR 0.65 (95% CI = 0.40–0.87).[34] In a prospective study involving 21 patients who underwent liver transplantation after

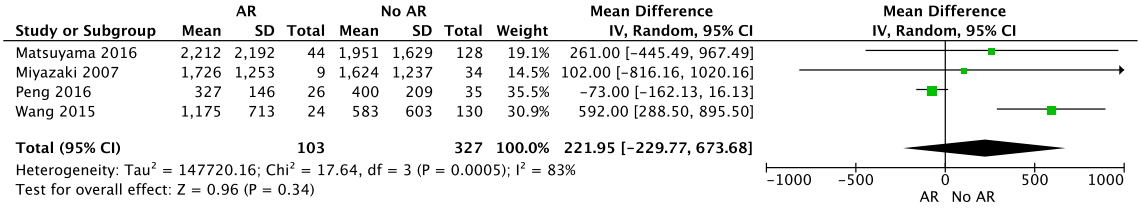


Figure 2 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding blood loss. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

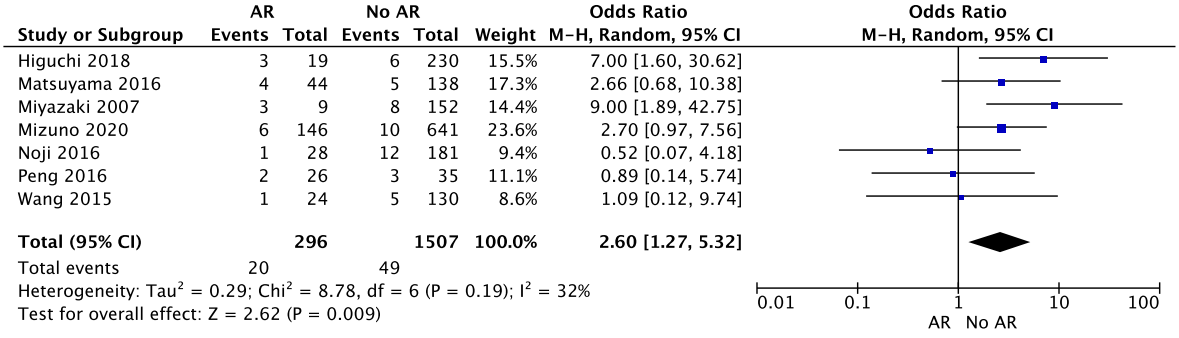


Figure 3 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding mortality. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

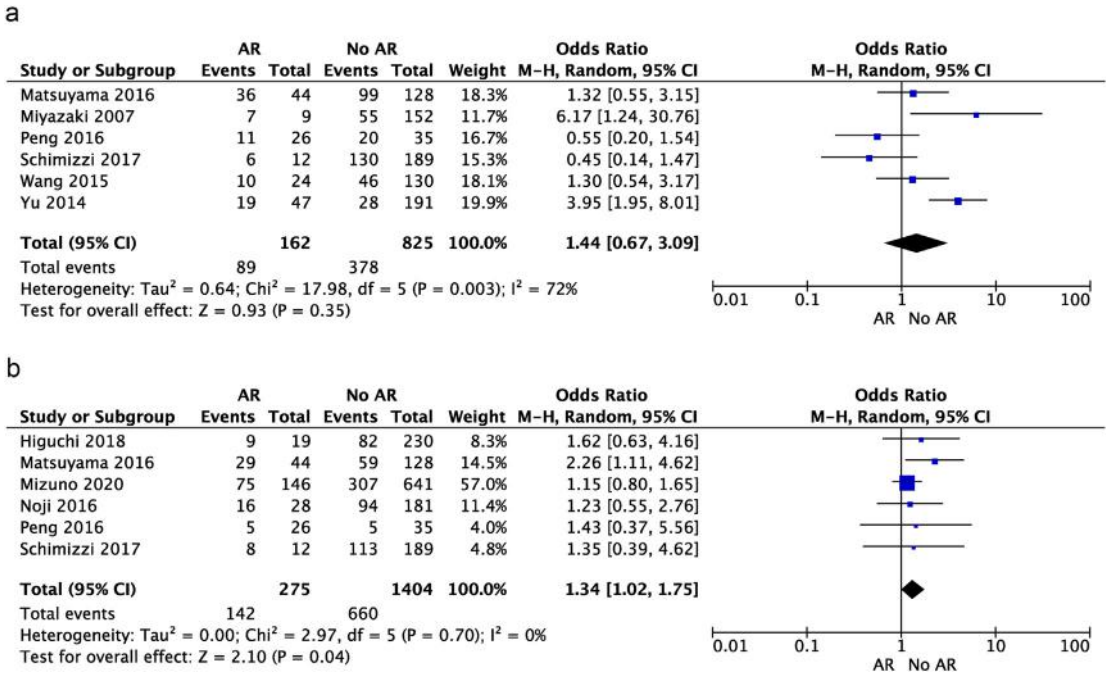


Figure 4 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding morbidity. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

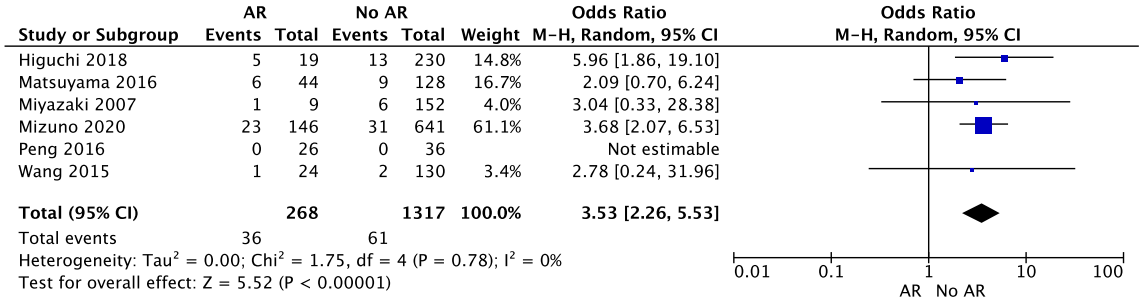


Figure 5 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding vascular complications. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

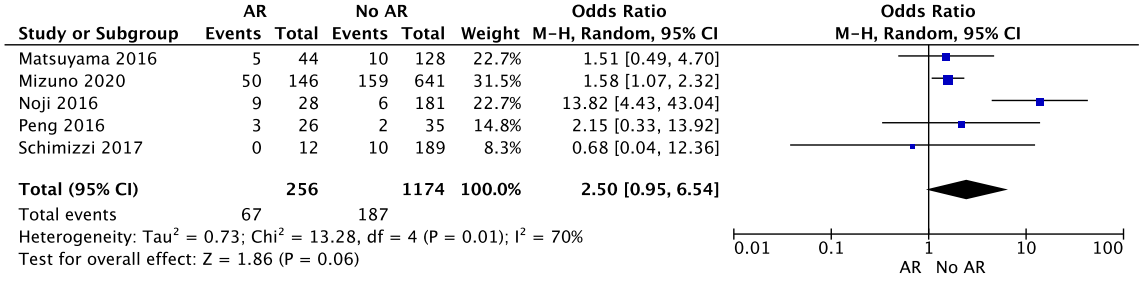


Figure 6 Forest plot of pooled odds ratio with 95% CI for AR vs no AR liver failure. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

neoadjuvant chemotherapy, overall survival was 100% (95% CI 100-100) at 1 year, 83.3% (27.3–97.5) at 3 years, and 83.3% (27.3–97.5) at 5 years.[35] None of the studies included in our meta-analysis reported on a liver transplantation group. A probable limitation of studies addressing this question is that only few patients qualify for liver transplantation due to the very strict indication criteria.[36]

This meta-analysis has some limitations. The main drawback is that it is exclusively based on retrospective studies with heterogeneous outcome definitions and study-arms. The retrospective study design could also represent a problem in terms of selection bias. The long inclusion period does not necessary reflect contemporary surgical techniques. The results are based on a non-randomized, uncontrolled comparison of patients with

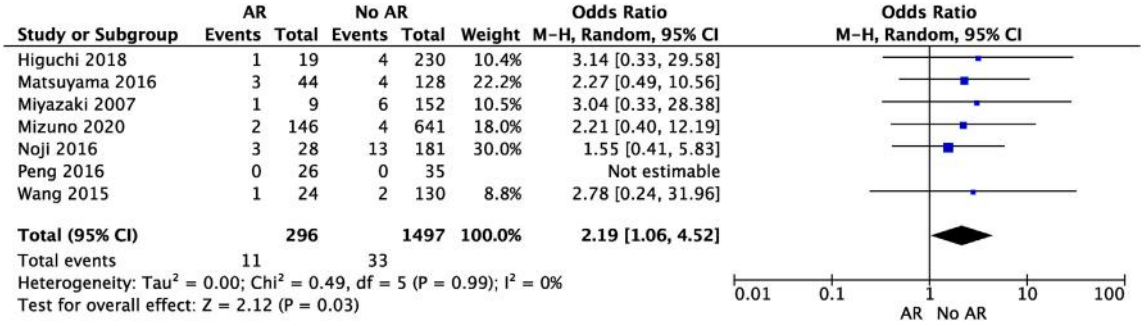


Figure 7 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding postoperative bleeding. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

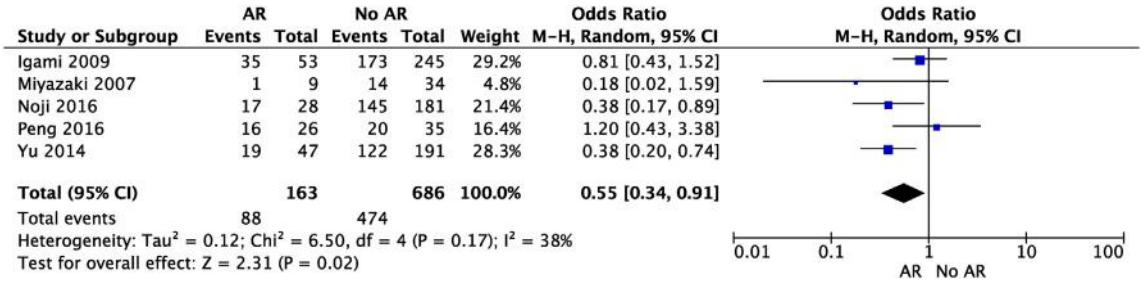


Figure 8 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding 1-year survival. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

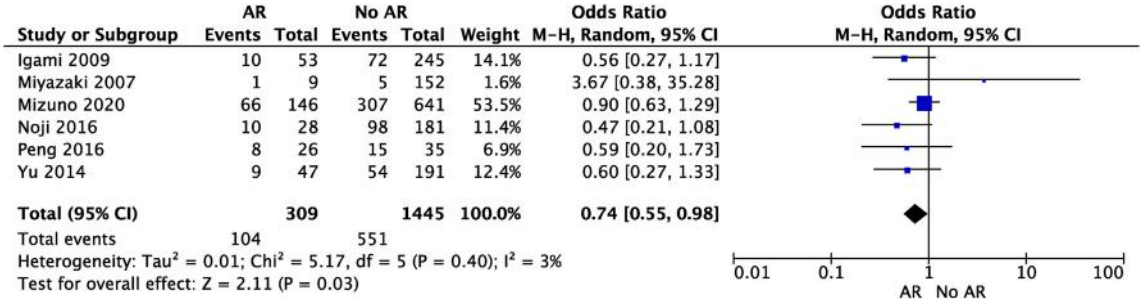


Figure 9 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding 3-year survival. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

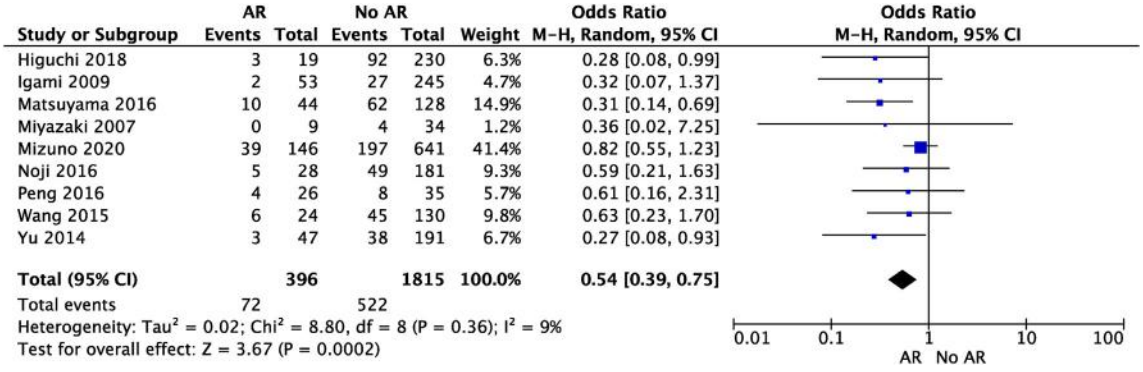


Figure 10 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding 5-year survival. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

different backgrounds. There was no clear distinction across all the studies concerning potential differences between groups receiving adjuvant therapy. Since individual patient data were not available, it is not possible to estimate the effects of adjuvant chemotherapy on outcome in this group of patients. When reported, more patients in the AR group received adjuvant chemotherapy so that this confounder should be taken in account when interpreting the results. Furthermore, a few of the studies reported on liver resection combined with pancreatic resection.[24,27,28] In these patients, pancreatic resection was performed if the tumor extended distally to the intrapancreatic bile duct or pancreatic head. This heterogeneity is another limitation of the study. The PRISMA guidelines were followed to ensure transparency and standardized reporting, but the risk of

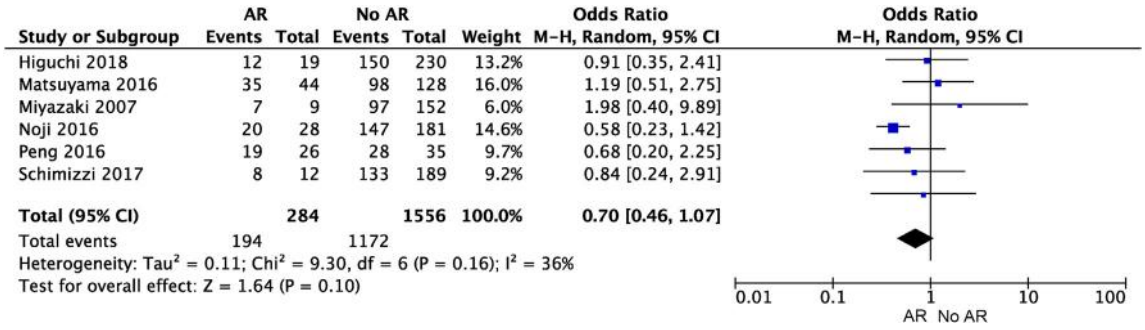


Figure 11 Forest plot of pooled odds ratio with 95% CI for AR vs no AR regarding R0. AR: Patients undergoing surgery for cholangiocarcinoma with arterial resection. No AR: Patients undergoing surgery for cholangiocarcinoma without arterial resection. The odds ratios presented are AR vs. no AR (with no AR being the reference)

bias is still considerable. Moreover, the number of studies and patients were relatively small. Therefore, the data should be carefully interpreted, and applied. Further, analysis, e.g. a network-meta-analysis on comparing arterial resections with non-surgical therapies are necessary in the future. The strength of this meta-analysis is that all available studies providing comparative information on the outcome of patients undergoing surgery for cholangiocarcinoma with arterial resection with a control group were included.

Conclusion

Evidence from non-randomized studies shows higher morbidity and mortality rates and shorter long-term survival in patients with cholangiocarcinoma undergoing AR. However, the results are prone to selection bias, and only randomized trials comparing AR with and without neoadjuvant therapy and palliative treatment in patients with cholangiocarcinoma and arterial invasion might reveal a possible benefit of arterial resection.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Authors' contributions

AR and MG conducted the literature search. AR conducted the statistical analysis. AR outlined, wrote, and drafted the manuscript. All authors critically revised the manuscript and read and approved the final version of the manuscript.

Acknowledgements

Not applicable.

Funding sources

No Funding was received.

Conflict of interest

None declared.

References

1. Young AL, Prasad KR, Toogood GJ, Lodge JP. (2010) Surgical treatment of hilar cholangiocarcinoma in a new era: comparison among leading Eastern and Western centers, Leeds. *J Hepatobiliary Pancreat Sci* 17:497–504. https://doi.org/10.1007/s00534-009-0203-6.
2. Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. (2005) Cholangiocarcinoma. *Lancet (London, England)* 366:1303–1314. https://doi.org/10.1016/S0140-6736(05)67530-7.
3. Ito F, Cho CS, Rikkers LF, Weber SM. (2009) Hilar cholangiocarcinoma: current management. *Ann Surg* 250:210–218. https://doi.org/10.1097/SLA.0b013e3181afe0ab.
4. Hidalgo E, Asthana S, Nishio H, Wyatt J, Toogood GJ, Prasad KR *et al*. (2008) Surgery for hilar cholangiocarcinoma: the Leeds experience. *Eur J Surg Oncol* 34:787–794. https://doi.org/10.1016/j.ejso.2007.10.005.
5. Klatskin G. (1965) Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis. An unusual tumor with distinctive clinical and pathological features. *Am J Med* 38:241–256.
6. Serrablo A, Serrablo L, Alikhanov R, Tejedor L. (2021) Vascular resection in perihilar cholangiocarcinoma. *Cancers* 13:5278. https://doi.org/10.3390/cancers13215278.
7. She W, Cheung TT, Ma KW, Tsang SHY, Dai WC, Chan ACY *et al*. (2020 Sep) Vascular resection and reconstruction in hilar cholangiocarcinoma. *ANZ J Surg* 90:1653–1659.
8. Matsuyama R, Mori R, Ota Y, Homma Y, Kumamoto T, Takeda K *et al*. (2016 Aug) Significance of vascular resection and reconstruction in surgery for hilar cholangiocarcinoma: with special reference to hepatic arterial resection and reconstruction. *Ann Surg Oncol* 23:475–484.

9. Heinrich S, Baumgart J, Mittler J, Lang H. (2016 Feb) [Vascular reconstruction in hepatic surgery]. *Chirurg* 87:100–107.
10. Mizuno T, Ebata T, Yokoyama Y, Igami T, Yamaguchi J, Onoe S *et al*. (2020 Sep 24) Combined vascular resection for locally advanced perihilar cholangiocarcinoma. *Ann Surg* 1.
11. Govil S, Reddy MS, Rela M. (2014 Aug) Surgical resection techniques for locally advanced hilar cholangiocarcinoma. *Langenbeck's Arch Surg* 399:707–716.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD *et al*. (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372:n71. https://doi.org/10.1136/bmj.n71, 7 https://www.crd.york.ac.uk/prospero/.
13. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=223396.
14. Rebelo A, Ukkat J, Klose J, Ronellenfitsch U, Kleeff J. (2021 Oct 5) Surgery with arterial resection for hilar cholangiocarcinoma: protocol for a systematic review and meta-analysis. *JMIR Res Protoc* 10:e31212. https://doi.org/10.2196/31212. PMID: 34609321.
15. Dindo D, Demartines N, Clavien P-A. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 240:205–213. https://doi.org/10.1097/01.sla.0000133083.54934.ae.
16. Sterne JAC, Hernán MA, McAleenan A, Reeves BC, Higgins JPT. (Feb 16, 2020) Assessing risk of bias in a non-randomized study. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, *et al*. eds. *Cochrane handbook for systematic reviews of interventions*. London: Cochrane.
17. Green S, Higgins J, Alderson P, Clarke M, Mulrow C, Oxman A. (2008) *Cochrane handbook for systematic reviews of interventions*. West Sussex, England: John Wiley & Sons.
18. Hozo SP, Djulbegovic B, Hozo I. (2005) Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 5:13. https://doi.org/10.1186/1471-2288-5-13.
19. Miyazaki M, Kato A, Ito H, Kimura F, Shimizu H, Ohtsuka M *et al*. (2007) Combined vascular resection in operative resection for hilar cholangiocarcinoma: does it work or not? *Surgery* 141:581–588. https://doi.org/10.1016/j.surg.2006.09.016.
20. Yu W, Shao M, Gu Z, Shi S, Shen N, Zhang Y. (2014) Effect evaluation of vascular resection for patients with hilar cholangiocarcinoma: original data and meta-analysis. *Hepato-Gastroenterology* 61:307–313.
21. Wang ST, Shen SL, Peng BG, Hua YP, Chen B, Kuang M *et al*. (2015) Combined vascular resection and analysis of prognostic factors for hilar cholangiocarcinoma. *Hepatobiliary Pancreat Dis Int* 14:626–632. https://doi.org/10.1016/s1499-3872(15)60025-x.
22. Peng C, Li C, Wen T, Yan L, Li B. (2016) Left hepatectomy combined with hepatic artery resection for hilar cholangiocarcinoma: a retrospective cohort study. *Int J Surg* 32:167–173. https://doi.org/10.1016/j.ijsu.2016.06.038.
23. Noji T, Tsuchikawa T, Okamura K, Tanaka K, Nakanishi Y, Asano T *et al*. (2016) Concomitant hepatic artery resection for advanced perihilar cholangiocarcinoma: a case-control study with propensity score matching. *J Hepatobil Pancreat Sci* 23:442–448. https://doi.org/10.1002/jhbp.363.
24. Matsuyama R, Mori R, Ota Y, Homma Y, Kumamoto T, Takeda K *et al*. (2016) Significance of vascular resection and reconstruction in surgery for hilar cholangiocarcinoma: with special reference to hepatic arterial resection and reconstruction. *Ann Surg Oncol* 23:475–484. https://doi.org/10.1245/s10434-016-5381-2.
25. Igami T, Nishio H, Ebata T, Yokoyama Y, Sugawara G, Nimura Y *et al*. (2010) Surgical treatment of hilar cholangiocarcinoma in the "new era": the Nagoya University experience. *J Hepatobil Pancreat Sci* 17:449–454. https://doi.org/10.1007/s00534-009-0209-0.
26. Higuchi R, Yazawa T, Uemura S, Izumo W, Ota T, Kiyohara K *et al*. (2018) Surgical outcomes for perihilar cholangiocarcinoma with vascular invasion. *J Gastrointest Surg* 23:1443–1453. https://doi.org/10.1007/s11605-018-3948-x.
27. Schimizzi GV, Jin LX, Davidson JT, Krasnick BA, Ethun CG, Pawlik TM *et al*. (2018) Outcomes after vascular resection during curative-intent resection for hilar cholangiocarcinoma: a multi-institution study from the US extrahepatic biliary malignancy consortium. *HPB* 20:332–339. https://doi.org/10.1016/j.hpb.2017.10.003.
28. Mizuno T, Ebata T, Yokoyama Y, Igami T, Yamaguchi J, Onoe S *et al*. (2020) Combined vascular resection for locally advanced perihilar cholangiocarcinoma. *Ann Surg*. https://doi.org/10.1097/sla.0000000000004322.
29. Rangarajan K, Simmons G, Manas D, Malik H, Hamady ZZ. (2020 Apr) Systemic adjuvant chemotherapy for cholangiocarcinoma surgery: a systematic review and meta-analysis. *Eur J Surg Oncol* 46:684–693. https://doi.org/10.1016/j.ejso.2019.11.499. Epub 2019 Nov 15. PMID: 31761507.
30. Abbas S, Sandroussi C. (2013 Jul) Systematic review and meta-analysis of the role of vascular resection in the treatment of hilar cholangiocarcinoma. *HPB* 15:492–503. https://doi.org/10.1111/j.1477-2574.2012.00616.x. Epub 2013 Jan 8. PMID: 23750491; PMCID: PMC3692018.
31. European Association for the Study of the Liver. (2016) EASL clinical practice guidelines: liver transplantation. *J Hepatol* 64:433–485.
32. Mantel HT, Westerkamp AC, Adam R, Bennet WF, Seehofer D, Settmacher U, Sánchez-Bueno F, Fabregat Prous J, Boleslawski E, Friman S Porte RJ, &, European liver and intestine transplant association (ELITA). (2016) Strict selection alone of patients undergoing liver transplantation for hilar cholangiocarcinoma is associated with improved survival. *PLoS One* 11:e0156127.
33. Ethun CG, Lopez-Aguiar AG, Anderson DJ, Adams AB, Fields RC, Doyle MB *et al*. (2018) Transplantation versus resection for hilar cholangiocarcinoma: an argument for shifting treatment paradigms for resectable disease. *Ann Surg* 267:797–805.
34. Gu J, Bai J, Shi X, Zhou J, Qiu Y, Wu Y *et al*. (2012) Efficacy and safety of liver transplantation in patients with cholangiocarcinoma: a systematic review and meta-analysis. *Int J Cancer* 130:2155–2163.
35. Lunsford KE, Javle M, Heyne K, Shroff RT, Abdel-Wahab R, Gupta N *et al*. (2018 May) Methodist–MD Anderson Joint Cholangiocarcinoma Collaborative Committee (MMAJCCC). Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. *Lancet Gastroenterol Hepatol* 3:337–348. https://doi.org/10.1016/S2468-1253(18)30045-1. Epub 2018 Mar 13. Erratum in: Lancet Gastroenterol Hepatol. 2018 Jun;3(6):e3. PMID: 29548617.
36. Le Roy B, Gelli M, Pittau G, Allard M-A, Pereira B, Serji B *et al*. (2017) Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. *Br J Surg*. https://doi.org/10.1002/bjs.10641.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2022.04.002.

diagnostics

MDPI

Article

Association of Tumor Volumetry with Postoperative Outcomes for Cervical Paraganglioma

Carola Marie Hoffmann-Wieker [1,*], Artur Rebelo [2], Martin Moll [3], Ulrich Ronellenfitsch [2], Fabian Rengier [3], Philipp Erhart [1], Dittmar Böckler [1] and Jörg Ukkat [2]

[1] Department of Vascular and Endovascular Surgery, University Hospital Heidelberg, 69120 Heidelberg, Germany
[2] Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle (Saale), 06097 Halle (Saale), Germany
[3] Department of Diagnostic and Interventional Radiology, University Hospital Heidelberg, 69120 Heidelberg, Germany
* Correspondence: carola.hoffmann-wieker@med.uni-heidelberg.de; Tel.: +49-6221-566249

Abstract: Objectives: To analyze the association of tumor volume with outcome after surgery for cervical paraganglioma. **Materials and Methods:** This retrospective study included consecutive patients undergoing surgery for cervical paraganglioma from 2009–2020. Outcomes were 30-day morbidity, mortality, cranial nerve injury, and stroke. Preoperative CT/MRI was used for tumor volumetry. An association between the volume and the outcomes was explored in univariate and multivariable analyses. A receiver operating characteristic (ROC) curve was plotted, and the area under the curve (AUC) was calculated. The study was conducted and reported according to the STROBE statement. **Results:** Volumetry was successful in 37/47 (78.8%) of included patients. A 30-day morbidity occurred in 13/47 (27.6%) patients with no mortality. Fifteen cranial nerve lesions occurred in eleven patients. The mean tumor volume was 6.92 cm^3 in patients without and 15.89 cm^3 in patients with complications (p = 0.035) and 7.64 cm^3 in patients without and 16.28 cm^3 in patients with cranial nerve injury (p = 0.05). Neither the volume nor Shamblin grade was significantly associated with complications on multivariable analysis. The AUC was 0.691, indicating a poor to fair performance of volumetry in predicting postoperative complications. **Conclusions:** Surgery for cervical paraganglioma bears a relevant morbidity with a particular risk of cranial nerve lesions. Tumor volume is associated with morbidity, and MRI/CT volumetry can be used for risk stratification.

Keywords: cervical paraganglioma; carotid body tumor; preoperative imaging; volumetry; cranial nerve injury

Citation: Hoffmann-Wieker, C.M.; Rebelo, A.; Moll, M.; Ronellenfitsch, U.; Rengier, F.; Erhart, P.; Böckler, D.; Ukkat, J. Association of Tumor Volumetry with Postoperative Outcomes for Cervical Paraganglioma. *Diagnostics* **2023**, *13*, 744. https://doi.org/10.3390/diagnostics13040744

Academic Editor: Daniel Thomas Ginat

Received: 21 November 2022
Revised: 11 February 2023
Accepted: 12 February 2023
Published: 15 February 2023

1. Introduction

Paragangliomas are vascularized neoplasms that derive from the neural crest and occur sporadically or due to a hereditary predisposition [1–4]. They commonly occur in the cervical region [5]. Carotid body tumors (CBTs) are paragangliomas located in the carotid bifurcation [6]. Their incidence is estimated at 1/100,000 persons per year. Most of them have a benign biological behavior, but 5–16% of these tumors show malignant transformation and metastasis. Lymphatic as well as distant metastases can occur [7]. The risk of metastasis, multilocular appearance and recurrences represent challenging aspects in the care of these patients [8]. A definite differentiation between benign and malignant lesions can only be made by a histopathological assessment of the specimen, and resection is therefore generally recommended [9].

Preoperative imaging of cervical paraganglioma allows to confirm the diagnosis, identify multifocal disease, and determine the extent of the tumor. Magnetic resonance imaging (MRI) including MR angiography is considered the non-invasive imaging modality of choice, but computed tomography (CT) angiography is an appropriate alternative [10–12].

Because of the close proximity to vascular and nerval structures, surgical resection of cervical paraganglioma can be challenging. There is a relevant risk of resection-related neurological complications, such as cranial nerve injury in 27–53.8% of patients [13,14]. Based on preoperative imaging, cervical paraganglioma is commonly described using the Shamblin classification. This system stratifies tumors according to the extent of their anatomic contact with the carotid vessels in three groups: I = minimal contact to III = full encasement [15]. This classification shows a good correlation with postoperative morbidity and cranial nerve injury [9]. However, it remains unclear if other features, which can be assessed on preoperative imaging, such as tumor volume and tumor location, also correlate with postoperative morbidity.

The aim of this study was to explore a possible association between tumor volume and tumor location determined on preoperative imaging and postoperative outcomes for the resection of cervical paraganglioma.

2. Materials and Methods

2.1. Study Design

This retrospective study comprised consecutive patients undergoing open surgical therapy for cervical paraganglioma in two vascular centers between January 2009 and January 2020. Demographic and clinical data as well as follow-up data were collected retrospectively from patient charts, hospital information systems, and Picture Archiving and Communication Systems (PACS). Patients were followed up routinely in hospital and in an outpatient clinic 30 days postoperatively.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the competent ethics committee (Medical Faculty of the University of Heidelberg, Germany, reference number: S-026/2021; approval date: 26 February 2021). The study is reported according to the guidelines of the STROBE statement (Supplemental Figure S1) [16].

2.2. Endpoints and Definitions

Endpoints were 30-day morbidity, 30-day incidence of cranial nerve injury and Horner syndrome, 30-day stroke incidence and 30-day mortality. Morbidity was adjudicated by the investigators based on the exams and treatment noted. All cranial nerve lesions had to be determined by an ENT specialist or neurologist. Nerve lesions were considered temporary if the associated symptoms had subsided at 30-day follow-up and permanent if the symptoms prevailed. Stroke was defined as any new-onset neurological deficit lasting more than 24 h, diagnosed by a neurologist. A neurological impairment lasting less than 24 h was considered a transient ischemic attack (TIA).

2.3. Image Analysis

Preoperative contrast-enhanced CT or contrast-enhanced MRI of the neck region, depending on availability, were used as preoperative imaging. In the case of bilateral tumors, each side was analyzed individually. A three-dimensional tumor segmentation for tumor volume calculation was performed using three-dimensional image processing software (mint Lesion^{TM} software platform, v3.4.5; Mint Medical) by manual delineation of the tumor margins (Figure 1).

The carotid arteries were included into the segmentation if the encasement was $\geq$180°. The axial slice with the largest tumor area, as defined by the three-dimensional tumor segmentation, was identified, and the long and short axis diameters were recorded at this slice. The same slice was used to manually measure the distance between the internal and external carotid arteries. Furthermore, the encasements of the internal and the external carotid arteries were evaluated and visually graded as 0–89°, 90–179°, 180–269°, 270–359° or 360°. Finally, the level of the carotid bifurcation was assessed in relation to the spine. Using sagittal reconstructions, a line was drawn perpendicularly to the spine through the

upper border of the carotid bifurcation to identify the level of the carotid bifurcation at the upper/mid/lower third of the respective vertebra or at the intervertebral disc.

Volumetry was performed by one board-certified fellow radiologist in consensus with a board-certified attending radiologist. Both radiologists were blinded to the outcomes of patients.

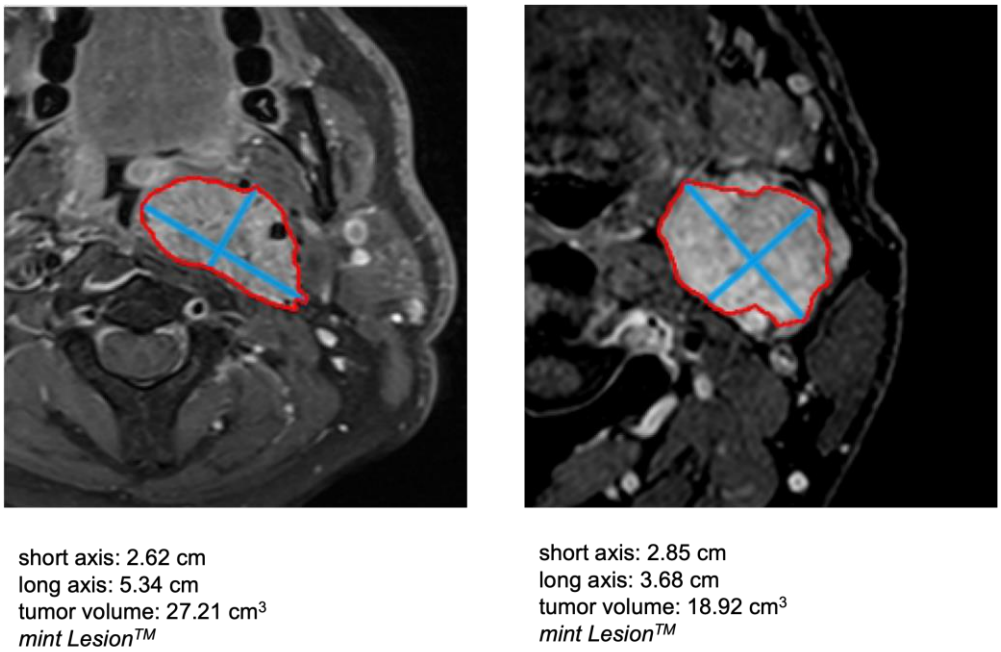


Figure 1. Three-dimensional tumor segmentation for tumor volume calculation (mint Lesion™).

2.4. Surgical Technique

All procedures were conducted in general anesthesia and were performed by a board-certified vascular surgeon alone or in an interdisciplinary team with an ENT specialist. In most cases, tumors were dissected in a periadventitial plane by using a bipolar knife to avoid bleeding. If an unplanned vascular reconstruction necessitating clamping of the internal carotid artery was performed, transcranial oxygen saturation measurement (Invos® Cerebral Oximeter) was used. In such cases, completion angiography was performed to rule out stenosis, dissection, or thrombosis of the vascular reconstruction. Selected patients underwent preoperative angiography to attempt the embolization of tumor-feeding vessels.

2.5. Statistical Analysis

Descriptive data were given as a mean ± standard deviation and as a median and interquartile range in the case of non-parametric data. Continuous data were compared using the Mann–Whitney-U test. Proportions were compared using the Fisher-exact test (if there were fewer than five observations per category) or chi-square test. Patients with missing information for single variables were not included in the respective analyses. A multivariable logistic regression analysis was performed with postoperative complications as the dependent variable and with age, sex, and the two significant predictors on univariate analysis, quartile of tumor volume and Shamblin grade, as independent variables. Only patients with information for all used variables were included in the analysis. Goodness-of-fit was assessed with the Hosmer–Lemeshow test. All p values (significance level $p < 0.05$) and 95% confidence intervals (CIs) were two-sided. A receiver operating characteristic (ROC) curve was plotted and the area under the curve (AUC) calculated to assess the diagnostic performance of volumetry as a predictor of postoperative complications [17].

3. Results

3.1. Patient Characteristics and Procedural Results

The study included 47 patients (mean age 49 years, range 17–77 years, 63.8% female). All patients had carotid body paraganglioma. Tumor characteristics and demographics of the patients are shown in Table 1. Three patients (6.4%) showed preoperative symptoms, such as local pain, dysphagia, and hoarseness. The Shamblin classification was ascertained in 97.9% of patients (n = 46): most patients (n = 19, 40.4%) had a type I tumor followed by type III (n = 14, 29.8%) and type II (n = 13, 27.6%).

Table 1. Tumor characteristics and demographics. MRI: magnetic resonance imaging; CT: computed tomography.

	***n* = 47**	**Percentage (%)**
age (median, range)	49 (17–77)	
gender		
female	30	63.8
male	17	36.2
Shamblin classification		
type I	19	40.4
type II	13	27.6
type III	14	29.8
not assessable	1	2.1
preoperative imaging		
Duplex scan	32	68.1
MRI scan	30	63.8
CT scan	26	55.3
angiography	1	2.1
time until diagnosis (mean)	20 months	
preoperative symptoms	3	3.4
preoperative embolization attempt	6	12.8

Five patients (10.6%) underwent successful preoperative embolization. In one patient (2.1%), preoperative angiography with unsuccessful embolization was performed; the patient suffered from an intraprocedural stroke. Six (12.7%) patients had a prior cervical surgical intervention. In five (10.6%) of these patients, this was a prior paraganglioma resection. In one patient, only cervical lymph nodes had been removed before without a resection of the paraganglioma.

In all patients, a complete tumor resection was technically successful. Two tumors showed criteria of malignancy on histopathology (4.3%). In a seventeen-year-old patient, systemic metastasis was observed; this patient underwent postoperative chemoradiotherapy because of pulmonary and bone metastases. Two patients had bilateral tumors (4.3%), and in one patient with a family history of paragangliomas, an SDHD-gene mutation was found.

In 17% (n = 8) of patients, surgery was performed in an interdisciplinary team with ENT specialists. The mean procedural time was 132 min. In four patients (8.5%), a vascular reconstruction of the internal carotid artery was necessary. Three patients (6.4%) received an alloplastic carotid interposition graft and one patient an autologous interposition graft. In one patient with preoperative embolization and endovascular occlusion of the internal carotid artery, a resection of the internal carotid artery with reconstruction of the external carotid artery was performed. Operative characteristics are summarized in Table 2.

Table 2. Operative characteristics. ICA: internal carotid artery; CAS: carotid artery stenting; ENT: ear, nose, and throat specialist.

	***n* = 47**	**Percentage (%)**
redo operation	*n* = 6	12.7
operating time (mean)	132 min	
general anesthesia	*n* = 47	100
interposition graft ICA	*n* = 4	8.5
autologous	*n* = 1	2.1
allogenous	*n* = 3	6.4
ICA resection	*n* = 1	2.1
CAS	*n* = 1	2.1
interdisciplinary operation with ENT specialist	*n* = 8	17.0

3.2. Results of Study Endpoints

Thirty-day mortality was 0%. The overall perioperative complication rate was 27.6% (n = 13). Fifteen cranial nerve lesions in eleven patients (23.4%) were observed: four hypoglossal nerve, seven vagal nerve, three glossopharyngeal nerve and one facial nerve lesion. Three patients (6.4%) suffered from postoperative Horner syndrome. In eight patients, the cranial nerve lesion was permanent at 30-day follow-up. Three patients with a perioperative cranial nerve lesion were lost to follow-up.

Thirty-day stroke incidence was 4.2% (n = 2). One patient had an infiltrative tumor requiring an autologous interposition graft; in addition, internal carotid artery stenting at the skull base was necessary. Postoperatively, the patient developed hemiparesis and aphasia. The second patient had an uneventful intraoperative course and developed immediate postoperative sensory aphasia. Both patients still showed neurological symptoms at 30-day follow-up.

3.3. Association with Imaging Findings

Duplex imaging was performed in all patients. Among the 47 included patients, preoperative MRI (63.8%, n = 30) and/or CT (55.3%, n = 26) was conducted. The volume measurement was successful in 78.8% (n = 37/47): eight CT and twenty-nine MRI. The mean horizontal tumor extension was 2.9 cm (range 1.1–5.5 cm), and the mean vertical extension was 2.2 cm (range 0.8–3.9 cm). The degree of encasement of the carotid vessels (Shamblin classification) showed no significant correlation with cranial nerve injury (p = 0.44) but did so with overall postoperative morbidity (cranial nerve injury, Horner syndrome, and stroke) (p = 0.037).

There was a significant difference in tumor volume, as ascertained by volumetry, between patients with and without overall postoperative complications. Patients without complications had a mean tumor volume of 6.92 cm^3, while patients with complications had one of 15.89 cm^3 (p = 0.035). The mean tumor volume was 7.64 cm^3 in patients with no cranial nerve injury and 16.28 cm^3 in patients with cranial nerve injury (p = 0.05). Most tumors projected to the fourth cervical vertebra (n = 18; 38.3%) and were located at the lower third of the vertebra. There was no significant correlation between the tumor location in relation to the vertebra and the occurrence of cranial nerve lesions (p = 0.42). The degree of encasement of the carotid vessels showed no significant correlation with cranial nerve injury (p = 0.44). The results are summarized in Table 3.

Table 3. Comparison of volumetry and imaging characteristics between patients with and without postoperative complications. ICA: internal carotid artery.

	Perioperative Complications (*n* = 13)	**No Perioperative Complications (*n* = 34)**	***p*-Value**
tumor volume (cm^3/median)	15.89	6.92	0.035
Shamblin classification			
type I	2	17	
type II	3	10	
type III	8	6	0.016
tumor localization in projection to cervical vertebrae			
cervical vertebrae 2/3	6	9	
cervical vertebrae 4/5	6	16	0.416
tumor encasement of the carotid arteries			
0–89°	0	0	
90–179°	2	9	
180–169°	3	8	
270–359°	2	3	
360°	5	5	0.442
ICA interposition graft			
yes	2	2	
no	11	32	0.304
preoperative embolization			
yes	3	3	
no	9	31	0.173

The results of the multivariable logistic analysis, which was based on 35 cases with complete information for all variables, are displayed in Table 4. Neither the tumor volume nor the Shamblin grade showed a significant association with postoperative complications on multivariable analysis.

Table 4. Results of logistic regression analysis with postoperative complications as dependent variable. Hosmer–Lemeshow test: $p = 0.84$.

Variable	**Category**	**OR**	**95% CI**
Age (continuous)		0.97	0.91–1.03
Sex	female	reference	
	male	1.14	0.17–7.54
Shamblin classification	1	reference	
	2	2.54	0.18–34.89
	3	12.10	0.94–156.35
Tumor volume	per quartile	1.63	0.65–4.09

The receiver operating characteristic (ROC) curve yielded an area under the curve (AUC) of 0.691, which indicates a poor to fair performance of volumetry as a predictor of postoperative complications (Figure 2).

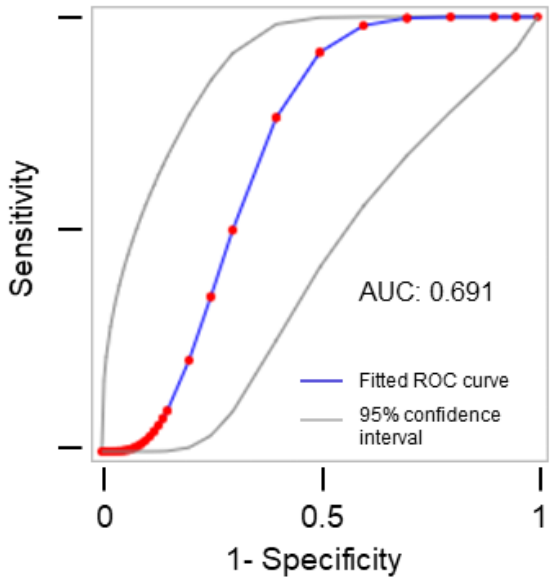


Figure 2. Receiver operating characteristic (ROC) curve for the diagnostic performance of volumetry as a predictor of overall postoperative complications. AUC: area under the curve.

4. Discussion

The present study aimed to evaluate the utility of preoperative-imaging-based volumetry in assessing the risk of perioperative morbidity and cranial nerve injury in patients undergoing open surgery for cervical paraganglioma. The results show that the preoperative tumor volume is associated with surgical morbidity and that MRI/CT volumetry using a dedicated radiological software can be used for risk stratification as an adjunct to the long-established Shamblin classification.

In 2017, Kim et al. analyzed the relationship of the Shamblin grade, tumor distance to the base of the skull and tumor volume with complications from cervical paraganglioma resection, including bleeding and cranial nerve injury. A total of 332 patients with 356 resections were included. Similar to the results of the present study, the most commonly injured cranial nerves were the hypoglossal and vagal nerves (11% and 10%). Both the Shamblin grade and tumor distance to base of the skull were associated with blood loss and cranial nerve injuries, whereas the tumor volume was associated only with blood loss but not with cranial nerve injuries [18].

In 2022, Ivanjko et al. aimed to confirm the findings reported by Kim et al. The authors analyzed the effect of the distance to the base of the skull and tumor-size characteristics on cranial nerve injuries in carotid body tumor resections. A total of 48 CBTs were included. The distance to the base of the skull, craniocaudal tumor diameter, and tumor volume were statistically significantly associated with cranial nerve lesions on univariate analysis, while the distance to the base of the skull was the only parameter that retained significance on multivariable analysis. While in the study by Ivanjko et al. cranial nerve lesions occurred in 37.5% of patients, in our study population this was the case for 23.4% of patients. Contrary to our study, in which the vagal nerve was the most affected cranial nerve, in Ivanjko et al.'s study population this was the case for the hypoglossal nerve. The main methodological difference between the two studies is that our study assessed not only cranial nerve lesions but all postoperative complications, including clinically important events such as stroke or hemorrhage. Moreover, volumetry in Ivanjko's study was calculated using a rigid formula, whereas in our study it was determined with a dedicated radiological software [19].

In 2012, Power et al. analyzed 132 patients with 144 cervical paraganglioma resections. The authors determined that the most common postoperative complication was temporary cranial nerve injury and that it was significantly associated with the tumor volume, which was however calculated using three axes and no dedicated algorithm. Thirty-three percent

of patients suffered from cranial nerve injury, and the majority of patients (58%) had Shamblin type III tumors. Preoperative embolization, the operating time, and a greater blood loss were also associated with temporary cranial nerve injury [20].

In line with these previous studies, we can confirm that the resection of cervical paraganglioma bears a relevant risk of morbidity and, in particular, of cranial nerve injury and stroke. Resection is recommended for all tumors of the carotid bifurcation region in light of their potentially malignant behavior. However, given that most cervical paragangliomas are asymptomatic and of benign histology, a thorough risk-benefit assessment needs to be performed, and procedural risks need to be well discussed with patients prior to surgery. The findings of our study show that, in addition to the established Shamblin classification, which was also significantly associated with the study outcome perioperative complications, tumor volume measured with a dedicated software on the basis of preoperative cross-sectional imaging can be used to predict the risk of perioperative complications, with larger tumors bearing a higher risk of complications. This information can be used in shared decision-making with patients [21]. Moreover, surgeons can anticipate the procedural risks based on tumor volumetry and take particular precautions during the operation. In a multivariable analysis, we attempted to determine which of the two modalities, volumetry or the Shamblin classification, is a more suitable predictor for postoperative complications. However, neither of the two showed significance on the analyses, which is probably due to collinearity and the rather small sample size included in the multivariable analyses. The receiver operating characteristic (ROC) curve showed a poor to fair performance of the tumor volume as a predictor of postoperative complications, which shows that this measure is not a perfectly discriminating test, but rather an indicative predictor.

This study has some methodological limitations. It has a retrospective design, and volumetry was conducted retrospectively using available imaging material, which was not acquired with the explicit aim of volumetry. Therefore, volumetry was not in all patients technically possible. However, the imaging assessment followed a defined protocol, and assessors were blinded towards patients' outcomes. Data on outcomes were extracted from prospectively kept institutional databases but might have still been incomplete for some patients. Nevertheless, a systematic bias regarding the completeness of data seems unlikely. Cranial nerve lesions were ascertained by ENT specialists not involved in the surgical treatment of patients, thus reducing the risk of observer bias. The sample size and thus statistical power of the study was rather small. It is a strength of the study that all consecutive patients undergoing resection of cervical paraganglioma in the two participating institutions were included and analyzed, thus minimizing a possible selection bias and increasing the external validity of the findings.

5. Conclusions

This study shows an association between the tumor volume of cervical paraganglioma and postoperative morbidity on univariate analysis, which loses significance when adjusting for other covariables such as the Shamblin classification. Tumor volume can be used as additional information in a risk-benefit analysis and discussions with patients prior to cervical paraganglioma resection. Volumetry should be considered to become part of routine preoperative diagnostics prior to cervical paraganglioma resection.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/diagnostics13040744/s1.

Author Contributions: C.M.H.-W., U.R., D.B. and J.U. devised the project and the main conceptional ideas. C.M.H.-W., A.R. and P.E. carried out the data collection. M.M. and F.R. performed volume measurements. C.M.H.-W. drafted the manuscript with input from all authors. All authors contributed to the final manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding. For the publication fee, we acknowledge financial support by Deutsche Forschungsgemeinschaft within the funding programme "Open Access Publikationskosten" as well as by Heidelberg University.

Institutional Review Board Statement: Medical Faculty of the University of Heidelberg, Germany, reference number: S-026/2021; approval date: 26 February 2021.

Informed Consent Statement: The competent ethics committee waived the need for informed consent given the retrospective nature of the study and the anonymized analysis of the data.

Data Availability Statement: Data available on request due to privacy restrictions.

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

References

1. Rangwala, A.F.; Sylvia, L.C.; Becker, S.M. Soft tissue metastases of a chemodectoma: A case report and review of the literature. *Cancer* **1978**, *42*, 2865–2869. [CrossRef]
2. Schipper, J.; Boedeker, C.C.; Maier, W.; Neumann, H.P.H. Paragangliomas in the head-/neck region. I: Classification and diagnosis. *HNO* **2004**, *52*, 569–574, quiz 575.
3. Lee, J.H.; Barich, F.; Karnell, L.H.; Robinson, R.A.; Zhen, W.K.; Gantz, B.J. National Cancer Data Base report on malignant paragangliomas of the head and neck. *Cancer* **2002**, *94*, 730–737. [CrossRef]
4. Fathalla, A.E.; Elalfy, M.A. Clinical Outcome of Carotid Body Paraganglioma Management: A Review of 10-Year Experience. *J. Oncol.* **2020**, *2020*, 6081273. [CrossRef]
5. Persky, M.; Tran, T. Acquired Vascular Tumors of the Head and Neck. *Otolaryngol. Clin. N. Am.* **2018**, *51*, 255–274. [CrossRef]
6. Pelliteri, P.; Rinaldo, A.; Myssiorek, D.; Jackson, C.; Bradley, P.; Devaney, K. Paragangliomas of the head and neck. *Oral Oncol.* **2004**, *40*, 563–575. [CrossRef]
7. Manolidis, S.; Shohet, J.A.; Jackson, C.G.; Glasscock, M.E. Malignant glomus tumors. *Laryngoscope* **1999**, *109*, 30–34. [CrossRef]
8. Erhart, P.; Körfer, D.; Hoffmann-Wieker, C.; Gieldon, L.; Dikow, N.; Wielpütz, M.O.; Plinkert, P.K.; Kender, Z.; Szendrödi, J.; Schaaf, C.P.; et al. Paraganglioma of the carotid artery. An interdisciplinary and heterogeneous pathology. *Gefässchirurgie* **2022**, *27*, 517–523. [CrossRef]
9. Sajid, M.; Hamilton, G.; Baker, D. A Multicenter Review of Carotid Body Tumour Management. *Eur. J. Vasc. Endovasc. Surg.* **2007**, *34*, 127–130. [CrossRef]
10. Guichard, J.-P.; Fakhry, N.; Franc, J.; Herman, P.; Righini, C.-A.; Taieb, D. Morphological and functional imaging of neck paragangliomas. *Eur. Ann. Otorhinolaryngol. Head Neck Dis.* **2017**, *134*, 243–248. [CrossRef]
11. van den Berg, R. Imaging and management of head and neck paragangliomas. *Eur. Radiol.* **2005**, *15*, 1310–1318. [CrossRef]
12. Berger, G.; Łukasiewicz, A.; Grinievych, V.; Tarasów, E. Carotid Body Tumor—Radiological imaging and genetic assessment. *Pol. J. Surg.* **2020**, *92*, 39–44.
13. Antonitsis, P.; Saratzis, N.; Velissaris, I.; Lazaridis, I.; Melas, N.; Ginis, G. Management of cervical paragangliomas: Review of a 15-year experience. *Langenbeck's Arch. Surg.* **2006**, *391*, 396–402. [CrossRef]
14. Kruger, A.J.; Walker, P.J.; Foster, W.J.; Jenkins, J.S.; Boyne, N.S.; Jenkins, J. Important observations made managing carotid body tumors during a 25-year experience. *J. Vasc. Surg.* **2010**, *52*, 1518–1523. [CrossRef]
15. Shamblin, W.R.; ReMine, W.H.; Sheps, S.G.; Harrison, E.G. Carotid body tumor (chemodectoma): Clinicopathologic analysis of ninety cases. *Am. J. Surg.* **1971**, *122*, 732–739. [CrossRef]
16. von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gøtzsche, P.C.; Vandenbroucke, J.P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Epidemiology* **2007**, *18*, 800–804. [CrossRef]
17. Eng, J. ROC Analysis: Web-Based Calculator for ROC Curves. Baltimore: Johns Hopkins University. Available online: http://www.jrocfit.org (accessed on 31 January 2022).
18. Kim, G.Y.; Lawrence, P.F.; Moridzadeh, R.S.; Zimmerman, K.; Munoz, A.; Luna-Ortiz, K.; Oderich, G.S.; de Francisco, J.; Ospina, J.; Huertas, S.; et al. New predictors of complications in carotid body tumor resection. *J. Vasc. Surg.* **2017**, *65*, 1673–1679. [CrossRef]
19. Ivanjko, F.; Konstantiniuk, P.; Muehlsteiner, J.; Cohnert, T. Effect of distance to the base of skull and tumor size characteristics on cranial nerve injuries in carotid body tumor resections. *J. Vasc. Surg.* **2022**, *77*, 523–528. [CrossRef]
20. Power, A.H.; Bower, T.C.; Kasperbauer, J.; Link, M.J.; Oderich, G.; Cloft, H. Impact of preoperative embolization on out-comes of carotid body tumor resections. *J. Vasc. Surg.* **2012**, *56*, 979–989. [CrossRef]
21. Whitney, S.N.; McGuire, A.L.; McCullough, L.B. A Typology of Shared Decision Making, Informed Consent, and Simple Consent. *Ann. Intern. Med.* **2004**, *140*, 54–59. [CrossRef]

BMC Surgery

RESEARCH

Open Access

Acute and chronic mesenteric ischemia: single center analysis of open, endovascular, and hybrid surgery

Artur Rebelo*, Marat Mammadov, Jumber Partsakhashvili, Carsten Sekulla, Ulrich Ronellenfitsch, Jörg Kleeff, Endres John and Jörg Ukkat

Abstract

Background: The aim of the study was to analyse the outcome of open surgical, endovascular, and hybrid interventions in the treatment of acute (AMI) and chronic (CMI) mesenteric ischemia.

Methods: Retrospective review of a cohort of mesenteric ischemia patients at a single tertiary referral center from 2015 to 2021. Primary end point was postoperative in-hospital mortality. Secondary end points were the number of bowel resections, duration of the procedure, length of postoperative intensive care treatment, length of hospital stay, revision surgery (number and type), and the nature and severity of postoperative complications according to Dindo-Clavien.

Results: A total of 64 patients, 20 with CMI and 44 with AMI, underwent open, hybrid or endovascular surgery. Bowel resection was performed in 45.5% of the patients with AMI (29.5% small intestine, 2.3% colon and 13.6% both). There was no in-hospital mortality in the CMI cohort as compared to 29.5% in the AMI cohort ($p = 0.03$), with no differences regarding endovascular and open surgery (29.6 vs 29.4%). Severe postoperative morbidity (Dindo-Clavien ≥ 3) was also significantly more frequent in the AMI group when compared to the CMI group (20 vs 77.3%, $p < 0.001$). ASA classification and intensive care stay were identified as factors associated with mortality in AMI patients.

Conclusions: Morbidity and in-hospital mortality are low in CMI patients, but substantial in AMI patients. Early diagnosis and open or endovascular treatment may be decisive for the outcome of these patients.

Keywords: Mesenteric ischemia, Open surgery, Endovascular surgery, Hybrid surgery

Introduction

Mesenteric ischemia descriptions date back to 1900 [1, 2]. The first open atherectomy of the superior mesenteric artery was performed in 1958 [3]. Later in 1962, Crawford and DeBakey et al. described open revascularization of the celiac trunk and superior mesenteric artery [4]. Despite recent developments in endovascular and hybrid surgery, mesenteric ischemia mortality and morbidity rates are still high. (Fig. 1) [5].

Chronic mesenteric ischemia (CMI) is defined as symptomatic ischemia without irreversible tissue damage caused by insufficient blood supply to the gastrointestinal tract. The most common cause is atherosclerosis of the celiac trunk (CT), the superior mesenteric artery (SMA) or the inferior mesenteric artery (IMA) [6, 7]. CMI is the cause of abdominal pain in only 0.1% of hospital admissions for abdominal symptoms [8]. Symptoms are mostly postprandial abdominal pain (Stage II), "food anxiety", rest pain (Stage III) and weight loss. CMI

*Correspondence: artur.rebelo@uk-halle.de
Department of Visceral, Vascular and Endocrine Surgery, Martin-Luther-University Halle-Wittenberg, Halle, Germany

remains an underdiagnosed disease [9]. Therefore, most patients present in the late stages of the disease with weight loss, chronic malnutrition, or intestinal infarction, which is then termed acute or acute on chronic mesenteric ischemia (AMI, Stage IV) [10, 11]. In addition, AMI can also be caused by arterial embolism and non-occlusive mesenteric ischemia [15]. The mortality of AMI is between 30 and 65% [12]. Bowel resection performed in an emergency setting is characterized by higher mortality [26]. CT angiography should be performed if AMI or CMI is suspected and is also the gold standard for follow-up after open and endovascular procedures [9, 13]. The use of CT scanning to diagnose mesenteric ischemia has increased over time [14]. Early diagnosis and intervention are critical to AMI.

Several guidelines were published on this matter [27, 28]. Endovascular and open surgery in asymptomatic patients with chronic mesenteric ischemia (CMI) is rarely indicated. On the other hand, symptomatic CMI should be treated to prevent acute mesenteric ischemia (AMI), bowel infarction, and death. It is still controversial which patients should undergo open or endovascular interventions [16].

The study aims to show the outcome of open surgical, endovascular and hybrid interventions in the treatment of AMI and CMI in a single tertiary referral centre.

Methods

All patients 18 years and older at the time of surgery who underwent endovascular, open or hybrid surgery for mesenteric ischemia at the Department for Visceral, Vascular and Endocrine Surgery at the University Hospital Halle (Saale), Germany from 2015 to 2021 were included in the study. Patients with nonocclusive mesenteric ischemia and mesenteric venous occlusion were not included. Endovascular or hybrid treatment comprises mechanical thrombectomy, visceral artery angioplasty and stenting performed with or without laparotomy. Open revascularization comprises laparotomy with embolectomy, endarterectomy with or without patch angioplasty or bypass with prosthetic or venous grafting. Patients with AMI underwent emergency surgery. Patients with CMI underwent elective surgery. In our center we follow an endovascular first approach in the treatment of CMI. In AMI, when there is no clinical sign of bowel infarction, we perform an endovascular procedure. If there are clinical or radiological signs of bowel infarction, we perform a laparotomy and, depending on the extent of the arterial lesion, an exclusively open arterial bypass or hybrid procedure.

The primary outcome of the study is postoperative in-hospital mortality. Secondary outcomes are the number of bowel resections, type of operation (open surgical, endovascular, hybrid), duration of the procedure, length of postoperative intensive care treatment, length of hospital stay, and the nature and severity of postoperative complications according Dindo-Clavien Classification [21]. All outcomes and patients' demographic characteristics and co-morbidities were collected by retrospective chart review. All data were anonymized prior to the analyses.

The study was approved by the ethics committee of the University Hospital Halle (Saale), Germany (ID 2021-031).

Pearson's X^2 test was used to identify independent factors associated with early death and postoperative morbidity. Mann–Whitney-Test was used for continuous and ordinal variables and Chi-square-test to the categorical variables. A P value of 0.05 determined statistical significance. IBM SPSS Statistics 27 was used to perform the analysis.

Results

Demographics and clinical characteristics

A total of 64 patients, 20 with CMI (elective surgery) and 44 with AMI (emergency surgery), underwent open, endovascular or hybrid surgery. In the CMI and AMI groups, 60% and 64.6% of patients were male, respectively. Mean age was 66.9 and 70.7 years in the CMI and AMI groups, respectively. Patients in the CMI group had higher prevalence of obesity and COPD and lower prevalence of diabetes mellitus, cardiac comorbidities, renal insufficiency, and history of malignancy. All patients were classified as ASA (American Society of Anesthesiology) score 3 or 4. Patients in the AMI group were classified as higher ASA risk when compared to the CMI group. A summary of relevant demographics and comorbidities are presented in Table 1. There were no statistically significant differences between both groups.

Etiology, classification, laboratory values and outcomes

In the AMI group, 27.3% had an embolic and 72.7% a thrombotic occlusion. Bowel resection was performed in 45.5% of the patients with AMI (29.5% small intestine, 2.3% colon and 13.6% both). Second-look laparotomy was performed in 27.3% of the patients. Regarding the CMI group, 25% of the patients were classified as stadium II and 75% as stadium III. The most often revascularized artery was the SMA in both groups. In the CMI group, all patients underwent revascularization. In the AMI group, 15.9% of the patients underwent bowel resection alone. In the CMI group, only one patient underwent open surgery while 19 patients received endovascular treatment. 80% of the patients received treatment for AMS and 20% for TC stenosis/occlusion. In the AMI group, of a total of 44 patients, 27 underwent open surgery and 17

Table 1 Summary of the baseline and clinicopathologic features in 64 patients with AMI and CMI undergoing arterial revascularization from 2016–2021 (Mann–Whitney-Test for continuous and ordinal variables and Chi-square-test to the categorical variables used to compare CMI and AMI groups)

Variable	CMI (n = 20)			AMI (n = 44)			P value
	Open (n = 1)	Endovascular (n = 19)	Total	Open (n = 27)	Endovascular/ Hybrid (n = 17)	Total	
Male Gender (%)	0%	63%	60%	48%	64.7%	54.4%	0.683
Age (years) Mean (SD)	75	66.5 (9.1)	66.9 (9)	67.9 (2.2)	75 (2.4)	70.7 (1.7)	0.16
ASA 3 (%)	100%	89.5%	90%	66.7%	76.4%	70.4%	0.087
DM (%)	0%	36.8%	35%	29.6%	47.1%	36.3%	0.916
Cardiac (%)	100%	73.7%	75%	81.5%	100%	88.6%	0.164
Renal Insufficiency (%)	0%	26.3%	25%	29.6%	52.9%	38.6%	0.287
Neoplasm (%)	0%	15.8%	15%	11.1%	17.6%	13.6%	0.884
Obesity (%)	0%	15.9%	15%	14.8%	0%	9%	0.483
COPD (%)	0%	26.3%	25%	14.8%	5.9%	11.3%	0.164

AMI acute mesenteric ischemia, *CMI* chronic mesenteric ischemia

DM diabetes mellitus

COPD chronic obstructive pulmonary disease

ASA American Society of Anesthesiologists Physical Status Classification System

endovascular treatments. The AMS was treated in 52.3% of the patients, TC in 13.6% and both in 23.5% of the patients.

Regarding the preoperative laboratory values, leukocytosis (gpt/l) and elevated lactate (mmol/l) were more frequent in the AMI group when compared to the CMI group (10.95 (±1.69) vs 18.3 (±1.9), p = 0.011 and 1.45 (±0.27) vs 4.42 (±0.79), p = 0.016). No statistically significant differences in CRP levels were observed between groups.

Concerning in-hospital mortality, no CMI patient died. In contrast, a mortality rate of 29.5% (p = 0.03) was observed in the AMI group, with no differences regarding endovascular and open surgery (29.6% vs 29.4% mortality). Severe morbidity (Dindo-Clavien ≥ 3) was also significantly more frequent in the AMI group when compared to the CMI group (77.3% vs 20%, p < 0.001). Endovascular surgery was associated with fewer postoperative complications when compared to open surgery (64.7% vs 85.2%, p < ***0.001***).

The length of intensive care stay, and hospital stay were different between the CMI and AMI groups (0.5 (±0.45) vs 7.2 (±1.9) days, p < 0.001 and 5.8 (±1.2) vs 22.7 (±3.3), p = 0.003). A summary of these results is presented in Table 2.

Factors associated with postoperative morbidity and mortality in AMI patients

The ASA classification was found to be associated with postoperative mortality in the AMI group. Patients who died had a longer intensive care stay (10 (±12.9) vs 6 (±12) days, p = 0.05), and more often bowel resections (61.5% vs 38.7%, p = 0.14) than those who survived.

Severe postoperative morbidity (Dindo-Clavien ≥ 3) was associated with bowel resections (55.8% vs 10%, p = 0.065) and inversely associated with second-look laparotomy rates (20.5% vs 50%, p = 0.066). A summary of these results is presented in Table 3.

Discussion

In this retrospective study, we report our single center experience regarding the treatment of CMI and AMI, both with endovascular and open surgery.

The major finding from this study concerns the zero in-hospital mortality in CMI patients and the elevated in-hospital mortality in the AMI group. Severe postoperative morbidity (Dindo-Clavien ≥ 3) was also significantly more frequent in the AMI group when compared to the CMI group (20% vs 77.3%, p < 0.001). Endovascular surgery had fewer postoperative complications in AMI patients when compared to open surgery (64.7% vs 85.2%), not affecting mortality rates (29.6% vs 29.4). An elevated leukocyte count and lactate levels were present in the AMI group when compared to the CMI group. Finally, ASA classification and longer intensive care stay were identified as factors associated with mortality in the AMI group.

Our results regarding outcomes of AMI are comparable with a 12-year retrospective analysis in which 72 patients with AMI were analyzed. Perioperative morbidity and 30-day mortality rates were 39% and 31%, respectively, and second-look surgery was performed in

Table 2 Preoperative laboratory values, technical details, and postoperative outcomes in 64 patients with AMI and CMI undergoing arterial revascularization from 2016–2021 (Mann–Whitney-Test for continuous and ordinal variables and Chi-square-test to the categorical variables used to compare CMI and AMI groups)

Variable	CMI			AMI (n = 44)			P value
	Open (n = 1)	Endovascular (n = 19)	Total (n = 20)	Open (n = 27)	Endovascular/ Hybrid (n = 17)	Total	
Etiology (%)	–	–	–	–	–	–	–
Embolic	–	–	–	33.3%	17.4%	27.3%	–
Acute on Chronic	–	–	–	66.7%	82.4%	72.7%	–
CMI Stadium (%)				–	–	–	–
2	0%	26.3%	25%	–	–	–	–
3	100%	73.7%	75%	–	–	–	–
Bowel Resection (%)	–	–	–	62.96%	17.65%	45.5%	–
Small intestine	–	–	–	40.7%	11.7%	29.5%	–
Colon	–	–	–	3.7%	0%	2.3%	–
Both	–	–	–	18.5%	5.88%	13.6%	–
Second-look laparotomy (%)	–	–	–	18.52%	41.18%	27.3%	–
Artery	–	–	–	–	–	–	–
None	0%	0%	0%	22.2%	5.9%	15.9%	–
AMS	100%	78.9%	80%	48.15%	58.8%	52.3%	–
TC	0%	21.1%	20%	14.8%	11.8%	13.6%	–
Both	0%	0%	0%	14.8%	23.5%	18.1%	–
Leukocytes(gpt/l)	18	10.6 (1.7)	10.95 (1.69)	20.14 (2.7)	15.4 (2.22)	18.3 (1.9)	0.011
CRP (mg/l)	30	37 (11.9)	37.5 (11.3)	96.12 (23.1)	110.97 (29.84)	101.89 (18.1)	0.072
Lactate (mmol/l)	2.2	1.4 (0.285)	1.45 (0.273)	4.267 (0.998)	4.665 (1.342)	4.42 (0.793)	0.016
In-Hospital mortality (%)	0%	0%	0%	29.6%	29.4%	29.5%	0.028
Dindo-Clavien ≥ 3	100%	15.8%	20%	85.2%	64.7%	77.3%	< 0.001
Surgery duration (min)	219	66.3 (8.1)	73.95 (10.8)	112.6 (14.1)	107.7 (24.16)	110.7 (12.6)	0.032
ITU Stay (d)	9	0.05 (0.229)	0.5 (0.45)	8.3 (2.8)	5.35 (1.87)	7.16 (1.85)	< 0.001
Hospital stay (d)	18	5.1 (1.01)	5.75 (1.16)	27.26 (4.7)	15.35 (3.68)	22.66 (3.3)	0.003

AMI acute mesenteric ischemia, *CMI* chronic mesenteric ischemia

AMS superior mesenteric artery

CT celiac trunk

ITU intensive care unit

53% of the patients [12]. In another retrospective study, data from a 20-year period revealed a 30-day mortality rate of 27% in the 1990s and 17% during the 2000s. As in our study, no significant differences in outcomes between open and endovascular revascularization were observed [17]. In another retrospective analysis, summarizing a 12-year experience with endovascular treatment of AMI due to embolic occlusion of the SMA, the total in-hospital mortality was 27.0%. Laparotomy was performed in 73.0% and bowel resection in 40.5% of the patients [20]. In a meta-analysis of 30-day mortality after open and endovascular therapy of AMI, five non- randomized studies were included. Endovascular therapy had lower bowel resection rates (OR 0.37, $p = 0.03$) and lower 30-day mortality rates (OR 0.50; $p = 0.002$) when compared to open surgery. The pooled overall 30-day mortality rate after endovascular therapy was 17.2% compared with 38.5% after open surgery [6].

Concerning patients with CMI, we observed no mortality or severe (Clavien-Dindo ≥ 3) morbidity. These findings could be related to the small patient collective. Nevertheless, in another retrospective analysis, similarly low mortality rates were observed. In a retrospective study from the Mayo Clinic (Rochester, Minnesota, USA), 343 patients showed a procedure-related mortality of 2.6% [18]**.** Given these favorable outcomes, CMI should be treated timely and before disease progression exposing patients to acute or acute on chronic disease at a higher age, in a poorer physical status and with co-morbidities. Therefore, early diagnosis of CMI and presentation in a vascular surgery center for treatment already at Stage II may be decisive for a better outcome of these patients.

Table 3 Pearson's X2 test for factors associated with postoperative mortality and morbidity (Dindo-Clavien ≥ 3) in patients with acute mesenteric ischemia

Mortality	**Yes (n = 13)**	**No (n = 31)**	**P value**
Male gender (%)	46.2%	58.1%	0.469
Age (years)	72.8 (10.3)	69.77 (11.9)	0.832
ASA 3 (%)	23.1%	90.3%	< 0.001
DM (%)	53.8%	70.9%	0.118
Cardiac (%)	92.3%	87.1%	0.619
Renal failure (%)	46.1%	35.5%	0.507
Neoplasm (%)	0%	19.4%	0.088
Obesity (%)	7.7%	9.8%	0.834
COPD (%)	15.4%	9.68%	0.586
Etiology—Embolic (%)	15.39%	32.26%	0.252
Open surgical approach (%)	61.54%	61.29%	0.998
Bowel resection (%)	61.54%	38.71%	0.141
Second-look laparotomy (%)	30.78%	25.8%	0.736
Leukocytes (gpt/l) Mean (SD)	13.9 (7.8)	20.17 (13.64)	0.465
CRP (mg/l) Mean (SD)	89.49 (94.66)	107.1 (130.23)	0.603
Lactate (mmol/l) Mean (SD)	4.51 (3.33)	4.38 (5.935)	0.272
surgery duration (min) Mean (SD)	148.38(113)	94.4 (61.2)	0.482
ICU Stay (d)	10 (12.92)	5.97 (12)	0.05
Hospital stay (d)	13.85 (15.4)	26.35 (23.5)	0.144
Morbidity	**Yes (n = 34)**	**No (n = 10)**	**P value**
Male Gender (%)	60%	52.9%	0.694
Age (years)	72.1 (11.3)	65.8 (11.1)	0.283
ASA 3 (%)	67.6%	80%	0.452
DM (%)	38.2%	30%	0.634
Cardiac (%)	85%	100%	0.198
Renal Failure (%)	35.3%	50%	0.401
Neoplasm (%)	11.8%	20%	0.505
Obesity (%)	11.7%	0%	0.255
COPD (%)	11.8%	10%	0.877
Etiology—Embolic (%)	29.4%	20%	0.557
Open surgical approach (%)	67%	40%	0.114
Bowel resection (%)	55.8%	10%	0.065
Second-look laparotomy (%)	20.5%	50%	0.066
Leukocytes (gpt/l) Mean (SD)	19.98 (1.72)	12.66 (13.86)	0.601
CRP (mg/l) Mean (SD)	110.9 (124.8)	71.1 (101.56)	0.307
Lactate (mmol/l) Mean (SD)	4.64 (4.71)	3.66 (7.065)	0.293
surgery duration (min) Mean (SD)	125.2 (80.07)	62.7 (76.9)	0.36
ICU Stay (d) Mean (SD)	7.79 (13.298)	5 (8.138)	0.352
Hospital stay (d) Mean (SD)	26.6 (23.14)	9.2 (9.331)	0.494

AMI acute mesenteric ischemia, *CMI* chronic mesenteric ischemia

ICU intensive care unit

DM diabetes mellitus

COPD chronic obstructive pulmonary disease

ASA American Society of Anesthesiologists Physical Status Classification System

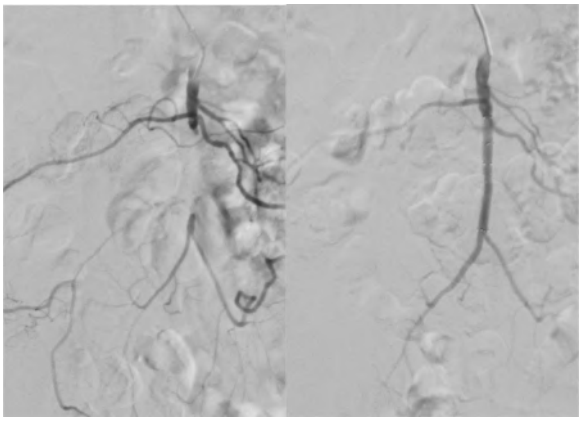


Fig. 1 Patient with SMA occlusion treated with stent angioplasty

In our analysis, no significant difference in terms of mortality between endovascular and open treatment for AMI was observed, despite higher morbidity rates on the open surgery group. In an analysis of register data from the Johns Hopkins Hospital, Baltimore, USA, 679 patients underwent vascular intervention for AMI. Mortality was significantly higher after open revascularization compared with endovascular intervention (39.3% vs 24.9%; P = 0.01) [19]. A meta-analysis regarding mortality after open and endovascular revascularization for CMI was published within the ESVS guidelines. In single center cohorts from highly specialized centers, no difference in mortality was identified (OR 1.12). In administrative data from the Nationwide Inpatient Sample from the USA, the mortality was lower after endovascular compared to open revascularization (OR 0.20) [6].

We observed a higher leukocyte count and elevated lactate levels in the AMI group when compared to the CMI group. According to the recent ESVS guidelines, in patients with acute abdominal pain, D-dimer measurement is recommended to exclude AMI. In contrast, lactate measurement is not recommended to diagnose AMI [6]. In our study, no data on preoperative D-dimer was available, as it is not commonly used at our centre in this context.

In our analysis, ASA classification and length of intensive care stay were associated with mortality in patients with AMI. Some small single center studies showed comparable results [22–25]. In another retrospective study, congestive heart failure and chronic kidney disease predicted postoperative mortality, and bowel resection and cerebrovascular disease predicted postoperative morbidity [17].

Our study has some limitations. The main drawback is that it is based on a small number of patients. In addition, the retrospective design is another significant limitation, increasing the risk of bias considerably. Therefore, the results should be carefully interpreted, and applied. Nevertheless, the findings of this work may provide useful information for clinicians treating mesenteric ischemia and should be included in future meta-analyses.

Conclusion

Mesenteric ischemia remains a challenge. Morbidity and in-hospital mortality are low when treating CMI and high for AMI. Early diagnosis and open or endovascular treatment may be decisive for the outcome of these patients. Which treatment is better for which indication remains an open question and should be addressed in future studies.

Acknowledgements
Not applicable

Authors' contributions
AR outlined, wrote, and drafted the manuscript. All authors critically revised the manuscript, read, and approved the final version of the manuscript. All authors read and approved the final manuscript.

Funding
Open Access funding enabled and organized by Projekt DEAL. No Funding was received.

Availability of data and materials
The data that support the findings of this study are available from the authors, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of ethics committee of the University Hospital Halle (Saale).

Declarations

Ethics approval and consent to participate
The study was performed in accordance with the Declaration of Helsink. The study was approved by the ethics committee of the University Hospital Halle (Saale), Germany (ID 2021-031), according to whom the informed consent was waived as all data were processed anonymously.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 6 December 2021 Accepted: 7 February 2022
Published online: 13 February 2022

References

1. Tiedemann F. Von der Verengung und Schliessung der Pulsadern in Krankheiten. Groos, 1843.
2. Dunphy JE. Abdominal pain of vascular origin. Am J Med Sci. 1936;192:109–12.
3. Shaw RS, Maynard EP 3rd. Acute and chronic thrombosis of the mesenteric arteries associated with malabsorption; a report of two cases successfully treated by throm - boendarterectomy. N Engl J Med. 1958;258:874–8.
4. Morris GC, Crawford ES, Cooley DA, DeBakey ME. Revascularization of the celiac and superior mesenteric arteries. Arch Surg. 1962;84:95–107.

5. Schermerhorn ML, Giles KA, Hamdan AD, Wyers MC, Pomposelli FB. Mesenteric revascularization: management and outcomes in the United States, 1988–2006. J Vasc Surg. 2009;50:341-8.e1.
6. Bjorck M, Koelemay M, Acosta S, et al. Editor's choice—Management of the diseases of mesenteric arteries and veins: Clinical practice guidelines of the European society of vascular surgery (ESVS). Eur J Vasc Endovasc Surg. 2017;53:460–510.
7. Mensink PB, Moons LM, Kuipers EJ. Chronic gastrointestinal ischaemia : shifting paradigms. Gut. 2011;60:722–37.
8. Clair DG, Beach JM. Mesenteric ischemia. N Engl J Med. 2016;374:959–68.
9. Terlouw LG, Moelker A, Abrahamsen J, Acosta S, Bakker OJ, Baumgartner I, Bruno MJ. European guidelines on chronic mesenteric ischaemia -owned joint United European gastroenterology, European association for gastroenterology, endoscopy and nutrition European society of gastrointestinal and abdominal radiology, Nether- lands association of, hepatogastroenterologists , Hellenic Society of gastroenterology , cardiovascular and interventional radiological society of Europe, and Dutch Mesenteric ischemia study group clinical guidelines on the diagnosis and treatment of patients with chronic mesenteric ischaemia. United Eur Gastroenterol J. 2020. https://doi.org/10.1177/2050640620916681.
10. Biolato M, Miele L, Gasbarrini G, et al. Abdominal angina. Am J Med Sci. 2009;338:389–95.
11. Pecoraro F, Rancic Z, Lachat M, et al. Chronic mesenteric ischemia: critical review and guidelines for management. Ann Vasc Surg. 2013;27:113–22.
12. Kougias P, Lau D, El Sayed HF, Zhou W, Huynh TT, Lin PH. Determinants of tomorrow tality and treatment outcome Following surgical interventions for acute mesenteric ischemia. J Vasc Surg. 2007;46:467–74.
13. Cudnik MT, Darbha S, Jones J, et al. The diagnosis of acute mesenteric ischemia: a systematic review and meta-analysis. Acad Emerg Med. 2013;20:1087–100.
14. Acosta-Mérida MA, Marchena-Gómez J, Saavedra-Santana P, Silvestre-Rodríguez J, Artiles-Armas M, Callejón-Cara MM. Surgical outcomes in acute mesenteric ischemia: has anything changed over the years? World J Surg. 2020;44(1):100–7. https://doi.org/10.1007/s00268-019-05183-9.
15 Lim S, Halandras PM, Bechara C, Aulivola B, Crisostomo P. Contemporary MAN agement of acute mesenteric ischemia in the endovascular era. Vasc Endovasc Surg. 2018;53(1):42–50. https://doi.org/10.1177/1538574418805228.
16. Rebelo A, Partsakhashvili J, John E, et al. Current concepts and evidence on open, endovascular and hybrid treatment of mesenteric ischemia: the retrograde open mesenteric stenting. Surg Pract Sci. 2021. https://doi.org/10.1016/j.sipas.2020.100022.
17. Ryer EJ, Kalra M, Oderich GS, Duncan AA, Gloviczki P, Cha S, Bower TC. Revascularization for acute mesenteric ischemia. J Vasc Surg. 2012;55(6):1682–9. https://doi.org/10.1016/j.jvs.2011.12.017.
18. Tallarita T, Oderich GS, Gloviczki P, Duncan AA, Kalra M, Cha S, Misra S, Bower TC. Patient survival after open and endovascular mesenteric revascularization for chronic mesenteric ischemia. J Vasc Surg. 2013;57(3):747–55. https://doi.org/10.1016/j.jvs.2012.09.047.
19. Beaulieu RJ, Arnaoutakis KD, Abularrage CJ, Efron DT, Schneider E, Black JH. Comparison of open and endovascular treatment of acute mesenteric ischemia. J Vasc Surg. 2014;59(1):159–64. https://doi.org/10.1016/j.jvs.2013.06.084.
20. Raupach J, Lojik M, Chovanec V, Renc O, Strýček M, Dvořák P, Hoffmann P, Guňka I, Ferko A, Ryška P, Omran N. Endovascular management of acute embolic occlusion of the superior mesenteric artery: a 12-year single-centre experience. Cardiovasc Intervent Radiol. 2016;39(2):195–203. https://doi.org/10.1007/s00270-015-1156-6.
21. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae.
22. Gagnière J, Favrolt G, Alfidja A, Kastler A, Chabrot P, Cassagnes L, Buc E, Pezet D, Boyer L. Acute thrombotic mesenteric ischemia: primary endovascular treatment in eight patients. Cardiovasc Intervent Radiol. 2011;34(5):942–8. https://doi.org/10.1007/s00270-011-0212-0.
23. Ozturk S, Unver M, Ozdemir M, Bozbıyık O, Turk Y, Firat O, Calıskan C. Prognostic factors in acute mesenteric ischemia and evaluation with multiple logistic regression analysis effecting morbidity and mortality. Pol Przegl Chir. 2020;93(1):25–33. https://doi.org/10.5604/01.3001.0014.5824.
24. Kassahun WT, Schulz T, Richter O, Hauss J. Unchanged high mortality rates from acute occlusive intestinal ischemia: six-year review. Langenbecks Arch Surg. 2008;393(2):163–71. https://doi.org/10.1007/s00423-007-0263-5.
25 Gawenda M, Scherwitz P, Walter M, Erasmi H. Letalitätsfaktoren des Darminfarkts primär vaskulärer Genese [Fatal outcome factors of intestinal infarct of primary vascular origin]. Langenbecks Arch Chir. 1997;382(6):319–24.
26. Lauro A, Sapienza P, Vaccari S, Cervellera M, Mingoli A, Tartaglia E, Canavese A, Canavese A, Caputo F, Falvo L, Casella G, Isaj E, Di Matteo FM, D'Andrea V, Tonini V. The surgical management of acute bowel ischemia in octogenarian patients to avoid Short Bowel Syndrome: a multicenter study. G Chir. 2019;40(5):405–12.
27. Bala M, Kashuk J, Moore EE, Kluger Y, Biffl W, Gomes CA, Ben-Ishay O, Rubinstein C, Balogh ZJ, Civil I, Coccolini F, Leppaniemi A, Peitzman A, Ansaloni L, Sugrue M, Sartelli M, Di Saverio S, Fraga GP, Catena F. Acute mesenteric ischemia: guidelines of the World Society of Emergency Surgery. World J Emerg Surg. 2017;7(12):38. https://doi.org/10.1186/s13017-017-0150-5.PMID:28794797;PMCID:PMC5545843.
28. Huber TS, Björck M, Chandra A, Clouse WD, Dalsing MC, Oderich GS, Smeds MR, Murad MH. Chronic mesenteric ischemia: clinical practice guidelines from the Society for Vascular Surgery. J Vasc Surg. 2021;73(1S):87S-115S. https://doi.org/10.1016/j.jvs.2020.10.029.

Publisher's Note

Original Article

Vascular

Vascular
2022, Vol. 0(0) 1–10

DOI: 10.1177/17085381221126318
journals.sagepub.com/home/vas
SAGE

Emergency treatment of popliteal aneurysms: Single center experience and systematic review and meta-analysis of endovascular versus open repair

Artur Rebelo, Jumber Partsakhashvili, Ulrich Ronellenfitsch, Endres John, Jörg Kleeff and Jörg Ukkat

Abstract

Background: Popliteal artery aneurysms (PAA) were traditionally treated by open repair (OR). Endovascular repair (ER) has become a new treatment strategy. The aim of this systemic review and meta-analysis was to evaluate and compare the current outcomes of OR and ER in the emergency treatment of PAA.

Methods: A systematic literature search of the PubMed/Medline database was carried out. Outcomes were 30-day mortality, morbidity, major amputation rate (30 days), major amputation rate (1 year), 1-year primary patency rate, 1-year secondary patency rate and 1-year survival. Additionally, we included clinical data of patients with popliteal aneurysms treated between 2009 and 2021 at the Martin-Luther University Halle-Wittenberg.

Results: We identified two cohort studies from 2014 and 2015 with a total of 199 patients that underwent emergent surgery (39 ER and 160 OR). We also included 26 patients from our institution. For emergency treatment, 30-day major amputation rates (18% vs 3%, Odds Ratio 5.82, 95% CI [1.75; 19.30], $p = .004$), 30-day mortality rates (10% vs 1%, Odds Ratio 5.57, 95% CI [1.01; 30.58], $p = .05$), 1-year major amputation rates (15% vs 6% Odds Ratio 3.61, 95% CI [1.18; 11.09], $p = .02$), 1-year loss of primary patency (54% vs 23%, Odds Ratio 3.19, 95% CI [0.91; 11.20], $p = .07$), and 1-year loss of secondary patency (44% vs 12%, Odds Ratio 6.91, 95% CI [3.01; 15.83], $p < .05$) were higher in the ER group when compared to the OR group.

Conclusion: Endovascular repair represents an alternative approach for the emergency treatment of PAA. Limited evidence from the available non-randomized studies shows unfavorable outcomes for patients undergoing ER. However, the results are prone to selection bias, and only randomized trials comparing ER to OR might reveal whether a subgroup of patients would benefit from ER as primary treatment of PAA in an emergency setting.

Keywords

Popliteal, aneurysm, vascular, surgery, endovascular surgery

Background

Since 1994 endovascular repair has been used as an alternative to the gold standard of open repair (OR) for the treatment of popliteal artery aneurysms (PAA).[1] When symptomatic, PAA should undergo repair regardless of its size. Risk factors associated with growth of popliteal aneurysms are a diameter of 20 mm or more, the presence of a luminal thrombus, and atrial fibrillation.[2]

There is no unique approach to OR. It is not clear which approach has the better outcomes: vein or prosthetic graft, posterior or medial approach.[3] Endovascular repair (ER) represents an attractive alternative approach due to its lower access morbidity and length of hospital stay.[4]

Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle (Saale), Martin-Luther-University Halle-Wittenberg, Germany

Corresponding author:
Artur Rebelo, FEBVS, Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle (Saale), Martin-Luther-University Halle-Wittenberg, Ernst-Grube-Str. 40, Halle (Saale) 06120, Germany.
Email: artur.rebelo@uk-halle.de

Several meta-analyses have been performed to evaluate the outcomes of OR and ER in the treatment of PAA.[5,6] Moreover, studies reporting on the use of fibrinolysis in the acute treatment of PAA have been published.[7] Recent guidelines from the Society of Vascular Surgery recommend a stratification of thrombotic or embolic complications of PAA depending on the severity of ischemia at presentation to decide if a thrombolysis or pharmacomechanical intervention should be performed.[8] Only one randomized controlled trial exists comparing OR with ER for elective asymptomatic PAA.[9] Registries such as those in Germany[10] or the Swedvasc[11] and Vascunet collaboration[12] represent a unique approach, making it possible to analyze the modern treatment of PAA. Recently, a meta-analysis also addressed the natural history of popliteal artery aneurysms.[13] However, no meta-analyses on the emergency treatment of PAA comparing OR with ER has been published. With the advances in endovascular repair in recent years, an analysis of the current outcomes of OR and ER in the treatment of popliteal aneurysms in an emergency setting is important. The aim of this meta-analysis was to summarize and compare the available evidence on outcomes of patients undergoing OR or ER for the emergency treatment of popliteal aneurysms. We also present and include into the analyses our single center experience on the treatment of PAA, reporting on 26 patients.

Methods

The literature search and data analysis were conducted in accordance with the MOOSE guidelines.[14] The study has been registered in the PROSPERO database.[15]

Search strategy

The PubMed/Medline database was searched for this study through its respective online search engine. The search was performed on studies published between database inception and a defined search date. The last search date was on 24.05.2021. The PICO (population, intervention, control, outcome) framework was used to develop the literature search strategy. A protocol was established according to the evidence-based PICO model to answer the following research question: "In Patients undergoing emergency treatment for popliteal aneurysms, what is the effect of endovascular repair on mortality, morbidity, limb salvage and other outcomes compared with open repair?" The following search strategy was used: ("Popliteal" [Mesh] OR Poplit*[tw]) AND ("Aneurysms" [Mesh] OR Aneurys*[tw]) AND ("Surgical Procedures, Operative" [Mesh] OR Operat*[tw] OR Surg*[tw] OR Excision*[tw] OR Dissection*[tw] OR resect*[tw] OR removal*[tw] OR ectomy [tw]) AND ("endovascular" [Mesh] OR endovasc*[tw]). Furthermore, the reference lists of the included studies were manually searched to find relevant articles. Abstracts and full-text reviews were evaluated independently in an unblinded standardized manner by two authors (AR and JP) to assess eligibility for inclusion or exclusion. Disagreements between reviewers were resolved by consensus; if no agreement could be reached, a third reviewer (JU) decided whether to include the respective study. If abstracts of unpublished studies were detected, contact with the authors was sought. In addition, data for all patients treated for popliteal aneurysms at our center from 2009 to 2021 were analyzed.

Inclusion and exclusion criteria

Articles in English, German, Spanish, Portuguese, and Italian language were considered. Studies reporting on outcomes for endovascular and open surgery both for elective and emergent treatment of popliteal aneurysms (as defined in the single studies) were included. Studies with an irrelevant abstract or title were excluded, and so were reviews, case reports, case series with less than five patients, comments, and letters. Details of the study selection process are summarized in a flowchart Figure 1.

From our institutional patient collective, patients were included if they underwent endovascular (stent graft, thrombolysis) or open (vein or prosthetic graft bypass) treatment for the diagnosis of a popliteal aneurysm (focal dilation of the popliteal artery by >50%). PAA diagnosis was performed by Doppler ultrasound or computed tomography. Emergency treatment was defined as immediate treatment (within 6 hours of diagnosis) for acute limb ischemia or aneurysm rupture.

Data collection

Studies were analyzed, and data were extracted separately by two investigators and presented in a tabular fashion. The following descriptive data were documented for each selected study: first author, year of publication, inclusion period, sample size, country where the study was conducted and study type. The following patient and operation characteristics were documented: total number of patients, mean or median age, sex, and comorbidities. The following predefined outcomes were extracted: mortality (30-day), morbidity (any type of complication, surgical and medical), major amputation rates (30 day and 1-year), 1-year primary patency rate, 1-year secondary patency rate, and 1-year survival. Each outcome was documented for ER and OR in both an elective and emergent setting. Risk of bias was assessed using the Newcastle-Ottawa Scale.[16]

The clinical data of consecutive patients with PAA treated at the University Hospital Halle (Saale), Germany, between 1 January 2009, and 31 March 2021, were retrospectively reviewed. Patients were asked to return at 1, 3, and 6 months and 1 year after intervention for physical examination, ankle-brachial index measurement, and

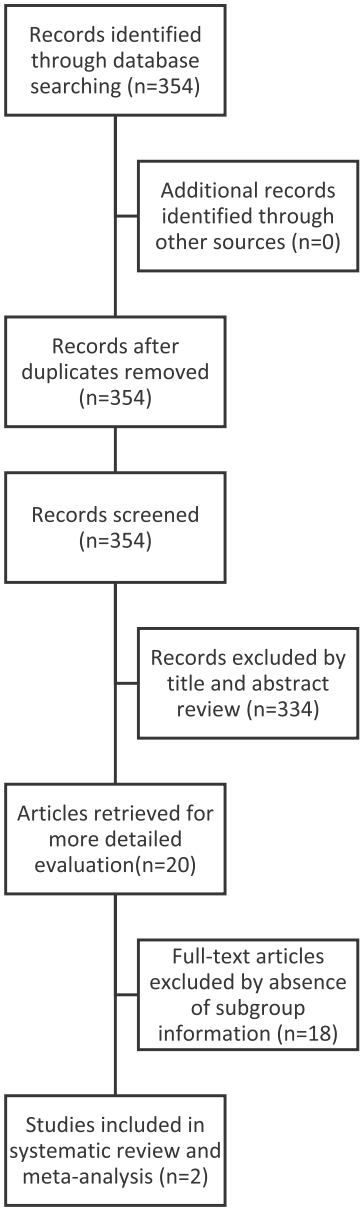


Figure 1. Flowchart with the number of studies identified, screened, assessed and finally included in the meta-analysis.

duplex ultrasound imaging. Patency rates were based on imaging studies. Follow-up information and patient vital status was obtained from the medical records and mailing questionnaires. The above-mentioned patient and operation characteristics and outcomes were extracted. Patients were divided in four groups by the type and urgency of the intervention: ER or OR and elective or emergency.

Statistical analysis

The Review Manager (RevMan) software, version 5.3 (Cochrane Collaboration, Oxford, UK) was used. If a given outcome was present in all studies, a meta-analysis was performed, firstly on emergency versus elective therapy, with both groups comprising ER as well as OR, and a subsequent subgroup analysis of ER and OR. Secondly, ER and OR were compared in an emergency setting. The magnitude of the effect estimate was visualized by forest plots. An odds ratio was calculated for binary data and the weighted mean difference for continuous data. The 95% confidence interval (CI), heterogeneity, and statistical significance was reported for each outcome. The X^2 test was used for the evaluation of statistical significance. $p < .05$ was statistically significant. Descriptive statistics from our patient collective are reported as number (percentage) or mean (standard deviation).

Results

From the 354 articles, one retrospective study[17] and one registry[11] from two countries were included in the meta-analysis. Our retrospective patient collective of 26 patients was also included. Publication years were 2014–2015. The inclusion period (including our own patients) ranged from 2005 to 2021. Within the two studies and our patient collective, a total of 199 patients underwent emergency surgery (39 ER and 160 OR). 543 patients underwent an elective procedure (102 ER and 441 OR). In the risk of bias assessment, no study was classified as low risk (Table 1). The age range was 68–86 years and 97% of the patients were male. Comorbidities are presented in Table 2. No meta-analysis of morbidity and 1-year survival could be performed because these outcomes were not reported by all studies (Table 3).

Concerning major amputation (30-day), our meta-analysis showed lower rates for the elective group (4% vs 0.7%, Odds Ratio 5.00, 95% CI [1.10; 22.72], $p = .04$), also in the ER subgroup analysis (18% vs 1% Odds Ratio 12.1, 95% CI [2.35; 62.18], $p = .003$) but not for the OR subgroup analysis (0.6% vs 0.7%, Odds Ratio 0.81, 95% CI [0.08; 7.83], $p = .85$) (Figure 2). Major amputation (30 days) rates in emergency treatment were higher in the ER group when compared to the OR group (18% vs 3%, Odds Ratio 5.82, 95% CI [1.75; 19.30], $p = .004$). (Figure 3).

In the included studies, mortality (30-day) was higher in the emergency group than in the elective group (3% vs 0.2%, Odds Ratio 7.95, 95% CI [1.86; 34.06], $p = .005$, ER subgroup 10% vs 0% Odds Ratio 10.62, 95% CI [1.55; 72.80], $p = .002$), OR subgroup 1% vs 0.2%, Odds Ratio 5.41 95% CI [0.59; 49.87], $p = .14$) (Figure 4). Our analysis demonstrated higher mortality rates in the ER group compared to the OR group for emergency surgery (10% vs 1%, Odds Ratio 5.57, 95% CI [1.01; 30.58], $p = .05$) (Figure 5).

Regarding 1-year amputation rates in both the ER (15% vs 1%, Odds Ratio 12.46, 95% CI [1.87; 82.88], $p = .009$)

Table 1. Characteristics of included studies.

Reference	Year	Inclusion period	Sample size (emergent and elective ER/OR)	Country	Study type	Newcastle–Ottawa scale
Huang et al.	2014	2005–2012	10/14 32/93	USA	Retrospective	5 – Low quality
Cervin et al.	2015	2008–2012	27/138 68/335	Sweden	Registry	5 – Low quality
Rebelo et al.	2021	2009–2021	2/8 3/13	Germany	Retrospective	—
Overall	2014–2021	2005–2021	39/160 102/441	—	—	—

Table 2. Surgical complications and outcomes.

Reference	Group		Morbidity (%)	Major amputations 30 days (%)	Mortality 30 days (%)	Amputation 1 year (%)	1-Year primary patency (%)	1-Year secondary patency (%)	1-Year survival (%)
Cervi et al.	Emergence	ER	—	14.8	3.7	17.4	42.9	47.6	85.2
		OR	—	3.7	1.4	6.8	78.8	86.8	95.5
	Elective	ER	—	1.5	0	1.7	66	84	94
		OR	—	0.9	0	3	87	91	97.6
Huang et al.	Emergence	ER	80	20	20	0	48	79	—
		OR	64	0	0	0	57	93	—
	Elective	ER	13	0	0	0	84	90	—
		OR	28	0	1	1	79	84	—
Rebelo et al.	Emergence	ER	50	50	50	50	50	50	50
		OR	28	0	0	0	100	100	100
	Elective	ER	0	0	0	0	66	66	66
		OR	21	0	0	0	93	93	93

Table 3. Patient characteristics (M – Male, HLP – Hyperlipidemia, CRI – Chronic renal insufficiency).

Reference	Group		Age (median)	Sex (M%)	Hypertension	Cardiac	HLP	Diabetes	Respiratory	CRI
Cervi et al.	Emergency	ER	70	85	58	30	—	20	17	—
		OR	69	94	65	26	—	9	10	—
	Elective	ER	75	97	67	67	—	67	14	—
		OR	68	97	68	20	—	67	11	—
Huang et al.	Emergency	ER	86	100	90	60	80	—	5	10
		OR	69	100	71	7	71	—	1	0
	Elective	ER	80	100	76	24	80	—	3	0
		OR	72	99	71	9	74	—	12	4
Rebelo et al.	Emergency	ER	79	100	100	0	66	0	0	0
		OR	74	100	100	57	14	28	0	14
	Elective	ER	76	100	100	50	50	100	0	100
		OR	70	100	100	50	50	24	21	28
Overall	Emergency	ER	68–86	90	69	36	75	17	13	8
		OR		95	68	26	50	10	9	5
	Elective	ER		98	71	54	80	69	11	9
		OR		98	70	19	72	65	12	8

and OR (6% vs 2%, Odds Ratio 2.26, 95% CI [0.93; 5.48], $p = .07$) subgroup, higher rates were reported in the emergency group compared to the elective group (8% vs 2%, Odds Ratio 3.07, 95% CI [1.37; 6.86], $p = .006$) (Figure 6). In emergency surgery, higher rates were observed in the ER group compared to the OR group (15% vs 6% Odds Ratio 3.81, 95% CI [1.24; 11.75], $p = .02$) (Figure 7).

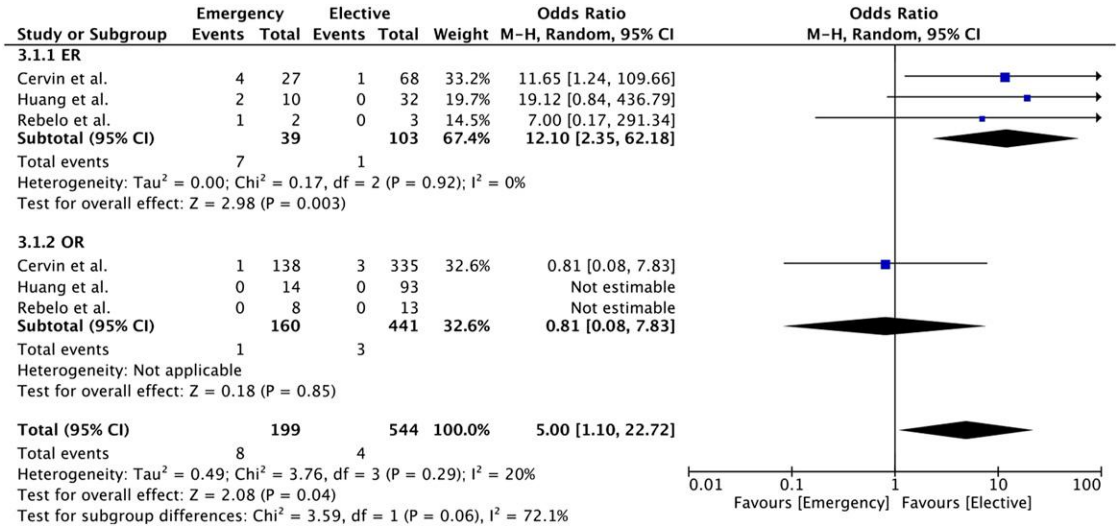


Figure 2. Forest plot of pooled odds ratio with 95% CI for emergency versus elective surgery regarding Major Amputation (30 Days) with subgroup analysis for ER and OR.

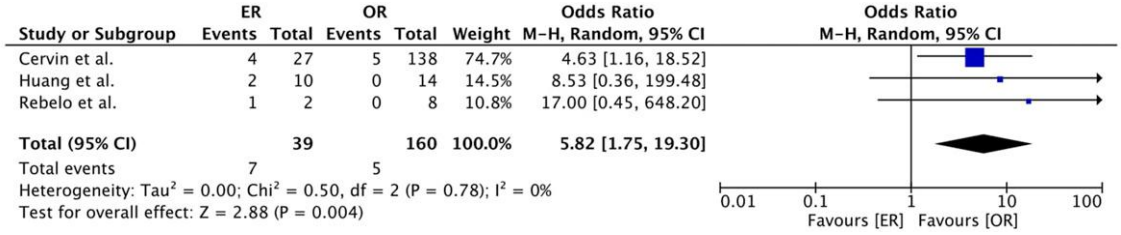


Figure 3. Forest plot of pooled odds ratio with 95% CI for ER versus OR in emergency surgery regarding Major Amputation (30 Days).

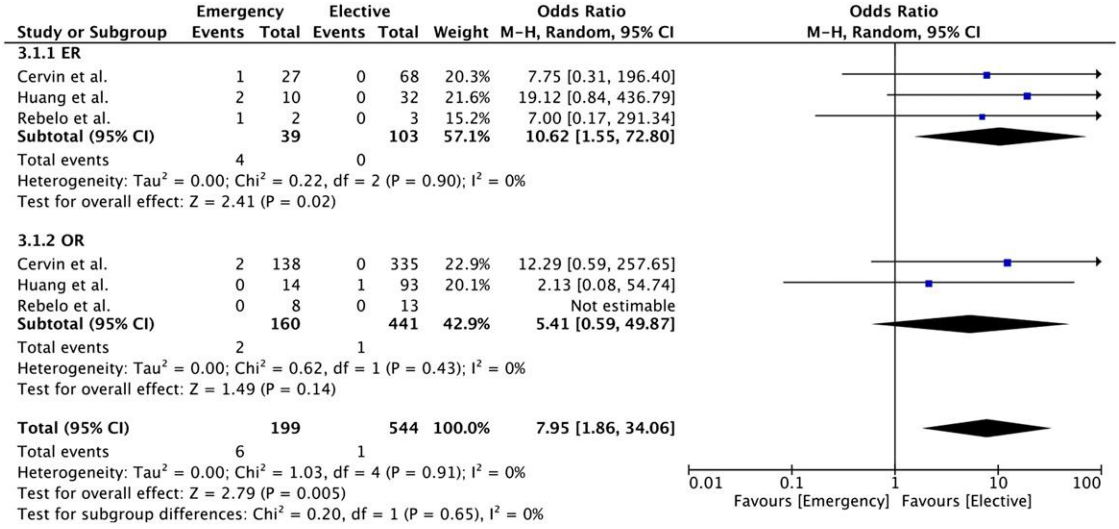


Figure 4. Forest plot of pooled odds ratio with 95% CI for emergency versus elective surgery regarding Mortality with subgroup analysis for ER and OR.

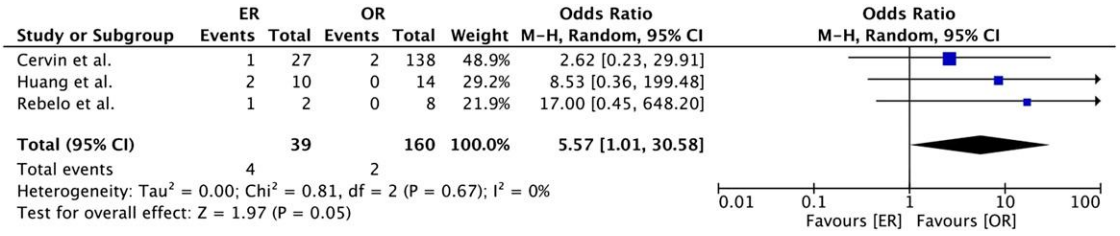


Figure 5. Forest plot of pooled odds ratio with 95% CI for ER versus OR in emergency surgery regarding Mortality.

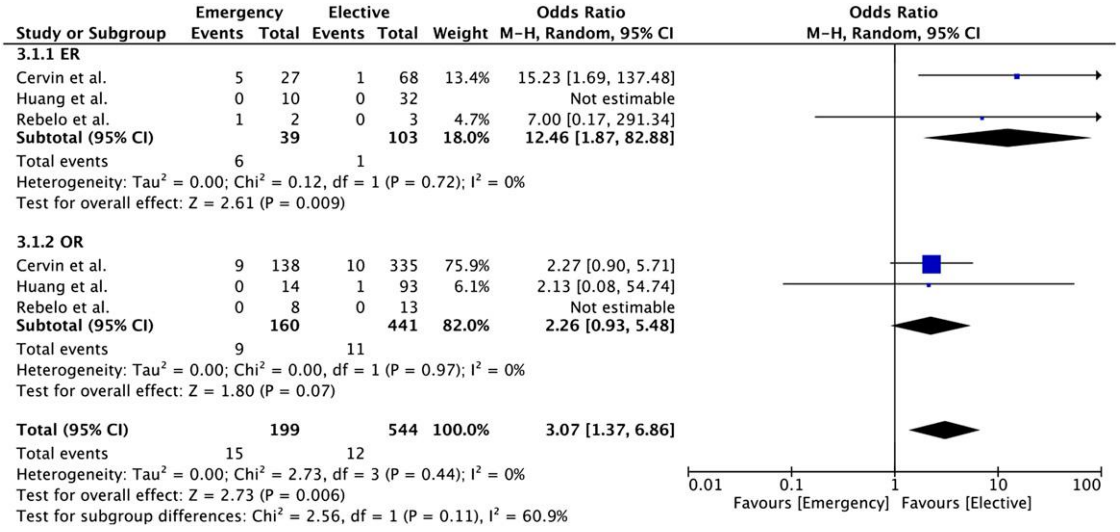


Figure 6. Forest plot of pooled odds ratio with 95% CI for emergency versus elective surgery regarding Amputation Rate (1 Year) with subgroup analysis for ER and OR.

A higher loss of primary patency (1 year) was observed in the emergency group when compared to the elective group (29% vs 17%, Odds Ratio 2.16, 95% CI [1.45; 3.23], $p < .05$). The same observation persisted in the ER (54% vs 28%, Odds Ratio 2.94, 95% CI [1.36; 6.34], $p = .006$) and OR (23% vs 15%, Odds Ratio 1.93, 95% CI [1.21; 3.09], $p = .006$) subgroup analysis (Figure 8). When comparing ER and OR in emergency surgery, no statistically significant result was obtained (54% vs 23%, Odds Ratio 3.19, 95% CI [0.91; 11.20], $p = .07$) (Figure 9).

Loss of secondary patency (1 year) was higher in the emergency group (18% vs 9%, Odds Ratio 2.41, 95% CI [1.21; 4.78], $p = .01$). In the subgroup analysis of ER and OR, a similar result was observed (44% vs 15%, Odds Ratio 4.48, 95% CI [1.90; 10.60], $p < .05$; 12% vs 8%, Odds Ratio 1.25, 95% CI [0.35; 4.49], $p = .73$) (Figure 10). In the meta-analysis of ER versus OR in emergency treatment, higher rates of loss of secondary patency (1 year) were observed in the ER group (44% vs 12%, Odds Ratio 6.91, 95% CI [3.01; 15.83], $p < .05$) (Figure 11).

Discussion

In our analysis, there are two major findings, concerning both short-term and long-term outcomes. The first is the higher 30-day mortality and major amputation rate for ER for emergency treatment. The second is that 1-year major amputation rates and rates of loss of 1-year primary and secondary patency are higher after endovascular repair in emergency surgery.

Our meta-analysis is the first one comparing OR and ER for emergency surgery. Studies concerning popliteal aneurysms are scarce and mostly reporting on asymptomatic patients undergoing elective repair without comparing ER and OR in an emergency setting. In a Cochrane Database Systematic Review on endovascular versus open repair of asymptomatic popliteal aneurysms, only one single RCT was identified.[18] In this study from Antonello et al., 15 patients underwent ER and 15 patients OR. The primary patency rate at 12 months was 100% for OR and 86.7% for ER.[9] In another study involving 390 patients with asymptomatic popliteal aneurysms, no mortality was observed. OR showed lower

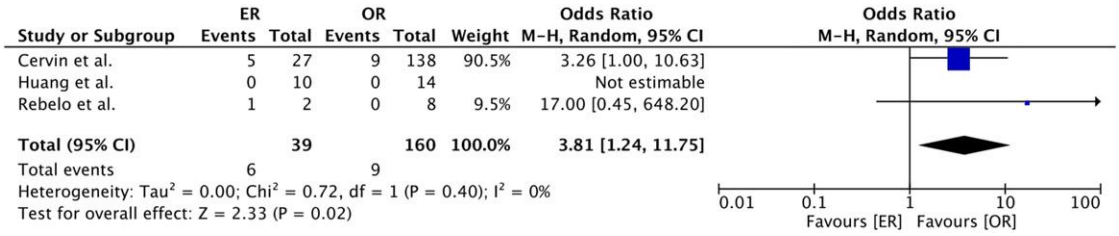


Figure 7. Forest plot of pooled odds ratio with 95% CI for ER versus OR in emergency surgery regarding Amputation Rate (1 Year).

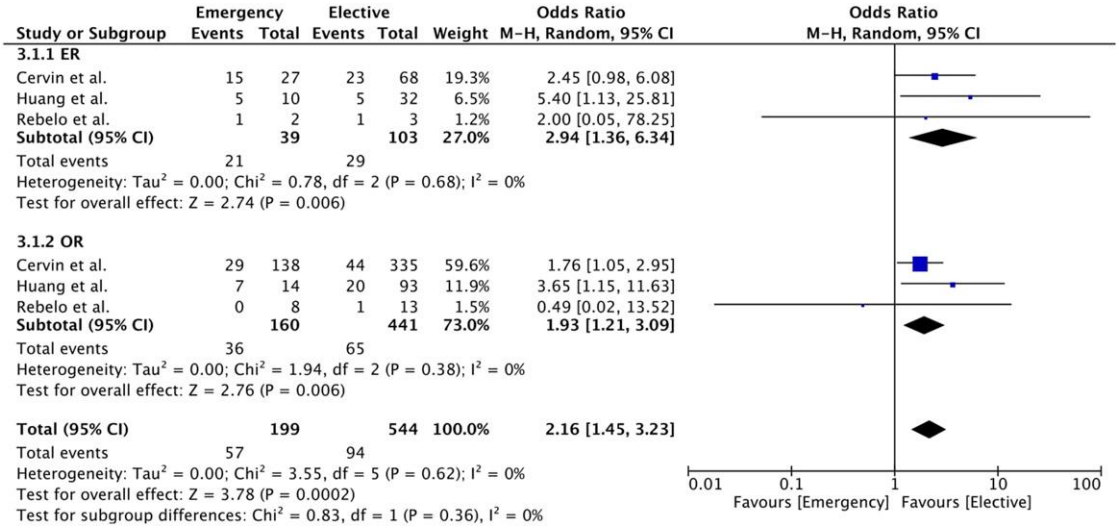


Figure 8. Forest plot of pooled odds ratio with 95% CI for emergency versus elective surgery regarding loss of primary patency (1 year) with subgroup analysis for ER and OR.

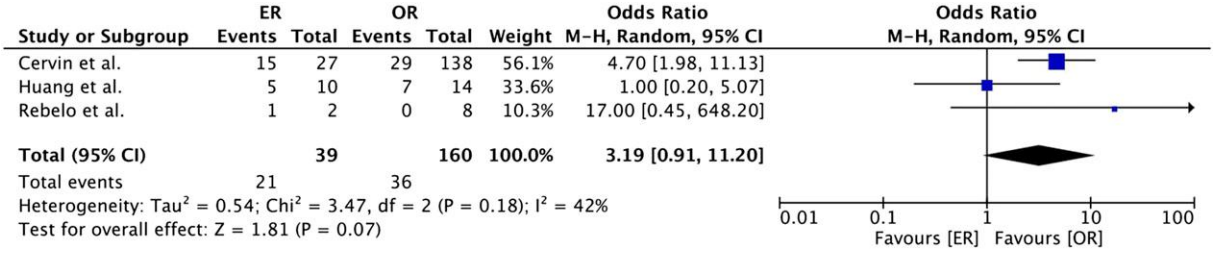


Figure 9. Forest plot of pooled odds ratio with 95% CI for ER versus OR in emergency surgery regarding loss of primary patency (1 year).

primary patency loss (HR 0.25; 95% CI, 0.10–0.58; $p < .05$).[19] In a Study from Germany including 206 patients with OR, overall mortality was 2% with no differences in 5-year primary patency between emergent and elective therapy.[20] Concerning ER, 1-year primary patency rates between 74.2% and 87% have been described.[21-25] In another study, Speziale et al. analyzed 53 patients who underwent ER. At a mean follow-up of 37.4 ± 29.3 months, primary patency, secondary patency, and limb salvage rate were 73.6, 92.4, and 100%, respectively.[26] In our analysis, major amputation rate at 30 days and 1 year, loss of 1-year primary patency and loss of 1-year secondary patency rates were higher for emergency surgery in both the ER and OR groups. This reinforces the need for an analysis including only emergency patients.

After emergency treatment, 30-day mortality and major amputation rates were higher for endovascular repair

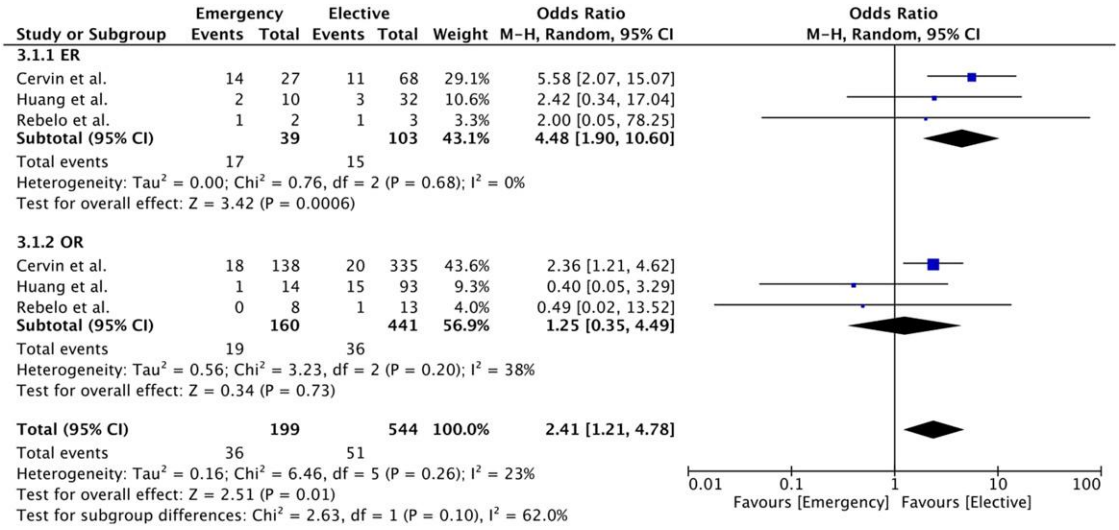


Figure 10. Forest plot of pooled odds ratio with 95% CI for emergency versus elective surgery regarding loss of secondary patency (1 year) with subgroup analysis for ER and OR.

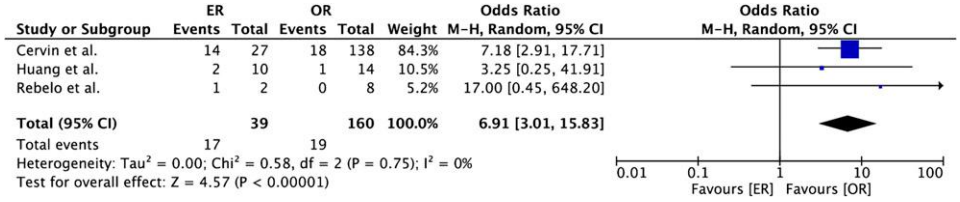


Figure 11. Forest plot of pooled odds ratio with 95% CI for ER versus OR in emergency surgery regarding loss of secondary patency (1 year).

In our analysis, the major amputation rate at 30 days was 0.7% for elective patients and 6% for emergency surgery. These results are comparable with a study from Vascunet, involving data from 1471 popliteal aneurysm repairs from 10 countries: the overall major amputation rate was 2.0% after elective and 6.5% after emergency surgery. Major amputation rates were higher for hybrid repair (26.3%) compared to OR (1.8%) and ER (1.0%, $p < .0001$).[27] In another study from Italy, involving 234 open procedures, the 30-day major amputation rate was 3.8%.[28] Concerning acute popliteal artery aneurysm thrombosis and leg ischemia, a study analyzed the outcomes of preoperative and intraoperative use of intra-arterial thrombolysis reporting 30-day amputation rates of 18% and 29%, respectively.[7] Leak et al. reported on 186 popliteal aneurysms (110 OR, 76 ER). OR was performed in more patients with thrombosis (41.8% vs 5.3%; $p < .001$), acute ischemia (24.5% vs 9.2%; $p < .010$), and ischemic rest pain (34.5% vs 6.6%; $p < .001$). There was no difference in major amputation rates (OR, 3.7%; ER, 1.3%; $p = .65$).[29] In a meta-analysis comparing ER with OR and comprising 652 patients, there were no differences regarding limb salvage between groups (Odds Ratio 0.59, 95% CI 0.16–2.15).[30] These data highlight again the need to separate emergency and elective treatment when comparing ER and OR. According to our analysis OR is superior to ER concerning both short-term major amputation and mortality.

Higher rates of 1-year major amputation and loss of primary and secondary patency were observed in the ER group in emergency treatment

Regarding long-term outcomes, the available data mostly do not separate between elective and emergency treatment. In a retrospective study, Saunders et al. reported primary and secondary patency for ER of 88% and 90%, respectively.[31] In a study from Italy, no differences on secondary patency were observed at 1 year between ER and OR (94% vs 94%, $p = .9$).[32] In a 2016 meta-analysis, 14 studies with 4880 popliteal artery aneurysm repairs (OR, 3915 and ER, 1210) were identified. One-year Primary patency was better for OR (Hazard Ratio 0.607, $p = .01$) and no difference in 1-year secondary patency (Hazard Ratio 0.770, $p = .46$) was observed.[5] Another meta-analysis from 2015 reported outcomes for 514 popliteal artery aneurysm repairs. Pooled primary and secondary patency rates at 5 years were 69.4%

(95% CI 63.3%–76.2%) and 77.4% (95% CI 70.1%–85.3%), respectively. No difference in primary patency (Hazard Ratio 1.30, 95% CI 0.79 to 12.14, $p = .189$) was described.[6] The data on long-term results of ER after emergency surgery are scarce, but long-term results of OR are superior to ER. Better patient selection regarding suitable anatomy for ER and improvement of endovascular stent grafts could improve results for this approach.

The main limitation of this meta-analysis is that it is based exclusively on two small non-randomized studies and a small unpublished and not peer-reviewed single center patient collective. Furthermore, the lack of patient-level data from the included studies and potential publication bias are also important limitations, leading to a potentially high risk of bias. Because of the low statistical power and corresponding wide 95% confidence intervals, the results should be appreciated with caution. Multicentric RCTs and registries with patients who underwent emergency repair of popliteal aneurysms are needed to identify which patients could benefit from ER or OR.

Conclusion

In this meta-analysis, all relevant studies providing comparative information on the outcome of patients undergoing ER or OR for the treatment of PAA in the emergency setting were included. Limited evidence from the available non-randomized studies shows unfavorable outcomes for patients undergoing ER. However, the results are prone to selection bias, and only randomized trials comparing ER to OR might reveal whether a subgroup of patients would benefit from ER as primary treatment of PAA in an emergency setting.

Authors' contributions

AR outlined, wrote, and drafted the manuscript. All authors critically revised the manuscript and read and approved the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Jörg Ukkat https://orcid.org/0000-0001-7834-950X
Artur Rebelo https://orcid.org/0000-0002-5267-079X

References

1. Marin ML, Veith FJ, Panetta TF, et al. Transfemoral endoluminal stented graft repair of a popliteal artery aneurysm. *J Vasc Surg* 1994; 19: 754–757.
2. Cousins RS, Dexter DJ, Ahanchi SS, et al. Determining patient risk factors associated with accelerated growth of popliteal artery aneurysms. *J Vasc Surg*; 67: 838–847.
3. Kropman RHJ, van Santvoort HC, Teijink J, et al. The medial versus the posterior approach in the repair of popliteal artery aneurysms: A multicenter case-matched study. *J Vasc Surg* 2007; 46(1): 24–30. DOI: 10.1016/j.jvs.2007.03.019.
4. Ghotbi R, Sotiriou A, Schönhofer S, et al. Stent-graft placement in popliteal artery aneurysms: midterm results. *Vasc Dis Manage* 2007; 4(4): 123–127.
5. Leake AE, Segal MA, Chaer RA, et al. Meta-analysis of open and endovascular repair of popliteal artery aneurysms. *J Vasc Surg*; 65(1): 246–256.
6. Patel SR, Hughes CO, Jones KG, et al. A systematic review and meta-analysis of endovascular popliteal aneurysm repair using the Hemobahn/Viabahn stent-Graft. *J Endovascular Ther* 2015; 22(3): 330–337, DOI: 10.1177/1526602815579252.
7. Gabrielli R, Rosati MS, Carra A, et al. Outcome after preoperative or intraoperative use of intra-arterial urokinase thrombolysis for acute popliteal artery thrombosis and leg ischemia. *Thorac Cardiovasc Surg*; 63: 164–167.
8. Farber A, Angle N, Avgerinos E, et al. The society for vascular surgery clinical practice guidelines on popliteal artery aneurysms. *J Vasc Surg* 2022; 75(1): 109S–120S. DOI: 10.1016/j.jvs.2021.04.040.
9. Antonello M, Frigatti P, Battocchio P, et al. Open repair versus endovascular treatment for asymptomatic popliteal artery aneurysm: results of a prospective randomized study. *J Vasc Surg*; 42(2): 185–193.
10. Schmitz-Rixen T, Debus ES, Torsello G, et al. Poplitealarterienaneurysma Was ist die beste Behandlungsoption? *Gefässchirurgie* 2014; 19(5): 459–467. DOI: 10.1007/s00772-014-1368-0.
11. Cervin A, Tjärnström J, Ravn H, et al. Treatment of popliteal aneurysm by open and endovascular surgery: a contemporary study of 592 procedures in Sweden. *Eur J Vasc Endovascular Surg* 2015; 50(3): 342–350. DOI: 10.1016/j.ejvs.2015.03.026.
12. Grip O, Mani K, Altreuther M, et al. Contemporary treatment of popliteal artery aneurysms in 14 countries: a vascunet report. *Eur J Vasc Endovascular Surg Official J Eur Soc Vasc Surg* 2020; 60(5): 721–729. DOI: 10.1016/j.ejvs.2020.07.005.
13. Beuschel B, Nayfeh T, Kunbaz A, et al. A systematic review and meta-analysis of treatment and natural history of popliteal artery aneurysms. *J Vasc Surg* 2021; 75(21): 121S–125S. Epub ahead of print. PMID: 34058308. DOI: 10.1016/j.jvs.2021.05.023.
14. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for

reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283(15): 2008–2012.
15. https://www.crd.york.ac.uk/prospero
16. Deeks J, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003; 7(27): 1–173.
17. Huang Y, Gloviczki P and Oderich GS. Outcomes of endovascular and contemporary open surgical repairs of popliteal artery aneurysm. *J Vasc Surg*; 60(3): 631–638.
18. Joshi D, Gupta Y, Ganai B, et al. Endovascular versus open repair of asymptomatic popliteal artery aneurysm. *Cochrane Database Syst Rev* 2019; 12: CD010149. DOI: 10.1002/14651858.CD010149.pub3. PMID: 31868929.
19. Eslami MH, Rybin D, Doros G, et al. 2015 Open repair of asymptomatic popliteal artery aneurysm is associated with better outcomes than endovascular repair. *J Vasc Surg*; 2018 61(3): 663–669.
20. Dorweiler B, Gemechu A, Doemland M, et al. 2016 Durability of open popliteal artery aneurysm repair. *J Vasc Surg* 2016; 60: 951–957.
21. Golchehr B, Zeebregts CJ, Reijnen MMPJ, et al. Long-term outcome of endovascular popliteal artery aneurysm repair. *J Vasc Surg* 2018; 67(6): 1797–1804. DOI: 10.1016/j.jvs.2017.09.040
22. Kumar HR, Rodriguez HE and Eskandari MK. Mid-term outcomes of self-expanding covered stent grafts for repair of popliteal artery aneurysms. *Surgery* 2015; 157(5): 874–880. DOI: 10.1016/j.surg.2014.11.016.
23. Piazza M, Menegolo M, Ferrari A, et al. Long-term outcomes and sac volume shrinkage after endovascular popliteal artery aneurysm repair. *Eur J Vasc Endovascular Surg* 2014; 48(2): 161–168. DOI: 10.1016/j.ejvs.2014.04.011.
24. Jung G, Leinweber ME, Karl T, POPART Registry Collaborators, et al. Real-world data of popliteal artery aneurysm treatment: Analysis of the POPART registry. *J Vasc Surg* 2022; 75(5): 1707–1717. Epub 2022 Jan 20. PMID: 35066058. DOI: 10.1016/j.jvs.2021.12.079.
25. Martinelli F, Pratesi G, Di Giulio L, et al. IMedPub journals comparison open and endovascular popliteal aneurysm repairs in a single center experience abstract 2019: 1–7.
26. Speziale F, Sirignano P, Menna D, et al. Ten years' experience in endovascular repair of popliteal artery aneurysm using the Viabahn endoprosthesis: a report from two Italian vascular centers. *Ann Vasc Surg* 2015; 29(5): 941–949. DOI: 10.1016/j.avsg.2015.01.008.
27. Björck M, Beiles B, Menyhei G, et al. Editor's choice: contemporary treatment of popliteal artery aneurysm in eight countries: A report from the vascunet collaboration of registries. *Eur J Vasc Endovascular Surg* 2014; 47(2): 164–171. DOI: 10.1016/j.ejvs.2013.10.026.
28. Dorigo W, Pulli R, Innocenti AA, et al. A 33-year experience with surgical management of popliteal artery aneurysms. *J Vasc Surg* 2013; 62(5): 1176–1182. DOI: 10.1016/j.jvs.2015.06.216.
29. Leake AE, Avgerinos ED, Chaer RA, et al. 2015 Contemporary outcomes of open and endovascular popliteal artery aneurysm repair. *J Vasc Surg* 2015; 63(1): 70–76.
30. Von Stumm M. Two decades of endovascular repair of popliteal artery aneurysm d A. *Eur J Vasc Endovascular Surg* 2015; 50(3): 351–359. DOI: 10.1016/j.ejvs.2015.04.036.
31. Saunders JH, Abisi S, Altaf N, et al. Long-term outcome of endovascular repair of popliteal artery aneurysm presents a credible alternative to open surgery. *Cardiovasc Interv Radiol* 2014; 37(4): 914–919. DOI: 10.1007/s00270-013-0744-6.
32. Dorigo W, Fargion A, Masciello F, et al. A matched case-control study on open and endovascular treatment of popliteal artery aneurysms. *Scand J Surg* 2018; 107(3): 236–243. DOI: 10.1177/1457496917748230.

Angiology
2023, Vol. 0(0) 1–10

DOI: 10.1177/00033197231164286
journals.sagepub.com/home/ang
SAGE

Visceral Aneurysms: Systematic Review and Meta-analysis of Endovascular Versus Open Repair

Artur Rebelo, MD, FEBVS[1], Ulrich Ronellenfitsch, MD[1], Jumber Partsakhashvili, MD[1], Jörg Kleeff, MD, FACS, FRCS[1], Endres John, MD[1], and Jörg Ukkat, MD[1]

Abstract

The aim of this study was to analyse and compare the outcome of open surgery (OS) and endovascular repair (ER) for the treatment of visceral artery aneurysms (VAA). A systematic literature search was carried out. 25 comparative cohort studies with 4447 patients (2469 OS and 1978 ER) were included in the meta-analysis. Mortality (ER vs OS 1.8% vs 2.1%, OR .77, 95% CI [.51; 1.17], $P = .23$) and technical success rates (97% vs 98%, OR .50, 95% CI [.21; 1.16], $P = .11$) were comparable between both groups. Lower mortality rates for ER were observed for ruptured aneurysms (4.1% vs 31%, OR .43 95% CI [.13; 1.43], $P = .17$). Length of stay was shorter (mean difference −4.25 days, 95% CI [−5.52; −2.98], $P < .00001$) and 1-year reintervention rates were higher in the ER group (9% vs 5%, OR 1.55 95% CI [.58; 4.12], $P = .38$. The presented evidence suggests that ER should be considered a first-line treatment for VAAs, especially in an emergency setting, due to lower morbidity and comparable mortality and technical success. Follow-up should be offered to these patients due to the higher reintervention rates.

Systematic review registration: PROSPERO ID 348699

Keywords

visceral, aneurysm, endovascular, surgery

Introduction

Visceral artery aneurysms (VAA) are rare (prevalence 1–2%). Most VAA originate from the splenic artery (60%), followed by the hepatic artery (20–50%). An origin from the superior mesenteric artery (6%), the celiac trunk (4%) or other, smaller visceral arteries is considerably less common.[1-3]

The natural history of VAA is not entirely clear, and they are mostly asymptomatic.[4] The incidental detection of VAA has increased with evolving and more frequently used imaging modalities.[5] Risk factors associated with rupture are pancreatitis, rapid growth, size >2 cm, and pregnancy. The mortality associated with splenic artery aneurysm rupture has been reported at around 30%.[6] In pregnancy, these rates are higher, with maternal mortality of up to 75% and foetal mortality of up to 95%.[7-10]

Nowadays, conservative therapy, endovascular, and open or laparoscopic surgery are the treatment options for these patients. During the last decade, endovascular repair of VAAs has been increasingly done with several types of vascular implants.[11-16]

With the continuous development of endovascular technics, a contemporary meta-analysis comparing the available treatments for VAA is lacking. The last published meta-analysis included only studies until 2016.[17] The aim of the present meta-analysis was to summarize and compare the currently available evidence on outcomes of patients undergoing open surgery (OS) or endovascular repair (ER) for the treatment of VAA.

Patients and Methods

The literature search and data analysis were conducted in accordance with the PRISMA guidelines.[18] The study was prospectively registered in the PROSPERO database.[19]

[1]Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle (Saale), Martin-Luther-University Halle-Wittenberg, Halle, Germany

Corresponding Author:
Artur Rebelo, MD, FEBVS, Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle (Saale), Ernst-Grube-Straße 40, Halle 06097, Germany.
Email: artur.rebelo@uk-halle.de

Table 1. Study Characteristics.

Study	Sample size open Surgery	Sample size endovascular repair	Inclusion period	Country	Newcastle-Ottawa scale (total quality Score)
Boll 2016	3	13	1996–2015	USA	6
Buck 2016	1627	1082	1988–2011	USA	7
Chivot 2015	2	8	2007–2014	France	7
Cochennec 2011	17	15	1995–2010	France/UK	6
Erban 2015	17	5	1992–2015	USA	6
Giacomelli 2016	68	76	1982–2014	Italy	6
Grego 2003	10	3	1987–2000	Italy	7
Lawrence 2014	172	31	-	USA	5
Hislop 2009	124	91	2000–2006	USA	7
Huang 2007	13	19	1995–2005	Taiwan	6
Illuminati 2021	31	26	1994–2019	Italy/France	6
Kagaya 2010	9	8	1985–2008	Japan	7
Keschenau 2020	18	6	2006–2018	Netherlands/ Germany	6
Lakin 2010	13	49	1996–2009	USA	7
Martinelli 2017	69	56	1992–2017	Italy	7
Novak 2013	20	9	2000–2012	USA	7
Orion 2016	6	11	1995–2018	USA	7
Regus 2016	13	12	1996–2014	Germany	7
Saltzberg 2005	9	18	1990–2003	USA	6
Sessa 2004	29	13	1975–2022	France	6
Stark 2022	10	11	1999–2019	Canada	7
Sticco 2016	112	347	2008–2011	USA	6
Tsilimparis 2013	20	24	2000–2012	USA/Germany	7
Wolk 2020	37	23	1994–2020	Germany	7
Zhu 2018	20	22	2011–2017	China	6
Total: 25 studies 2004 - 2022	2469	1978	1975–2020	10 countries	

Search Strategy

The PubMed/Medline, Cochrane Library, Web of Science Core Collection, CINAHL, Clinical Trial Gov, and International Clinical Trials Registry Platform ICTRP (WHO Trials) databases were searched for this study through its respective online search engines. The search was performed on studies published between database inception and 18th November 2022. The details of the search are described in the supplemental material. Furthermore, the reference lists of the included studies were manually searched to identify relevant articles.

Inclusion and Exclusion Criteria

Articles in English, German, Spanish, Portuguese, and Italian language were considered. Comparative studies reporting on outcomes for both ER and OS for VAA were included. Studies reporting on pseudoaneurysms (defined as false aneurysm, which is confined only by the adventitia) were excluded. Studies with an irrelevant abstract or title were excluded, as were reviews, case reports, case series with less than ten patients, comments, and letters.

Data Collection

Data were extracted separately by two authors (AR and UR) and presented in a tabular fashion. The following descriptive data were documented for each selected study: first author, year of publication, inclusion period of the study, country and city where the study was conducted, and sample size. Patient and operation characteristics were documented: gender, age at diagnosis, use of diagnostic imaging techniques, aneurysm localization, aneurysm size and symptoms and therapy. The following predefined outcomes were also extracted: in-hospital and 30-day mortality, major morbidity (defined as Dindo-Clavien $\geq$3), length of hospital stay, technical success (defined as the ability to bridge an occluded segment and successfully open the artery), 1-year reintervention rates and 1-year mortality. Subgroup analysis was performed for aneurysm localization (gastroduodenal and pancreaticoduodenal

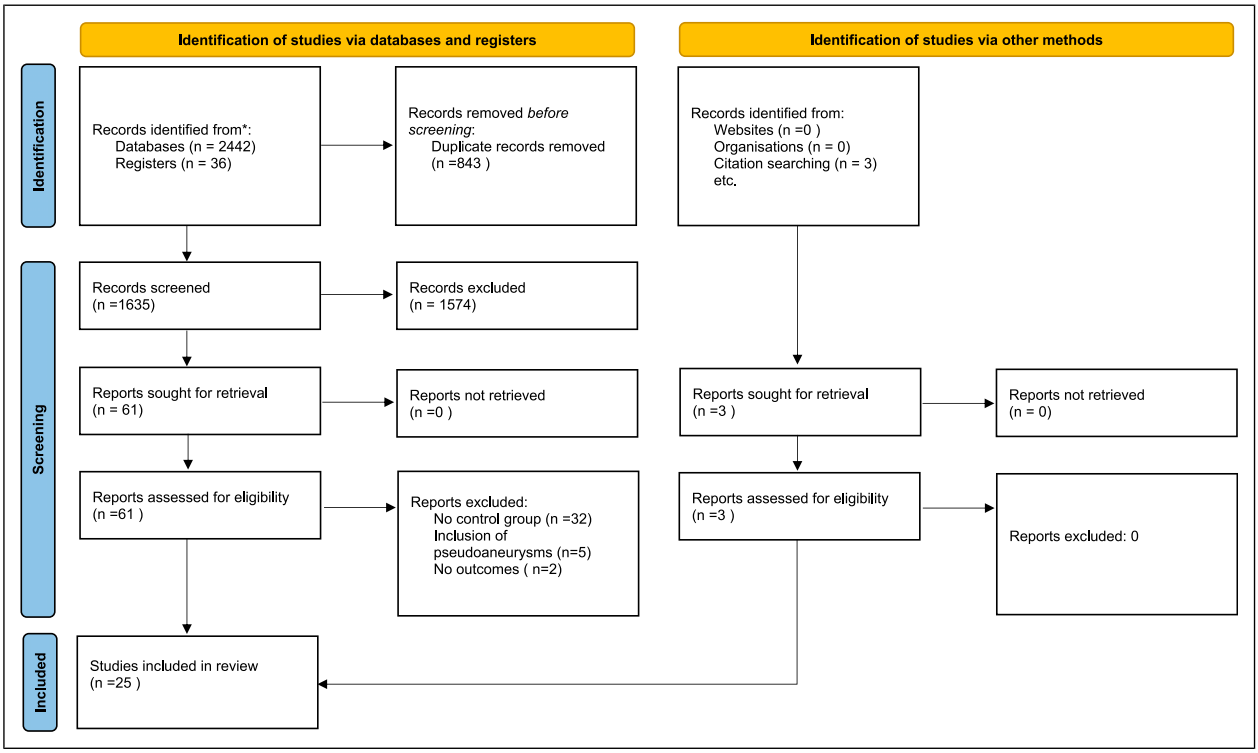


Figure 1. Prisma flow-chart.

arteries (GDA/PDA), hepatic artery (HA), renal artery (RA) and splenic artery (SA)) and ruptured vs non ruptured aneurysms. Risk of bias was assessed using the Newcastle–Ottawa Scale.[20,21]

Statistical Analysis

The Review Manager (RevMan) software, version 5.3 (Cochrane Collaboration, Oxford, UK) was used. If a given outcome was reported in two or more studies, meta-analysis was performed. Odds Ratios (OR) were calculated for binary data and weighted mean differences for continuous data. The 95% confidence interval (CI), heterogeneity and statistical significance are reported for each outcome. The χ^2 and the Kruskal–Wallis tests were used for evaluation of statistical significance. A 2-sided $P < .05$ was considered statistically significant. As not all studies reported time-to-event data and hazard ratios, the survival analysis was performed with weighted rates.

Results

From 1635 articles, 25 cohort studies from ten countries published between 2004 and 2022 were included in the meta-analysis (Table 1).[22-46] Details of the study selection process are summarized in a flowchart (figure 1). The enrolment period of these studies ranged from 1975 to 2020.4447 patients (2469 patients in the OS group and 1978 in the ER group) were included. Table 2 summarizes the data on gender, age at diagnosis, imaging diagnostics, aneurysm localization, aneurysm size and symptoms. The outcomes are presented in Tables 3 and 4 and the risk of bias assessment is presented in Table 1. Regarding 1-year mortality, no meta-analysis could be performed as all three studies reporting on this outcome did not report any mortality in this period.

Regarding in-hospital and 30-day mortality, slightly lower rates were observed in the ER group when compared to the OR group (1.8% vs 2.1%, OR .77, 95% CI [.51; 1.17], $P = .23$). ER had lower mortality compared to OS in three VAA location subgroups (GDA/PDA, HA, and SA: 0% vs 7%, OR .07 95% CI [.01; 10.81], $P = .03$; 0% vs 26%, OR .18 95% CI [.02; 1.62], $P = .13$; 2.3% vs 3.2%, OR .6 95% CI [.21; 1.69], $P = .33$). For VAA originating from the RA, higher mortality rates were observed for ER compared to OS (1.7% vs .9%, OR 1.72, 95% CI [.93; 3.17], $P = .08$). In the subgroup analysis of rupture vs no rupture, mortality was only observed in one study in the no rupture subgroup. In the rupture subgroup, lower mortality rates were observed in the ER group when compared to the OR group (4.1% vs 31%, OR .43 95% CI [.13; 1.43], $P = .17$) .

Regarding morbidity (defined as Clavien–Dindo grade ≥3), lower rates were observed in the ER group (5.6% vs 8.4%, OR

Table 2. Patient and operation characteristics. SA—Splenic artery; HA—Hepatic artery; PDA—Pancreaticoduodenal artery; GDA—Gastroduodenal artery; CT—Coeliac trunk; LGA: Left gastric artery; SMA—Superior mesenteric artery; IMA—Inferior mesenteric artery; RA—Renal artery; PGA—Pancreatic and gastric arteries.

Study	Therapy	Gender (% female)	Age at diagnosis (mean SD)	Imaging diagnostic	Aneurysm localization (n)	Aneurysm Size (mean SD cm)	Symptoms (symptomatic %)
Boll 2016	ER	55	61.5	-	GDA/PDA	-	85
	OS			-		-	
Buck 2016	ER	42	58	-	RA	-	-
	OS	57	57	-		-	-
Chivot 2015	ER	50	61	CTA	PDA	4.5	100
	OS	0				2.25	
Cochennec 2011	ER	47	57 (14.9)	-	RA-14 SA-11	2.1 (1.3)	-
	OS				CT-7 SMA-7 HA-4 PD-4 LGA-3 GD-1		
Erban 2015	ER	33	66	-	HA	4.5 (28)	52
	OS			-			
Giacomelli 2016	ER	-	-	-	SA-43 HA-6 RA-8 CT-5 PGA-11		
	OS	-	-	-	SA-34 HA-7 RA-8 CT-1 PGA-9		
Grego 2003	ER	56	-	CTA	SA-8 HA-4 SMA-3	-	19
	OS		-		CT-3 SMA-2 PD-1	-	
Lawrence 2014	ER	-	-	-	RA	2.3 (2)	-
	OS	-	-	-		2.1 (1)	-
Hislop 2009	ER	41.8	62 (17.02)	-	RA	-	-
	OS	47.6	65 (14.67)	-		-	-
Huang 2007	ER	32	56.4 (13.2)	-	11-SA 17-HA 8-GDA	-	-
	OS	38.5	45.6 (19.1)	-	6-PDA 5-SMA 2-IMA	-	-
Illuminati 2021	ER	35	58 (11)	Duplex/CTA	PDA-26	2.7 (6)	42
	OS	42	54 (11)		GDA-9 PDA-29	3.2 (8)	48
Kagaya 2010	ER	11	57	CTA/ Angiography	SA	3.1	33
	OS	50	57			2.8	13
Keschenau 2020	ER	16	70	-	CT-18 SA-11	-	29
	OS			-	SMA – 8 HA-5	-	-
Lakin 2010	ER	60	58 (10)	Duplex/MRA/ CTA	SA	2.9	50
	OS					4.4	

(continued)

Table 2. (continued)

Study	Therapy	Gender (% female)	Age at diagnosis (mean SD)	Imaging diagnostic	Aneurysm localization (n)	Aneurysm Size (mean SD cm)	Symptoms (symptomatic %)
Martinelli 2017	ER	41	65	CTA/MRA	RA-15 SA-25 HA-5	3.3	-
	OS				SMA-3 CT-4 PDA-1 LCA-1		
Novak 2013	ER	-	-	-	RA	2.2 (7.4)	-
	OS					1.9 (6)	
Orion 2016	ER	-	-	CTA	GDA	2.0	36
	OS					4.3	67
Regus 2016	ER	-	-	CTA/MRA	-	-	56
	OS						
Saltzberg 2005	ER	-	-	-	-	5.52	-
	OS	-	-	-	-	3.17	-
Sessa 2004	ER	62	57	-	SA-19 PDA-6 CT-5 SMA-5 HA-4 GDA-2 IMA-1	-	36
	OS				-		
Song 2017	ER	49	49.5 (13.6)	CTA	SA-22 SMA-12 RA-9 HA-7 CT-7 GDA-2	3.61 (1.86)	56
	OS		48.2 (12)		SA-23 SMA-3 RA-1 HA-0 CT-4 GDA-3	3.85 (1.14)	59
Stark 2022	ER	35	63 (15.6)	-	HA	4.8	28
	OS						
Sticco 2016	ER	53	54.2 (15.1)	-	SA	-	-
	OS	59	56.4 (16.3)	-		-	-
Tsilimparis 2013	ER	58	56 (14)	-	RA	2.2 (2.2)	8
	OS	85	53 (12)			2.5 (1.5)	40
Wolk 2020	ER	49.2	62.8 (13.3)	CTA	SA-22 HA-9 Renal artery 8 PDA-5 GDA-5 CT-5 LGA-2 SMA-2 IMA-2	3.0 (1.5)	40
	OS						
Zhu 2018	ER	61.9	55.9 (8.5)	CTA/MRA	Splenic artery	3.3 (1.6)	7.1
	OS		50.7 (13.9)				
Total	-	-	-	-	-	-	-

Table 3. Patient outcomes.

Study	Therapy	In-hospital mortality (%)	30-day mortality (%)	Major morbidity (Dindo–Clavien ≥3) (%)	Duration of hospital Stay (days, Median SD)	Technical Success	1-Year reintervention rate (%)	1-Year mortality (%)
Boll 2016	ER	0	-	-	-	-	-	-
	OS	0	-	-	-	-	-	-
Buck 2016	ER	1.8	-	-	4.6	-	-	-
	OS	0.9	-	-	6	-	-	-
Chivot 2015	ER	0	-	-	-	100	-	-
	OS	50	-	-	-	100	-	-
Cochennec 2011	ER	7	-	-	4	100	6.6	-
	OS	0	-	-	17	88	12	-
Erban 2015	ER	0	-	-	-	80	-	-
	OS	29	-	-	-	100	0	-
Giacomelli 2016	ER	2.6	-	-	-	96	-	-
	OS	1.4	-	-	-	100	-	-
Grego 2003	ER	0	-	-	-	-	0	0
	OS	0	-	-	-	-	0	0
Lawrence 2014	ER	3	-	-	-	-	-	-
	OS	0	-	-	-	-	-	-
Hislop 2009	ER	1.1	-	-	4 (9)	-	-	-
	OS	3.2	-	-	7 (19)	-	-	-
Huang 2007	ER	10.5	10.5	-	-	81	-	-
	OS	0	0	-	-	90	-	-
Illuminati 2021	ER	0	-	-	5	92	8	-
	OS	0	-	-	3	100	0	-
Kagaya 2010	ER	0	0	-	-	100	0	0
	OS	0	0	-	-	100	-	-
Keschenau 2020	ER	0	-	-	11	83	17	-
	OS	0	-	-	18	100	0	-
Lakin 2010	ER	0	-	-	1	96	-	-
	OS	15	-	-	9	100	-	-
Martinelli 2017	ER	-	0	9	-	98.3	-	-
	OS	-	12	6	-	-	-	-
Novak 2013	ER	-	-	-	2.37 (2.32)	-	-	-
	OS				8.94 (4.96)	-		
Orion 2016	ER	0	-	0	3	-	-	-
	OS	33	-	67	19	-	-	-
Regus 2016	ER	0	-	-	-	75	-	-
	OS	7.7	-	-	-	100	-	-
Saltzberg 2005	ER	0	-	-	-	94.4	-	-
	OS	11.1	-	-	-	100	-	-
Sessa 2004	ER	-	0	-	-	-	-	-
	OS	-	23	-	-	-	-	-
Song 2017	ER	0	-	-	1.19 (.74)	96.6	-	0
	OS	3	-	-		100	-	0
Stark 2022	ER	-	0	-	-	73	-	-
	OS	-	20	-	-	100	-	-
Sticco 2016	ER	3	2	-	4	-	-	-
	OS	3	3	-	6	-	-	-
Tsilimparis 2013	ER	0	-	-	2.3 (3.4)	98	18	-
	OS	0	-	-	6.3 (2.5)	95	18	-
Wolk 2020	ER	0	-	-	7.2 (6.9)	73	-	-
	OS	2.8	-	-	11.8 (6.7)	100	-	-
Zhu 2018	ER	0	0	0	5.6 (3.1)	100	4.5	0
	OS	0	0	0	10.8 (5.2)	100	0	0

Table 4. Patient outcomes regarding subgroups rupture and no rupture.

Study	Group	Therapy	In-hospital mortality (%)	30-day mortality (%)	Major morbidity (Dindo-Clavien ≥3) (%)	Duration of hospital Stay (days, Median SD)	Technical Success	1-Year reintervention rate (%)	1-Year mortality (%)
Cochennec 2011	Rupture	ER (n=2)	50	-	-	-	-	-	-
		OS (n=2)	0	-	-	-	-	-	-
	No rupture	ER (n=13)	0	-	-	-	-	-	-
		OS (n=14)	0	-	-	-	-	-	-
Martinelli 2017	Rupture	ER (n = 2)	-	0	-	-	-	-	-
		OS (n=20)	-	40	-	-	-	-	-
	No rupture	ER (n=54)	-	0	-	-	-	-	-
		OS (n=49)	-	0	-	-	-	-	-
Orion 2016	Rupture	ER (n=2)	0	-	-	-	-	-	-
		OS (n=3)	67	-	-	-	-	-	-
	No rupture	ER (n=9)	0	-	-	-	-	-	-
		OS (n=3)		-	-	-	-	-	-
Regus 2016	Rupture	ER (n=1)	0	-	-	-	-	-	-
		OS (n=4)	20	-	-	-	-	-	-
	No rupture	ER (n=12)	0	-	-	-	-	-	-
		OS (n=9)	0	-	-	-		-	-
Sessa 2004	Rupture	ER (n=2)	-	0	-	-	-	-	-
		OS (n=13)	-	25	-	-	-	-	-
	No rupture	ER (n=11)	-	0	-	-	-	-	-
		OS (n=16)	-	0	-	-	-	-	-
Stark 2021	Rupture	ER (n=4)	-	0	-	-	50	-	-
		OS (n=3)	-	33	-	-	100	-	-
	No rupture	ER (n=7)	-	0	-	-	86	-	-
		OS (n=7)	-	14	-	-	100	-	-
Wolk 2020	Rupture	ER (n=11)	0	-	-	11.2 (7.1)	-	-	-
		OS (n=7)	14.3	-	-	11.4 (4.5)	-	-	-
	No rupture	ER (n=12)	0	-	-	3.2 (2.9)	-	-	-
		OS (n=29)	0	-	-	11.9/7)	-	-	-

.61 95% CI [.21; 1.77], $P = .02$). Technical success rates were comparable between both groups (97% vs 98%, OR .50 95% CI [.21; 1.16], $P = .11$). Length of stay was shorter in the ER group (mean difference −4.25 days, 95% CI [−5.52; −2.98], $P < .00001$). 1-year reintervention rates were higher in the ER group (9% vs 5%, OR 1.55 95% CI [.58; 4.12], $P = .38$).

Discussion

In this systematic review and meta-analysis, we compared the outcomes of OS and ER for the treatment of VAA.

Mortality was comparable between ER and OS (1.8% vs 2.1%). Lower mortality for ER prevailed in the subgroup analysis for ruptured aneurysms. Considerable mortality is a known problem of this pathology in an emergency setting.[47] Our results are comparable to large cohort studies. In a retrospective study from the Mayo Clinic, reporting on endovascular management of VAA between 1999 and 2009, 185 aneurysms were identified in 176 patients. 46% of the patients were symptomatic with aneurysm rupture. While a 98% technical success rate was reported after the initial intervention, the 30-day overall and aneurysm-related mortality was 6.2% and 3.4%, respectively, in these patients. In contrast, no deaths were observed in patients undergoing elective treatment.[48] In another report from the same institution comprising 217 splenic artery aneurysms, operative mortality was 5% in the elective group and 20% in the emergency group.[49] These data suggest that, in terms of mortality, ER should be considered as first line treatment for VAA, especially in the emergency setting, if it is technically possible and the necessary experience in endovascular procedures is present.

Length of stay was shorter in the ER group (mean difference −4.25 days, 95% CI [−5.52; −2.98], $P < .00001$).

Comparable results regarding the length of stay were reported in a previous meta-analysis.[17] In the present meta-analysis, technical success rates were comparable between ER and OS (97% vs 98%). In a previous meta-analysis involving 1321 patients with true splenic artery aneurysms, endovascular surgery required more reinterventions (3.2%) compared with open surgery (.5%).[50] Despite the higher reintervention rates, endovascular repair is reported as the most cost-effective treatment when compared to open surgery, independent of the risk profile in the treatment of splenic artery aneurysms.[51] Contemporary evidence shows that ER is superior in terms of length of stay and morbidity. With comparable technical success, but higher reintervention rates, follow-up remains mandatory in these patients to avoid secondary problems such as stent occlusion, endoleaks or secondary growth and rupture of the aneurysm.

This meta-analysis has some limitations. The main drawback is that it is exclusively based on retrospective studies with heterogeneous outcome definitions and study patient populations in the single study groups. The long inclusion period does not necessarily reflect contemporary surgical and endovascular techniques. The results are based on a non-randomized, uncontrolled comparison of patients. There was no clear distinction across all the studies concerning potential differences between groups receiving treatment in an emergency setting. The PRISMA guidelines were followed to ensure transparency and standardized reporting, but the risk of bias is considerable. Moreover, the number of studies and patients were relatively small. The strength of this meta-analysis is that all available comparative studies providing information on the outcome of patients undergoing ER and OS surgery for VAA were included. The findings of this work may provide useful information for clinicians treating VAA. The data suggest that ER should be considered as first line treatment for patients with VAA in the elective and emergency setting in the light of comparable mortality and technical success and lower morbidity and length of stay when compared to OR. Due to the higher reintervention rates, a structured follow-up must be offered to patients treated with ER.

Conclusion

Evidence from non-randomized studies shows similar mortality and longer hospital stay for patients undergoing OS for VAA when compared to ER. With comparable technical success to OS, reintervention remains an issue of ER. Nevertheless, according to the available evidence, ER should be considered as first-line treatment for VAAs.

Authors' Contributions

AR outlined, wrote, and drafted the manuscript. All authors critically revised the manuscript, read, and approved the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Artur Rebelo https://orcid.org/0000-0002-5267-079X
Jorg Ukkat https://orcid.org/0000-0001-7834-950X

Supplemental Material

Supplemental material for this article is available online.

References

1. Beaussier M. Sur un anervrisme de l'artere splenique dont les parois se sont ossifiées. J Med Clin Pharm Paris. 1770;32:157.
2. MacLeod D, Maurice T. Rupture of branch of splenic artery associated with pregnancy. Lancet. 1940;1:924.
3. Meyer A, Uder M, Lang W, Croner R. Aneurysmen an visceralen Arterien. Zentralbl Chir. 2010;135:416-420.
4. Abbas MA, Stone WM, Fowl RJ, et al. Splenic artery aneurysms: Two decades experience at mayo clinic. Ann Vasc Surg. 2002;16:442-449.
5. Tulsyan N, Kashyap VS, Greenberg RK, et al. The endovascular management of visceral artery aneurysms and pseudoaneurysms. J Vasc Surg. 2007;45:276-283.
6. Herbeck M, Horbach T, Putzenlechner C, Klein P, Lang W. Ruptured splenic artery aneurysm during pregnancy: A rare case with both maternal and fetal survival. Am J Obstet Gynecol. 1999; 181:763-764.
7. Barrett JM, Van Hooydonk JE, Boehm FH. Pregnancy related rupture of arterial aneurysms. Obstet Gynecol Surv. 1982;37:557-566.
8. Lee PC, Rhee RY, Gordon RY, Fung JJ, Webster MW. Management of splenic artery aneurysms: The significance of portal and essential hypertension. J Am Coll Surg 1999;189:483-490.
9. Berceli SA. Hepatic and splenic artery aneurysms. Semin Vasc Surg. 2005;18:196-201.
10. Nanez L, Knowles M, Modrall JG, Valentine RJ. Ruptured splenic artery aneurysms are exceedingly rare in pregnant women. J Vasc Surg. 2014;60:1520-1523.
11. Iida A, Katayama K, Yamaguchi A. Laparoscopic resection for splenic artery aneurysm using the lateral approach: Report of two cases. Asian J Endosc Surg. 2013;6:147-150.
12. Kim Y, Johna S. Laparoscopic excision of splenic artery aneurysm. J Soc Laparoendosc Surg. 2013;17:132-134.
13. Pietrabissa A, Ferrari M, Berchiolli R, et al. Laparoscopic treatment of splenic artery aneurysms. J Vasc Surg. 2009;50:275-279.
14. Tiberio GAM, Bonardelli S, Gheza F, Arru L, Cervi E, Giulini SM. Prospective randomized comparison of open versus laparoscopic

management of splenic artery aneurysms: A 10-year study. Surg Endosc. 2012;■■■:■■■.
15. Balderi A, Antonietti A, Ferro L, et al. Endovascular treatment of visceral artery aneurysms and pseudoaneurysms: Our experience. Radiol Med. 2012;117:815-830.
16. Cappucci M, Zarco F, Orgera G, et al. Endovascular treatment of visceral artery aneurysms and pseudoaneurysms with stent-graft: Analysis of immediate and long-term results. Cir Esp 2017;95: 283-292.
17. Barrionuevo P, Malas MB, Nejim B, et al. A systematic review and meta-analysis of the management of visceral artery aneurysms. J Vasc Surg. 2020;72:40S-45S.
18. Page MJ, McKenzie JE, Bossuyt PM, et al. The Prisma 2020 statement: An updated guideline for reporting systematic reviews. Int J Surg. 2021;88:105-906.
19. Rebelo A. Endovascular and Open Surgery for Visceral Aneurysms: A Systematic Review and Meta-Analysis of Endovascular versus Open Repair. PROSPERO. 2022. CRD42022348699 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022348699
20. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240: 205-213.
21. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7:1-173.
22. Boll JM, Sharp KW, Garrard CL, Naslund TC, Curci JA, Valentine RJ. Does management of true aneurysms of peripancreatic arteries require repair of associated celiac artery stenosis? J Am Coll Surg. 2017;224:199-203.
23. Buck DB, Curran T, McCallum JC, et al. Management and outcomes of isolated renal artery aneurysms in the endovascular era. J Vasc Surg. 2016;63:77-81.
24. Chivot C, Rebibo L, Robert B, Regimbeau JM, YzeT T. Ruptured pancreaticoduodenal artery aneurysms associated with celiac stenosis caused by the median arcuate ligament: A poorly known etiology of acute abdominal pain. Eur J Vasc Endovasc Surg. 2016;51:295-301.
25. Cochennec F, Riga CV, Allaire E, et al. Contemporary management of splanchnic and renal artery aneurysms: Results of endovascular compared with open surgery from two european vascular centers. Eur J Vasc Endovasc Surg. 2011;42:340-346.
26. Erben Y, De Martino RR, Bjarnason H, et al. Operative management of hepatic artery aneurysms. J Vasc Surg. 2015;62: 610-615.
27. Giacomelli E, Dorigo W, Piffaretti G, et al. Early and long-term results of open and endovascular treatment of visceral artery aneurysms. J Vasc Surg. 2016;63:39-40.
28. Grego FG, Lepidi S, Ragazzi R, Iurilli V, StRamana R, Deriu GP. Visceral artery aneurysms: A single center experience. Cardiovasc Surg. 2003;11:19-25.
29. Klausner JQ, Harlander-Locke MP, Plotnik AN, Lehrman E, DeRubertis BG, Lawrence PF. Current treatment of renal artery aneurysms may be too aggressive. J Vasc Surg. 2014; 59:1356-1361.
30. Hislop SJ, Patel SA, Abt PL, Singh MJ, Illig KA. Therapy of renal artery aneurysms in New York state: Outcomes of patients undergoing open and endovascular repair. Ann Vasc Surg. 2009; 23:194-200.
31. Huang YK, Hsieh HC, Tsai FC, Chang SH, Lu MS, Ko PJ. Visceral artery aneurysm: Risk factor analysis and therapeutic opinion. Eur J Vasc Endovasc Surg. 2007;33:293-301.
32. Illuminati G, Hostalrich A, Pasqua R, Nardi P, Chaufour X, Ricco JB. Outcomes after open and endovascular repair of non-ruptured true pancreaticoduodenal and gastroduodenal artery aneurysms associated with coeliac artery compression: A multicentre retrospective study. Eur J Vasc Endovasc Surg. 2021;61:945-953.
33. Kagaya H, Miyata T, Koshina K, et al. Long-term results of endovascular treatment for splenic artery aneurysms. Int Angiol. 2011;30:359-365.
34. Keschenau PR, Kaisaris N, Jalaie H, et al. Management strategies for true and dissecting visceral artery aneurysms. J Cardiovasc Surg. 2020;61:340-346.
35. Lakin RO, Bena JF, Sarac TP, et al. The contemporary management of splenic artery aneurysms. J Vasc Surg. 2011;53: 958-964; discussion 965.
36. Martinelli O, Giglio A, Irace L, Di Girolamo A, Gossetti B, Gattuso R. Single-center experience in the treatment of visceral artery aneurysms. Ann Vasc Surg. 2019;60:447-454.
37. Novak Z, Passman MA, Matthews TC, Patterson MA, Jordan WD. Clinical outcomes after repair of renal artery aneurysms. J Vasc Surg. 2013;57:58.
38. Orion KC, Najafian A, Ehlert BA, Malas MB, Black JH, Abularrage CJ. Gender predicts rupture of pancreaticoduodenal artery aneurysms. Ann Vasc Surg. 2016;36: 1-6.
39. Regus S, and Lang W. Rupture risk and etiology of visceral artery aneurysms and pseudoaneurysms: A single-center experience. Vasc Endovasc Surg. 2016;50:10-15.
40. Saltzberg SS, Maldonado TS, Lamparello PJ, et al. Is endovascular therapy the preferred treatment for all visceral artery aneurysms? Ann Vasc Surg. 2005;19:507-515.
41. Sessa C, Tinelli G, Porcu P, Aubert A, Thony F, Magne JL. Treatment of visceral artery aneurysms: Description of a retrospective series of 42 aneurysms in 34 patients. Ann Vasc Surg. 2004;18:695-703.
42. Stark JC, Eisenberg N, Mafeld S, McGilvray I, Roche-Nagle G, Howe KL. Assessment of open surgical and endovascular management of true hepatic artery aneurysms over 20 years highlights increased rupture risk in females. J Vasc Surg. 2022;75:1334-1342.e2.
43. Sticco A, Aggarwal A, Shapiro M, Pratt A, Rissuci D, D'Ayala M. A comparison of open and endovascular treatment strategies for the management of splenic artery aneurysms. Vascular. 2016;24: 487-491.
44. Tsilimparis N, Reeves JG, Dayama A, Perez SD, Debus ES, Ricotta JJ 2nd. Endovascular vs open repair of renal artery

aneurysms: Outcomes of repair and long-term renal function. J Am Coll Surg. 2013;217:263-269.
45. Wolk S, Distler M, Radosa C, et al. Management and outcome of true visceral and renal artery aneurysm repair. Langenbeck's Arch Surg. 2021;406:623-630.
46. Zhu C, Zhao J, Yuan D, et al. Endovascular and surgical management of intact splenic artery aneurysm. Ann Vasc Surg. 2019;57:75-82.
47. Roberts KJ, McCulloch N, Forde C, et al. Emergency treatment of haemorrhaging coeliac or mesenteric artery aneurysms and pseudoaneurysms in the era of endovascular management. Eur J Vasc Endovasc Surg. 2015;49:382-389.
48. Fankhauser GT, Stone WM, Naidu SG, et al. The minimally invasive management of visceral artery aneurysms and pseudoaneurysms. J Vasc Surg. 2011;53:966-970.
49. Abbas MA, Stone WM, Fowl RJ, et al. Splenic artery aneurysms: Two decades experience at Mayo clinic. Ann Vasc Surg. 2002;16:442-449.
50. Hogendoorn W, Lavida A, Hunink MGM, et al. Open repair, endovascular repair, and conservative management of true splenic artery aneurysms. J Vasc Surg. 2014;60:1667-1676.
51. Hogendoorn W, Lavida A, Hunink MGM, et al. Cost-effectiveness of endovascular repair, open repair, and conservative management of splenic artery aneurysms. J Vasc Surg. 2015;61:1432-1440.

Endovascular and open repair of visceral aneurysms: A retrospective single-center analysis

ARTUR REBELO, ULRICH RONELLENFITSCH, JUMBER PARTSAKHASCHWILLI, JÖRG KLEEFF, ENDRES JOHN and JÖRG UKKAT

Department of Visceral, Vascular and Endocrine Surgery, Martin-Luther-University Halle-Wittenberg, D-06120 Halle (Saale), Germany

DOI: 10.3892/etm_xxxxxxxx

Abstract. The aim of the present study was to analyze the outcome of open surgical and endovascular interventions for the treatment of visceral aneurysms. A retrospective review of a cohort of visceral aneurysm patients treated at a single tertiary referral center was conducted. STROBE guidelines were followed. The primary endpoint was post-operative in-hospital mortality. Secondary endpoints were major morbidity (Dindo-Clavien score, >3), the duration of the procedure, technical success and the length of hospital stay. As a result, 12 patients underwent open or endovascular surgery. No 30-day mortality or major morbidity were observed. The median aneurysm diameter was 2.0 cm (range, 1.5-5.0 cm). The median postoperative stay was four days for all procedures and significantly longer after open surgery compared with endovascular repair (ER) (7 vs. 3 days). Overall, the evidence from the present retrospective analysis shows no mortality and a shorter length of stay for patients undergoing ER for the treatment of a visceral aneurysm (VAA). Although the results are in line with the fact that ER is considered to be the first line treatment for VAA, this may be prone to selection bias.

Introduction

Visceral artery aneurysms are defined in this retrospective analysis as a true aneurysm in the celiac trunk (CT), superior mesenteric artery (SMA), inferior mesenteric artery, and/or their branches. Visceral artery aneurysms (VAAs) are rare and mostly asymptomatic., Rapid growth, size >2 cm, and pregnancy are risk factors associated with rupture. True visceral aneurysms are aneurysms are the result of weakening and thinning of the artery wall. Atherosclerosis, connective tissue disorders, infection (for example pancreatitis) and abdominal surgery are known risk factors for the development of VAA. Nowadays, conservative therapy, endovascular, and open surgery are the treatment options for patients with visceral aneurysms (VAA). During the last decade, endovascular repair of VAAs has been increasingly used (1-6). Catheter-based embolization or stent-graft placement are two major treatment options. Most VAAs originate from the splenic artery (SA) (60%) (Figs. 1 and 2), followed by the hepatic artery (HA) (20-50%) (Figs. 3 and 4). An origin from the superior mesenteric artery (SMA) (6%) (Figs. 5 and 6), the celiac trunk (CT) (4%) or other, smaller visceral arteries is considerably less common (7).

Mostly, VAAs are asymptomatic and incidental findings owing to the evolving and more frequently used imaging modalities. Risk factors associated with rupture are pancreatitis, rapid growth, size >2 cm, and pregnancy. The mortality associated with splenic artery aneurysm rupture has been reported at around 30%. In pregnancy, these rates are higher. Higher flow rate through the splenic artery because of distal compression of the aorta and iliac arteries by the pregnant uterus, portal congestion, and the progressive weakening of the basic structure of the arterial media are possible factors that explain this high mortality (8-16).

The aim of the present study is to compare the outcomes of patients undergoing open surgery (OS) or endovascular repair (ER) for the treatment of VAAs. We present our single center experience on the treatment of VAAs, reporting on 12 patients.

Patiends and methods

All patients 18 years or older at the time of surgery who were treated for VAAs and underwent endovascular or open surgery at the Department of Visceral, Vascular and Endocrine Surgery at the University Hospital Halle (Saale), Germany from 2014 to 2022 were included in the study. The STROBE statement (a checklist of items that should be addressed in articles reporting on the three main study designs of analytical epidemiology: cohort, case-control, and cross-sectional studies) was followed for reporting on observational data (17).

Anastomotic pseudoaneurysms and aortic aneurysms involving the visceral arteries were excluded. The decision to perform an open or endovascular repair was made after

Correspondence to: Dr Artur Rebelo, Department of Visceral, Vascular and Endocrine Surgery, Martin-Luther-University Halle-Wittenberg Ernst-Grube-Straße 40, D-06120 Halle (Saale), Germany
E-mail: artur.rebelo@uk-halle.de

Key words: endovascular, open surgery, visceral aneurysms

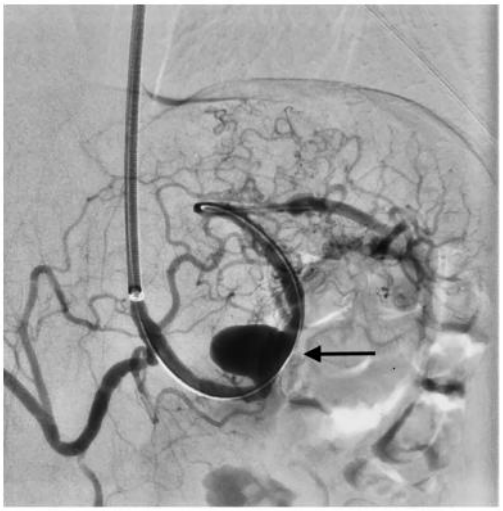


Figure 1. Angiography of an aneurysm of the splenic artery (black arrow) after positioning an 8F-Sheath in celiac trunk.

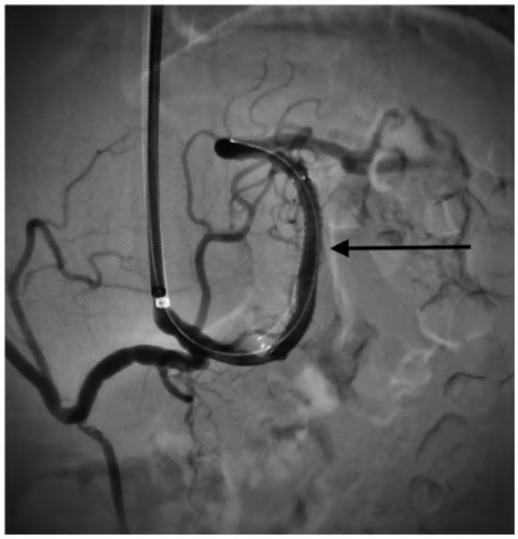


Figure 2. Angiography after endovascular treatment of a splenic artery aneurysm with a covered stentgraft (black arrow).

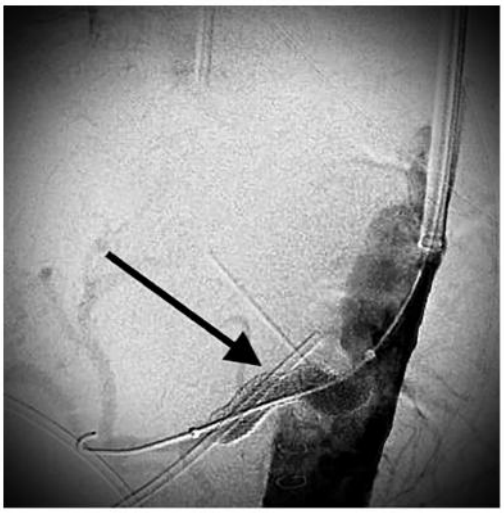


Figure 3. Angiography of an aneurysm of the common hepatic artery after endovascular treatment with a covered stentgraft (black arrow).

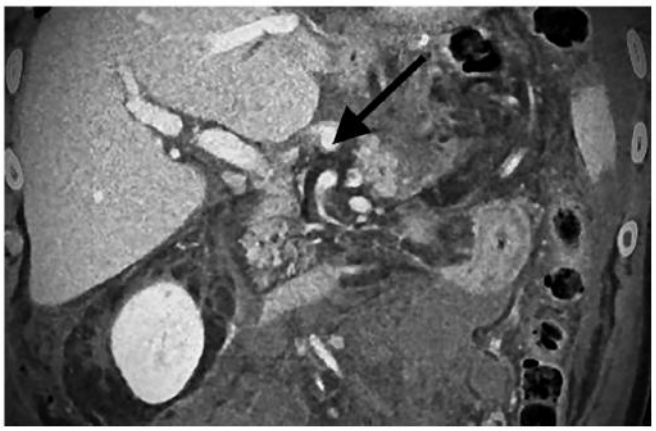


Figure 4. Computed tomography scan of a common hepatic artery aneurysm (black arrow) before endovascular treatment.

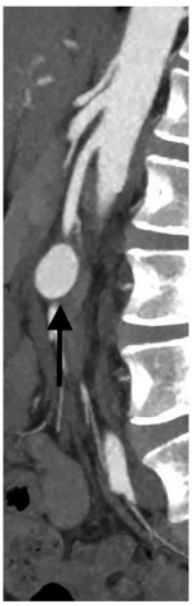


Figure 5. Computed tomography scan from an aneurysm of the superior mesenteric artery (black arrow) (sagittal plane).

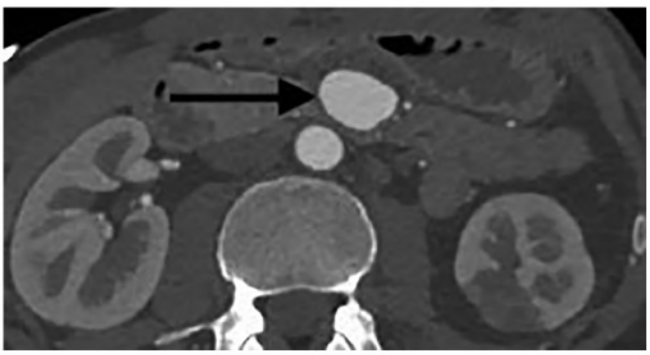


Figure 6. Computed tomography scan from an aneurysm of the superior mesenteric artery (black arrow) (axial plane).

discussion in a multidisciplinary meeting (angiology, radiology and vascular surgery). All ruptured VAAs underwent intervention. Open repair was performed in general anesthesia

as an aneurysmorrhaphy with or without vascular reconstruction by (direct end-to- end anastomosis or using a vein graft interposition). Endovascular treatment was performed in local anesthesia and consisted either of coilembolization or covered stent placement. If a stent graft placement was technically possible it was performed in order to maintain the vessel patency. If not, a coilembolization was performed.

Data was extracted and presented in a tabular fashion. The following descriptive patient and operation characteristics were documented: sex, age at diagnosis, use of diagnostic imaging techniques, aneurysm localization, aneurysm size and symptoms and therapy. The following predefined outcomes were also extracted: in-hospital mortality, major morbidity (when defined as Dindo-Clavien >III) (18), length of hospital stay and technical success (complete aneurysm occlusion in the postoperative CT-Scan). The Clavien Dindo Classification was used to rank the severity of surgical complications. This classification consists in a scale of several grades (Grade I, II, IIIa, IIIb, IV and V). Grade I complications consists in any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Grade II include complications requiring pharmacological treatment. Grade III refers to complications requiring surgical, endoscopic or radiological intervention (IIIa not under general anesthesia and IIIb under anesthesia). Grade IV regards life-threneting complications and Grade V represents the death of the patient (18). Descriptive statistics from our patient collective are reported as numbers or mean.

Results

From 2014 to 2022, 12 patients with VAAs, 11 females and one male were treated at the University Hospital Halle (Saale).

The median age was 59 years (range 40 to 87 years). Only one patient was male, and all were diagnosed by a CT-scan. The detailed patient and operative characteristics are given in Tables I and II.

There were eight patients with an aneurysm of the SA, two patients with aneurysms of the SMA, one patient with an aneurysm of the HA and one patient with an aneurysm of the CT. Only one patient was symptomatic and presented with signs of bleeding. All patients received a contrast-enhanced CT-scan.

The median aneurysm diameter was 2 cm (range 1.5 cm to 5 cm) for all aneurysms, 3.75 cm for aneurysms of the SMA, 2 cm for aneurysms of the SA and for aneurysms of the CT and 1.5 for the aneurysm of the HA.

Six aneurysms of SA, one aneurysm of the CT and one aneurysm of the HA were treated with ER (eight patients). Seven patients were treated with covered stents and one with coiling embolization. In total eight covered stents were implanted. Two patients with SA aneurysms and two patients with SMA aneurysms underwent OS. No allogeneic grafts were required. Three patients needed direct suture only and one a vein graft.

There was no in-hospital mortality and no major postoperative complications (Clavien-Dindo grade ≥3). Technical success was achieved in all patients. The median postoperative stay was four days for all procedures and significantly longer after OS when compared with ER (seven days vs. three days).

Table I. Patients and preoperative characteristics.

No.	Sex	Age	Year	Imaging	Location	Size, cm	Symptoms related to the aneurysm	Atherosclerosis	Connective tissue disorders	Infection	Previous abdominal surgery	Diabetes Mellitus Type II	Smoker
1	F	50	2019	CTA	SA	2.5	N	N	N	N	N	N	N
2	F	69	2017	CTA	SA	2	N	N	N	N	N	Y	N
3	F	61	2014	CTA	SMA	5	N	Y	N	N	Y	N	N
4	F	33	2021	CTA	SMA	2, 5	N	N	Y	N	N	N	Y
5	F	52	2020	CTA	SA	2	N	N	N	N	N	N	N
6	F	74	2021	CTA	SA	3.5	N	N	N	N	N	N	N
7	M	67	2020	CTA	HA	1.5	Bleeding	N	N	Y	Y	Y	N
8	F	64	2022	CTA	CT	2	N	Y	N	N	N	N	Y
9	F	54	2021	CTA	SA	2.2	N	N	N	N	N	N	N
10	F	57	2021	CTA	SA	1.5	N	N	N	N	N	N	N
11	F	53	2021	CTA	SA	2	N	N	N	N	N	N	N
12	F	87	2022	CTA	SA	2	N	N	N	N	N	N	N

M, male; F, female; SA, splenic artery; SMA, superior mesenteric artery; CT, celiac trunk; HA, hepatic artery; CTA, computed tomography angiography; Y, Yes; N, No.

Table II. Surgical characteristics and postoperative outcomes.

No.	Therapy	Implants	Morbidity (Dindo-Clavien)	In-Hospital Mortality	Duration of postoperative stay (Days)
1	OS; aneurysm resection, direct suture	-	0	N	6
2	OS; aneurysm resection, direct suture	-	0	N	4
3	OS; aneurysm Resection, Vein graft	-	0	N	19
4	OS; aneurysm resection, direct suture	-	0	N	8
5	ER; covered stentgraft	Viabahn 5x50 mm	0	N	1
6	ER; covered stentgraft	Viabahn 8x57 mm	0	N	3
7	ER; two covered stentgrafts	Gore Viabahn 5x50 mm and Bentley Begraft 6x18 mm	0	N	7
8	ER; covered stentgraft	Bentley Begraft 6x27 mm	0	N	3
9	ER; covered stentgraft	Bentley Begraft 6x37 mm	0	N	4
10	ER; covered stentgraft	Bentley Begraft 6x27 mm	0	N	3
11	ER; covered stentgraft	Viabahn 5x50 mm	0	N	2
12	ER; coiling	Platinum embolization coils	0	N	5

N, none; ER, endovascular; OS, open surgery.

Discussion

In this retrospective study we reported on our single center experience on the treatment of VAAs, both with endovascular and open surgery.

In our small patient collective, no mortality was observed. This may be due to the almost total absence of emergency repairs. Considerable mortality is described in the treatment of these patients in an emergency setting (19). In a retrospective study reporting on 185 aneurysms, 46% of the patients were symptomatic with bleeding or rupture. Despite 98% technical success on treating symptomatic patients, 30-day overall and aneurysm-related mortality was 6.2 and 3.4%, respectively. On the other hand, no deaths were observed in patients undergoing elective treatment (20). In another report of 217 splenic artery aneurysms, operative mortality was 5% in the elective group and 20% in the emergency group (8). In another study an operative mortality rate of 37.5% for ruptured superior mesenteric artery aneurysms was described. Also in this study, no mortality was observed for elective repair (21). In another large retrospective study, morbidity (19% vs. 4%; P=.003), 30-day mortality (13% vs. 0% P=0.001), 1-year (32.5% vs. 4.1%, P<.001), and 3-year mortality rates (36.4% vs. 8.3%; P<.001) were significantly higher for ruptured aneurysms than for intact aneurysms. Open surgery had higher 30-day mortality rates thanendovascular repair (28% vs. 7%; P= .06) (22). In our retrospective patient cohort, length of stay was shorter in the ER group (mean difference -4.25 days, 95% CI [-5.52; -2.98], P<0.00001; seven vs. four days). Comparable results regarding the length of stay were reported in a previous meta-analysis (23). The technical success of 100% when using endovascular stentgrafts or coiling observed in our patient collective may reflect the bias inherent in the analysis of a very small patient collective. In a systematic review and meta-analysis from 2016 comprising 22 studies reporting on endovascular treatment of VAAs, a 93.2% technical success rate was reported (24).

This study has limitations. The main limitation is that it is exclusively based on retrospective data, which could represent a problem in terms of selection bias. The long inclusion period does not necessarily reflect contemporary surgical and endovascular techniques. Another limitation is the small number of patients. The STROBE guidelines were followed to ensure transparency and standardized reporting. Nevertheless, the findings of this work may provide useful information, as it reports a case series of a rare disease with outcomes on open and endovascular treatment.

In conclusion, evidence from this retrospective small case series shows no mortality and a shorter length of stay for patients undergoing ER for the treatment of VAA. Although the results are in line with the fact that ER is nowadays considered the first line treatment for VAA, they may be prone to selection bias.

Acknowledgements

Not applicable.

Funding

This work was partially supported by the Advanced Clinician Scientist Program of the Medical Faculty of the Martin-Luther University Halle-Wittenberg, Halle (Saale), Germany (grant no. FKZ ACS23/06).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AR outlined, wrote and drafted the manuscript. AR, UR, JP, JK, EJ and JU performed analysis or interpretation of data for the work. All authors critically revised the manuscript and read and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AR and JP confirm the authenticity of all the raw data.

Ethics approval and consent to participate

A fully anonymized retrospective evaluation of the study data was conducted, and so the need for an ethical vote and patient consent was waived, according to section 17 of the Hospital Act of the Federal State of Saxony-Anhalt and section 15 of the Saxony-Anhalt Medical Association's professional code of conduct.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

References

1. Iida A, Katayama K and Yamaguchi A: Laparoscopic resection for splenic artery aneurysm using the lateral approach: Report of two cases. Asian J Endosc Surg 6: 147-150, 2013.
2. Kim Y and Johna S: Laparoscopic excision of splenic artery aneurysm. JSLS 17: 132-134, 2013.
3. Pietrabissa A, Ferrari M, Berchiolli R, Morelli L, Pugliese L, Ferrari V and Mosca F: Laparoscopic treatment of splenic artery aneurysms. J Vasc Surg 50: 275-279, 2009.
4. Tiberio GA, Bonardelli S, Gheza F, Arru L, Cervi E and Giulini SM: Prospective randomized comparison of open versus laparoscopic management of splenic artery aneurysms: A 10-year study. Surg Endosc: Jun 30, 2012 (Epub ahead of print).
5. Balderi A, Antonietti A, Ferro L, Peano E, Pedrazzini F, Fonio P and Grosso M: Trattamento endovascolare di aneurismi e pseudoaneurismi viscerali: la nostra esperienza. Radiologia Medica 117: 815-830, 2012.
6. Cappucci M, Zarco F, Orgera G, López-Rueda A, Moreno J, Laurino F, Barnes D, Tipaldi MA, Gomez F, Macho Fernandez J and Rossi M: Endovascular treatment of visceral artery aneurysms and pseudoaneurysms with stent-graft: Analysis of immediate and long-term results. Cir Esp 95: 283-292, 2017 (In English, Spanish).
7. Meyer A, Uder M, Lang W and Croner R: Visceral artery aneurysms. Zentralbl Chir 135: 416-420, 2010 (Article in German).
8. Abbas MA, Stone WM, Fowl RJ, Gloviczki P, Oldenburg WA, Pairolero PC, Hallett JW, Bower TC, Panneton JM and Cherry KJ: Splenic artery aneurysms: Two decades experience at mayo clinic. Ann Vasc Surg 16: 442-449, 2002.
9. Tulsyan N, Kashyap VS, Greenberg RK, Sarac TP, Clair DG, Pierce G and Ouriel K: The endovascular management of visceral artery aneurysms and pseudoaneurysms. J Vasc Surg 45: 276-283, 2007.
10. Herbeck M, Horbach T, Putzenlechner C, Klein P and Lang W: Ruptured splenic artery aneurysm during pregnancy: A rare case report with both maternal and fetal survival. Am J Obstet Gynecol 181: 763-764, 1999.
11. Barrett JM, Van Hooydonk JE and Boehm FH: Pregnancy related rupture of arterial aneurysms. Obstet Gynecol Surv 37: 557-566, 1982.
12. Trastek VF, Pairolero PC and Bernatz PE: Splenic artery aneurysms. World J Surg 9: 378-383, 1985.
13. Lee PC, Rhee RY, Gordon RY, Fung JJ and Webster MW: Management of splenic artery aneurysms: The significance of portal and essential hypertension. J Am Coll Surg 5: 483-490, 1999.
14. Berceli SA: Hepatic and splenic artery aneurysms. Semin Vasc Surg 18: 196-201, 2005.
15. Moore SW, Guida PM and Schumacher HW: Splénic artery aneurysm. Bull Soc Int Chir 29: 210-218, 1970.
16. Nanez L, Knowles M, Modrall JG and Valentine RJ: Ruptured splenic artery aneurysms are exceedingly rare in pregnant women. J Vasc Surg 60: 1520-1523, 2014.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP and STROBE Initiative: The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. J Clin Epidemiol 61: 344-349, 2008.
18. Dindo D, Demartines N and Clavien PA: Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240: 205-213, 2004.
19. Roberts KJ, McCulloch N, Forde C, Mahon B, Mangat K, Olliff SP and Jones RG: Emergency treatment of haemorrhaging coeliac or mesenteric artery aneurysms and pseudoaneurysms in the era of endovascular management. Eur J Vasc Endovasc Surg 49: 382-389, 2015.
20. Fankhauser GT, Stone WM, Naidu SG, Oderich GS, Ricotta JJ, Bjarnason H, Money SR and Mayo Vascular Research Center Consortium: The minimally invasive management of visceral artery aneurysms and pseudoaneurysms. J Vasc Surg 53: 966-970, 2011.
21. Stone WM, Abbas M, Cherry KJ, Fowl RJ and Gloviczki P: Superior mesenteric artery aneurysms: Is presence an indication for intervention? J Vasc Surg 36: 234-237; discussion 237, 2002.
22. Shukla AJ, Eid R, Fish L, Avgerinos E, Marone L, Makaroun M and Chaer RA: Contemporary outcomes of intact and ruptured visceral artery aneurysms. J Vasc Surg 61: 1442-1447, 2015.
23. Barrionuevo P, Malas MB, Nejim B, Haddad A, Morrow A, Ponce O, Hasan B, Seisa M, Chaer R and Murad MH: A systematic review and meta-analysis of the management of visceral artery aneurysms. J Vasc Surg 72: 40S-45S, 2020.
24. Kok HK, Asadi H, Sheehan M, Given MF and Lee MJ: Systematic review and single-center experience for endovascular management of visceral and renal artery aneurysms. J Vasc Interv Radiol 27: 1630-1641, 2016.

Original Article

Open Surgical Thrombendarterectomy Versus Endovascular Treatment in Occlusive Processes of the Femoral Artery Bifurcation

A Systematic Review and Meta-Analysis of Aggregate Data and Individual Patient Data

Carola Marie Hoffmann-Wieker*, Ulrich Ronellenfitsch*, Artur Rebelo, Nadine Görg, Guido Schwarzer, Enzo Ballotta, Yann Gouëffic, Dittmar Böckler

Summary

Background: The standard treatment of occlusive processes of the femoral artery bifurcation is thrombendarterectomy (TEA). Endovascular techniques (ENDO) have recently been put forward as a potential alternative. It is unclear so far which modality yields better outcomes with respect to long-term revascularization and periprocedural complications.

Method: Multiple databases were systematically searched for pertinent publications (publication date November 1965 to February 2022). From the included studies, individual patient data (IPD) were requested. Aggregate data (AD) were used when no IPD were available. Primary and secondary patency (PP and SP), perioperative morbidity/mortality, and further endpoints were determined separately for TEA and ENDO and compared with each other. AD for each modality were summarized in meta-analyses. Time-to-event analyses and comparative meta-analyses with PP as primary endpoint were carried out using IPD.

Results: 42 studies (3 IPD, 39 AD; 27 TEA, 12 ENDO, 3 comparisons of TEA versus ENDO) were included. In the combined meta-analysis of IPD and AD, PP for TEA was 97% at 6 months and 92% at 12 months, while PP for ENDO was 84% at 6 months and 85% at 12 months. The differences were not statistically significant. The comparative meta-analysis regarding PP did not reveal any significant differences either (TEA versus ENDO: HR 0.30 [0.06; 1.48]). SP at 12 months was 97% (TEA) and 93% (ENDO). The periprocedural morbidity was 16% for TEA and 9% for ENDO.

Conclusion: In light of a higher PP, even without formal statistical proof of superiority, TEA can still be considered the standard treatment for occlusive processes of the femoral artery bifurcation.

Cite this as
Hoffmann-Wieker CM, Ronellenfitsch U, Rebelo A, Görg N, Schwarzer G, Ballotta E, Gouëffic Y, Böckler D: Open surgical thrombarterectomy versus endovascular treatment in occlusive processes of the femoral artery bifurcation—a systematic review and meta-analysis of aggregate data and individual patient data. Dtsch Arztebl Int 2022; 119: 803–9. DOI: 10.3238/arztebl.m2022.0331

Two modalities are available for the revascularization of occlusive processes in the region of the femoral artery bifurcation in the setting of peripheral arterial disease. To date, open surgical thrombendarterectomy (TEA) has represented the gold standard (1–7). However, endovascular techniques (ENDO) are increasingly being proposed as alternative treatment forms (8).

TEA refers to the surgical removal of atherosclerotic plaques. It has high technical success rates of almost 100% with very good short- and long-term outcomes (6). However, TEA carries a relevant risk of morbidity of up to 20% (5, 8, 9). This includes in particular local complications such as impaired wound healing, hematomas, and hemorrhage. The postoperative mortality rate is 1–2 % (1, 3, 4, 7).

ENDO is performed via a percutaneous access. Removal of the occlusive process is carried out using transluminal angioplasty and, where necessary, stent implantation. The fact that the femoral artery bifurcation is located in the segment of motion poses problems such as mechanical alterations to the stent. In addition, there is the risk of covering outflow vessels, and thus the risk of obstruction of important collateral circulation, as well as renewed occlusive processes as a result of neointimal hyperplasia. Subsequent interventions are also hampered by stent material (10–17).

When indirectly comparing the two approaches, studies to date suggest a longer lasting vascularization success for TEA, albeit with more frequent postoperative complications (1, 4, 7, 16, 18). There are only two comparative randomized trials (19, 20). Since the results show significant heterogeneity, an evidence synthesis is needed in order to make valid statements with regard to advantages and disadvantages of the techniques.

*These authors share first authorship.

Department of Vascular and Endovascular Surgery, Heidelberg University Hospital: Dr. med. Carola Marie Hoffmann-Wieker, Nadine Görg, Prof. Dr. med. Dittmar Böckler

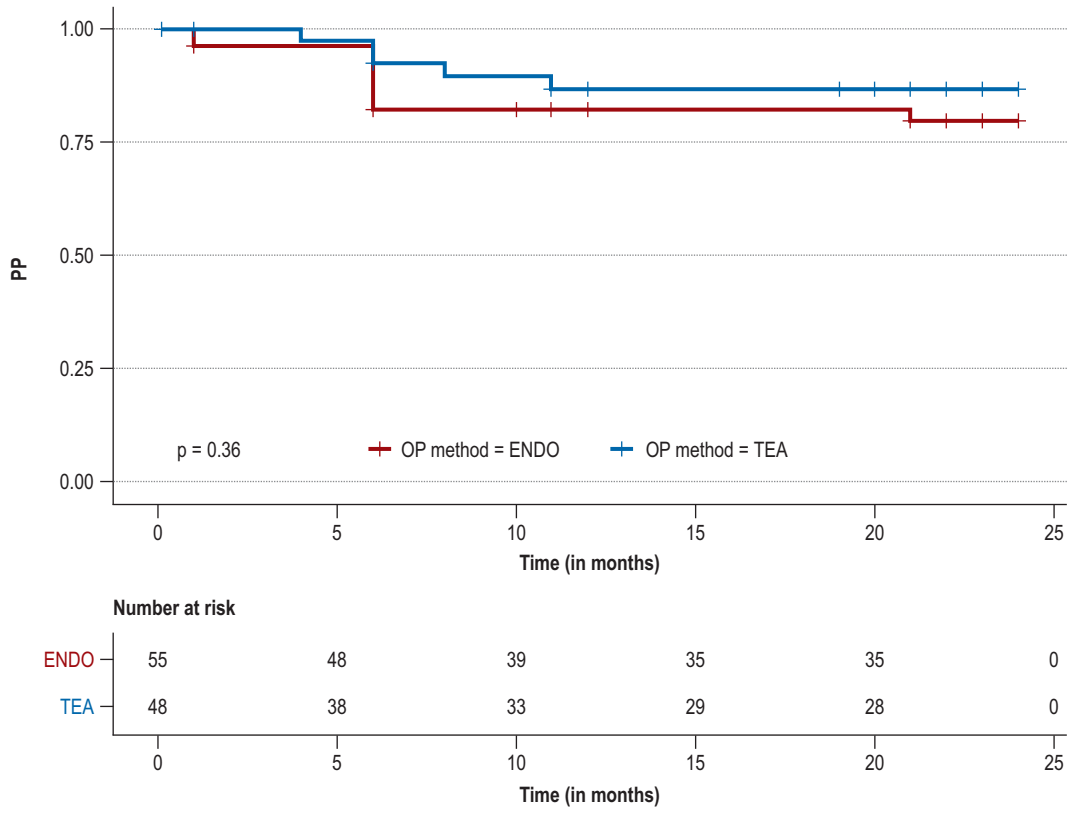
Department of Visceral, Vascular and Endocrine Surgery, University Medical Center, Martin-Luther-University Halle-Wittenberg (Saale): Prof. Dr. med. Ulrich Ronellenfitsch, Dr. med. Artur Rebelo

Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, Albert-Ludwigs-University of Freiburg: Dr. Guido Schwarzer

Department of Surgical, Oncological and Gastroenterological Sciences, University of Padova, School of Medicine, Padova, Italy: Prof. Enzo Ballotta

Department of Vascular Surgery, University Hospital of Nantes, France: Prof. Yann Gouëffic

FIGURE 1



Kaplan–Meier curve for primary patency (PP) from the TECCO trial (19) based on individual patient data (IPD); ENDO, endovascular treatment; TEA, thrombendarterectomy

Methods

The study was conducted according to Prisma Guidelines *(eFigure 1)* and prospectively registered (PROSPERO: CRD42018091539). PubMed, EMBASE, Cochrane Library, Web of Science, ClinicalTrials.gov, and ICTRP were searched using a predefined search strategy *(eBox; eMethods Section)* for the period 11/1965–02/2022.

For TEA, studies on patients with femoral artery bifurcation lesions who underwent surgical treatment were included.

For ENDO, studies on endovascular procedures on femoral artery bifurcation lesions were included. With the exception of case reports, all study designs were taken into consideration. The risk of bias of the individual studies was assessed.

A detailed description of methodology, including endpoints and statistical methods, can be found in the *eMethods Section*.

Results

The study selection is presented in *eFigure 1*. The literature search identified 671 studies, 42 of which met the inclusion criteria and were included in the meta-analysis. Three studies provided individual patient data (IPD) of 875 patients; these included one randomized controlled trial (19) and two non-comparative studies on TEA (1, 7). Aggregate data (AD) for 9822 patients were made available by 39 studies. In all, 27 studies investigated only TEA (3, 4, 9, 18, 21–40, e1), 12 ENDO (17, e2–e12), while two compared the two techniques (20, e13).

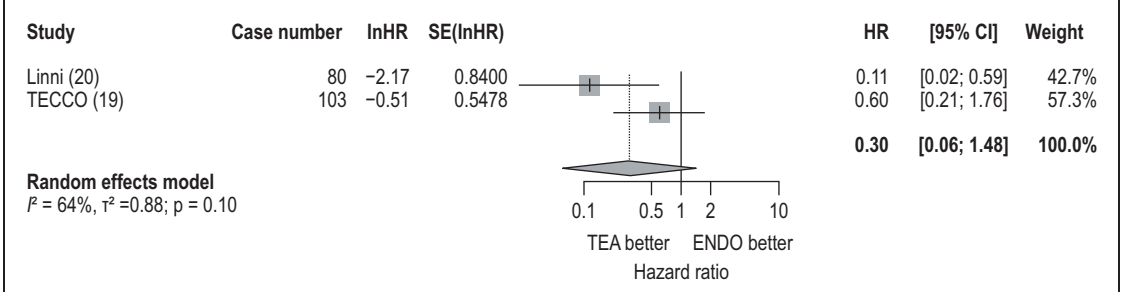
The randomized controlled trials (RCTs) on ENDO and TEA included 197 interventions. For studies on TEA, data from 8678 interventions were available, and for ENDO from 2331 interventions. Details on studies and endpoints as well as patient characteristics and the most important outcomes of the individual endpoints are presented in *eTables 1–3 (eMethods)*.

Primary endpoint: primary patency (PP)

A direct comparison of PP following ENDO and TEA was carried out based on IPD from the randomized TECCO trial. This showed a non-significantly lower PP at 6, 12, and 24 months for ENDO compared to TEA *(Figure 1)*. The meta-analysis of the two RCTs with AD and IPD likewise showed no significantly different PP with an HR of 0.3 in favor of TEA *(Figure 2)*.

The meta-analysis of IPD and AD revealed no significant difference in PP following TEA and

FIGURE 2



Meta-analysis for primary patency (PP) with individual patient data (IPD) and aggregate data (AD) from the two randomized controlled trials. ENDO, endovascular treatment; HR, hazard ratio; CI, confidence interval; SE, standard error; TEA, thrombendarterectomy

ENDO at the 6-month, 12-month, and 5-year time points *(Figure 3)*. A formal statistical comparison between the two techniques was deliberately not carried out in view of the high risk of bias.

Results of the analysis of IPD from three studies on TEA are presented in *eFigure 2*.

Secondary endpoints

Freedom from interventions

Only AD were included in the meta-analysis of freedom from interventions since no IPD were available for this endpoint. For the time point at 12 months post intervention, data from 13 studies were available. Here, as for the 6-month, 2-, 3-, and 5-year time points, higher freedom from interventions was seen for TEA compared to ENDO.

Secondary patency

No IPD were available for the meta-analysis of secondary patency. An analysis was carried out using AD for the 6-month, 1-, 2-, 3-, and 5-year time points post intervention. At 6 and 12 months post intervention, no significant differences were seen in secondary patency rates between ENDO and TEA, with patency rates of 87–93% for ENDO and 97–100% for TEA. The same was true at the 2-, 3-, and 5-year time points post intervention, whereby no data were available for secondary patency at 3 years. The fact that secondary patency was higher at some later follow-up time points than at earlier ones arises from the fact that not all studies reported results at all time points, and thus the studies included in the individual analyses differed *(eTable 2)*.

Limb preservation

The analysis on the endpoint of limb preservation was carried out using AD for the 12-month, 1-, 2-, 3-, and 5-year time points post intervention. At 12 months, limb preservation rates of 97% for TEA and 95% for ENDO were seen. No differences were seen at 2, 3, and 5 years post intervention, with values of 95–96% for TEA and 97–100% for ENDO.

The fact that limb preservation was higher at some later follow-up time points than at earlier ones arises from the fact that not all studies reported results at all time points, and thus the studies included in the individual analyses differed.

Duration of inpatient hospital stay

The meta-analysis of the two RCTs with AD and IPD found a weighted mean difference in the duration of inpatient hospital stay of 4.2 days (95% confidence interval [CI]: [2.5; 6.0]) in favor of ENDO. In the meta-analysis of IPD and AD, a mean length of stay of 2.5 days (95% CI: [1.45; 3.6]) was seen for ENDO and 6.4 days (95% CI: [4.0; 8.8]) for TEA.

Perioperative morbidity and mortality

An analysis of perioperative morbidity was initially carried out based on IPD from the randomized TECCO trial (19). This revealed a complication rate of 20.8% following TEA and 7.5 % following ENDO (risk ratio = 2.76; 95% CI: [0.93; 8.22]). The meta-analysis of AD and IPD found a complication rate of 16% (95% CI: [12; 20]) following TEA and 9% (95% CI: [5; 15]) following ENDO. There were no perioperative fatalities in the randomized TECCO trial, rendering a comparison of perioperative mortality based on randomized data impossible. A meta-analysis of AD and IPD revealed a cumulative perioperative mortality rate of 2% for both procedures (TEA: 95% CI: [2; 2], ENDO: 95% CI: [1; 2]).

Need for revision

An analysis of the need for revision was initially carried out based on IPD from the randomized TECCO trial (19). This revealed a frequency of need for revision of 3.6% following TEA and 2.1% following ENDO (risk ratio = 0.57; 95% CI: [0.05; 6.12]). The meta-analysis of AD and IPD found a need-for-revision frequency of 5% (95% CI: [3; 10]) for ENDO and 6% (95% CI: [4; 10]) for TEA.

Overall survival

A comparison of overall survival following the two treatment modalities was carried out with IPD from the randomized TECCO trial (19). This revealed no

difference, with a 2-year survival rate of 95% (95% CI: [89; 100]) for TEA and 91% (95% CI: [83; 99]) for ENDO.

Using IPD, it was possible to evaluate overall survival for TEA up to 6 years post intervention. Here, a difference was seen between TECCO and Ballotta et al. (1, 19) on the one hand and Wieker et al. (7) on the other, with a shorter overall survival time seen in the latter study *(eFigure 3)*.

Univariate Cox regression revealed an association between overall survival following TEA and age, Rutherford classification, length of lesion, ASA score, renal failure, and cardiac comorbidities. A multivariable analysis was carried out with these variables; all factors were negatively associated with overall survival.

In the meta-analysis of AD and IPD, an overall survival for TEA of 80–96% was seen for the 6-month, 12-month, 2-year, and 3-year time points. Overall survival at 5 years was 70%. For ENDO, the meta-analysis yielded a cumulative overall survival of 80–93% for the 12-month, 2-year, and 3-year post intervention time points. No 5-year outcomes were recorded for ENDO.

Change in ankle-brachial index

The pre- to postoperative change in ankle-brachial index was investigated based on IPD from the randomized TECCO trial (19). No difference was found here between TEA and ENDO with a cumulative difference of 0 (95% CI: [−0.13; 0.13]).

The meta-analysis with AD and IPD showed a change of 0.31 for TEA (95% CI: [0.24; 0.39]) and of 0.18 for ENDO (95% CI: [0.10; 0.27]).

Intervention duration

The meta-analysis with AD and IPD yielded a mean intervention duration of 165 min for TEA (95% CI: [123; 208]) and of 87 min for ENDO (95% CI: [50; 124]).

Risk of bias

The results of the assessment of bias risk of the individual studies can be found in *eTable 4*.

Discussion

This systematic review and meta-analysis summarizes the evidence comparing the two modalities used for the treatment of occlusive processes of the femoral artery bifurcation. Whereas TEA has long represented the gold standard (1, 3, 4, 7) and is recommended in the current German S3 guideline (5), ENDO has been proposed as an alternative in recent years (8).

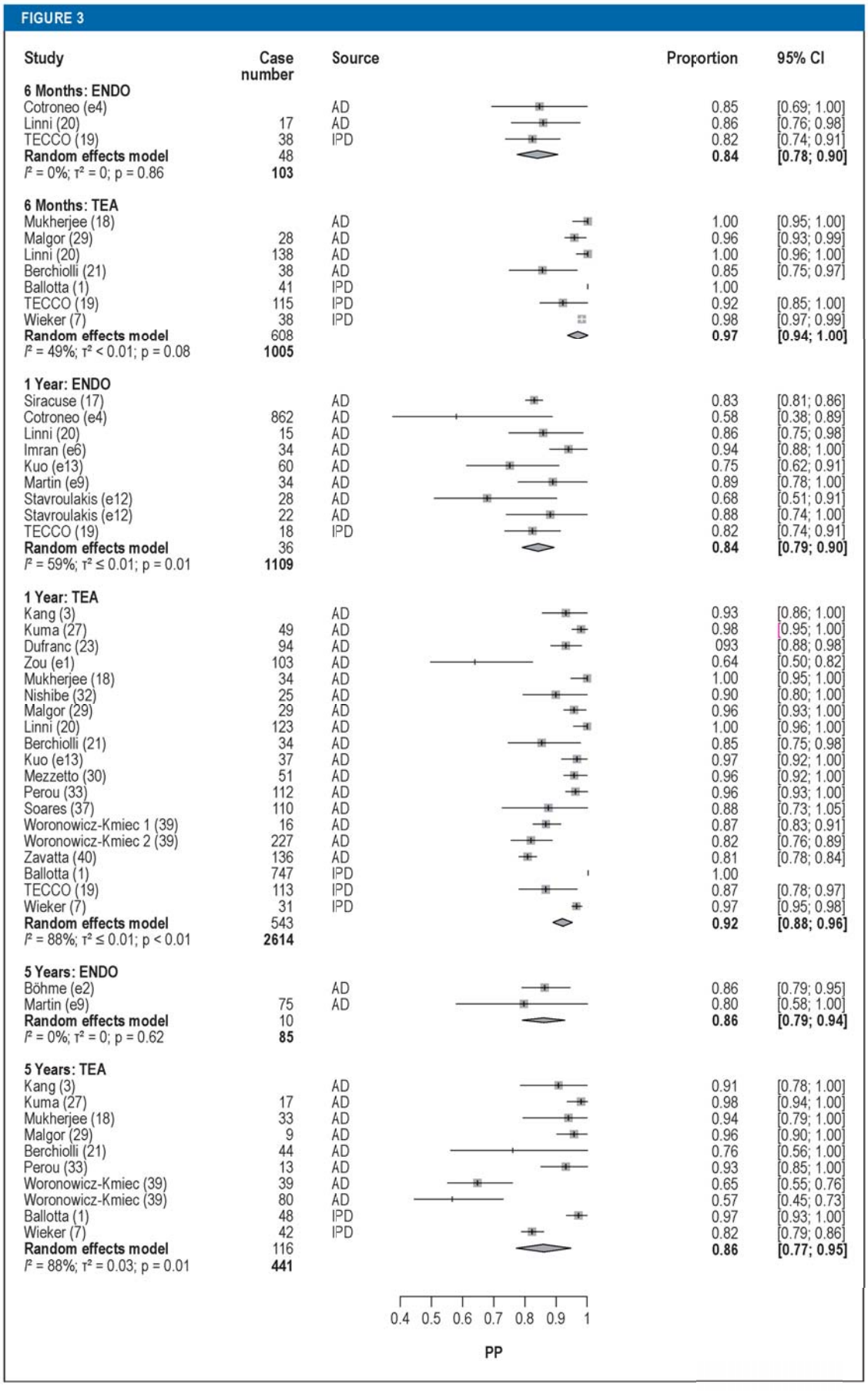
Primary patency was defined as the primary endpoint of the present analysis. The meta-analysis to directly compare the techniques showed better outcomes for TEA. Statistical significance was not achieved. The meta-analysis carried out separately for each procedure also yielded higher primary patency for TEA. Higher values were also found for freedom from interventions and secondary patency for TEA.

In view of the nominally more favorable results with TEA, ENDO can still not be considered as equivalent in terms of revascularization success. However, the available data are not able to identify the reasons for this with any certainty. Patients in the included studies on ENDO were treated with angioplasty, stent implantation, as well as atherectomy (17, 19, 20, e2–e12). A formal comparison of these techniques was not possible due to the small and heterogeneous study populations. An indication can be found in Mehta et al. (e10). In their study, 38 patients received angioplasty and 15 additional stenting. Primary patency following stent implantation was 100%, while it was only 77% following angioplasty alone (e10). Both RCTs comparing ENDO with TEA placed stents in the ENDO arm. Whereas no differences regarding revascularization rates were seen in the TECCO trial Linni et al. showed stenting to be inferior compared to TEA (19, 20). Relevant problems of stent implantation, particularly when using covered stents, include the obstruction of collateral circulation as well as the difficulty of vessel puncture for subsequent interventions. In younger patients, stenting in a segment of motion is to be viewed critically due to the poorer long-term outcomes and greater physical activity in this group (15).

The safety of the procedures was assessed on the basis of morbidity, mortality, and need for revision procedures. In the analysis of IPD from one of the RCTs, a disadvantage in terms of perioperative morbidity was found for TEA. The meta-analysis of AD and IPD confirmed this higher probability of complications; however, the difference between the procedures was much smaller here. In terms of the need for revision and mortality, there were no differences between the procedures, with both techniques having a perioperative mortality rate of 2%. Since these endpoints are much more homogeneously defined and recorded, the results can be deemed valid.

In 2019, Changal et al. published a meta-analysis on the same question, albeit with a separate consideration of endovascular procedures with selective and routine stenting (14). The authors conclude that ENDO with routine stenting is an equivalent alternative to TEA in selected patients. On closer scrutiny, however, the results of that particular meta-analysis do not differ significantly from the results of the present meta-analysis. For example, in Changal et al.'s study, primary patency at 12 months was 93% for TEA and 84% and 78%, respectively, for the two endovascular techniques. In the present study, primary patency at 12 months was 94% for TEA and 83% for ENDO. Changal et al.'s perioperative complication rate was 5% and 7%, respectively, for the endovascular techniques, and 22% for TEA, whereas the present analyses of AD and IPD revealed a complication rate of 16% following TEA and of 9% following ENDO. How Changal et al. come to the conclusion, based on the cited data, that endovascular procedures are an equivalent alternative remains unclear, given that the

FIGURE 3



Results of the meta-analyses with individual patient data (IPD) and aggregate data (AD) for the endpoint of primary patency (PP) at 6 months, 12 months, and 5 years post intervention; ENDO: endovascular treatment; CI, confidence interval; TEA: thrombendarterectomy

authors were unable to carry out a formal statistical comparison for the pooled data of nonrandomized studies. Moreover, analyzing selective and routine stenting separately is a different approach. The aim of the present analysis was to compare the "class effect" of endovascular and open surgical management without going into greater detail regarding subspecifications of the treatment.

The study has a number of limitations. The comparison of TEA and ENDO is hampered by predominantly non-randomized study designs, heterogeneous study populations and treatment methods, as well as the limited availability of IPD. As a result, no statistical comparison of the two groups was undertaken since comparisons of this kind are not randomized and are thus invalid (13). A considerable proportion of the included studies had a high risk of bias according to the prespecified criteria. Likewise, there is a possibility of a publication bias in terms of of a more likely publication of particularly impressive results for one of the two treatment methods in non-comparative studies or of results showing a particularly large difference between the two treatment methods in comparative studies. Formal testing for possible publication bias was not carried out due to the low number of comparative studies.

The strength of the present evaluation lies in the fact that data on the clinically most relevant and clearly defined endpoint of primary patency were evaluated from virtually all studies, meaning that a reliable statement can be made on the revascularization success of the respective procedure, but not on the direct comparison of the two procedures. However, the long-term results at 5 years post intervention are based, particularly for ENDO, on data from only a handful of studies, making any estimate of true patency at that time point subject to a degree of uncertainty. A selective follow-up, which could distort these long-term results, is conceivable since some of the comparative studies have attrition bias, that is, differences in follow-up between the two groups.

In summary, the current study demonstrates that TEA is the more effective procedure compared to ENDO in terms of patency, re-intervention, and limb preservation, albeit with a higher probability of perioperative complications. Due to the study design and available data, it was not possible to generate formal statistical proof of superiority. Nevertheless, at present, TEA can continue to be considered the gold standard in the treatment of occlusive processes of the femoral artery bifurcation. Endovascular procedures should only be used in exceptional cases and following critical interdisciplinary evaluation. In order to generate broader evidence to inform the treatment decision between TEA and ENDO, randomized controlled studies meeting quality standards and with sufficient statistical power (case number) and follow-up duration need to be conducted.

Conflict of interest statement
The authors declare that no conflict of interest exists.

Manuscript received on 7 December 2021, revised version accepted on 21 September 2022.

Translated from the original German by Christine Rye.

References

1. Ballotta E, Gruppo M, Mazzalai F, Da Giau G: Common femoral artery endarterectomy for occlusive disease: an 8-year single-center prospective study. Surgery 2010; 147: 268–74.
2. Diehm C, Schuster A, Allenberg JR, et al.: High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. Atherosclerosis 2004; 172: 95–105.
3. Kang JL, Patel VI, Conrad MF, Lamuraglia GM, Chung TK, Cambria RP: Common femoral artery occlusive disease: contemporary results following surgical endarterectomy. J Vasc Surg 2008; 48: 872–7.
4. Kechagias A, Ylönen K, Biancari F: Long-term outcome after isolated endarterectomy of the femoral bifurcation. World J Surg 2008; 32: 51–4.
5. Lawall H, Huppert P, Espinola-Klein C, Rümenapf G: The diagnosis and treatment of peripheral arterial vascular disease. Dtsch Arztebl Int 2016; 113: 729–36.
6. Nasr B, Kaladji A, Vent PA, et al.: State-of-the-art treatment of common femoral artery disease. J Cardiovasc Surg (Torino) 2015; 56: 309–16.
7. Wieker CM, Schönefeld E, Osada N, et al.: Results of common femoral artery thromboendarterectomy evaluation of a traditional surgical management in the endovascular era. J Vasc Surg 2016; 64: 995–1001.
8. Wong G, Lahsaei S, Aoun J, Garcia LA: Management of common femoral artery occlusive disease: a review of endovascular treatment strategies and outcomes. Catheter Cardiovasc Interv 2019; 93: 514–21.
9. Elbadawy A, Ali H, Saleh M: Midterm outcomes of common femoral endarterectomy combined with inflow and outflow endovascular treatment for chronic limb threatening ischaemia. Eur J Vasc Endovasc Surg 2020; 59: 947–55.
10. Andrews RT, Venbrux AC, Magee CA, Bova DA: Placement of a flexible endovascular stent across the femoral joint: an in vivo study in the swine model. J Vasc Interv Radiol 1999; 10: 1219–28.
11. Azéma L, Davaine JM, Guyomarch B, et al.: Endovascular repair of common femoral artery and concomitant arterial lesions. Eur J Vasc Endovasc Surg 2011; 41: 787–93.
12. Bonvini RF, Rastan A, Sixt S, et al.: Endovascular treatment of common femoral artery disease: medium-term outcomes of 360 consecutive procedures. J Am Coll Cardiol 2011; 58: 792–8.
13. Bucher HC, Guyatt GH, Griffith LE, Walter SD: The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997; 50: 683–91.
14. Changal KH, Syed MA, Dar T, Mangi MA, Sheikh MA: Systematic review and proportional meta-analysis of endarterectomy and endovascular therapy with routine or selective stenting for common femoral artery atherosclerotic disease. J Interv Cardiol 2019; 2019: 1593401:1–12.
15. Davaine JM, Quérat J, Guyomarch B, et al.: Incidence and the clinical impact of stent fractures after primary stenting for TASC C and D femoropopliteal lesions at 1 year. Eur J Vasc Endovasc Surg 2013; 46: 201–12.
16. McGovern PJ, Jr., Stark KR, Kaufman JL, Rosenberg N: Management of common femoral artery occlusion. A report of ten cases. J Cardiovasc Surg (Torino) 1987; 28: 38–41.
17. Siracuse JJ, Van Orden K, Kalish JA, et al.: Endovascular treatment of the common femoral artery in the Vascular Quality Initiative. J Vasc Surg 2017; 65: 1039–46.
18. Mukherjee D, Inahara T: Endarterectomy as the procedure of choice for atherosclerotic occlusive lesions of the common femoral artery. Am J Surg 1989; 157: 498–500.
19. Gouëffic Y, Della Schiava N, Thaveau F, et al.: Stenting or surgery for de novo common femoral artery stenosis. JACC Cardiovasc Interv 2017; 10: 1344–54.
20. Linni K, Ugurluoglu A, Hitzl W, Aspalter M, Hölzenbein T: Bioabsorbable stent implantation vs. common femoral artery endarterectomy: early results of a randomized trial. J Endovasc Ther 2014; 21: 493–502.
21. Berchiolli RN, Marconi M, Mocellin DM, Adami D, Ferrari M: Hybrid procedures and femoral endarterectomy in diabetic patients. Eur Rev Med Pharmacol Sci 2019; 23: 1257–65.

22. DeCarlo C, Boitano LT, Sumpio B, et al.: Comparative analysis of outcomes in patients undergoing femoral endarterectomy plus endovascular (hybrid) or bypass for femoropopliteal occlusive disease. Ann Vasc Surg 2021; 72: 227–36.
23. Dufranc J, Palcau L, Heyndrickx M, et al.: Technique and results of femoral bifurcation endarterectomy by eversion. J Vasc Surg 2015; 61: 728–33.
24. Elsherif M, Tawfick W, Elsharkawi M, Campell R, Hynes N, Sultan S: Common femoral artery endarterectomy in the age of endovascular therapy. Vascular 2018; 26: 581–90.
25. Esposito A, Menna D, Baiano A, Benedetto P, Di Leo F, Cappiello AP: Eversion endarterectomy of the femoral bifurcation: technique, results and potential advantages. Ann Vasc Surg 2020; 66: 580–5.
26. Jorshery SD, Skrip L, Sarac T, Ochoa Chaar CI: Hybrid femoropopliteal procedures are associated with improved perioperative outcomes compared with bypass. J Vasc Surg 2018; 68: 1447–54.
27. Kuma S, Tanaka K, Ohmine T, et al.: Clinical outcome of surgical endarterectomy for common femoral artery occlusive disease. Circ J 2016; 80: 964–9.
28. Langenberg JCM, Te Slaa A, de Groot HGW, et al.: Infection risk following common femoral artery endarterectomy versus a hybrid procedure. Ann Vasc Surg 2018; 53: 148–53.
29. Malgor RD, Ricotta JJ, 2nd, Bower TC, et al.: Common femoral artery endarterectomy for lower-extremity ischemia: evaluating the need for additional distal limb revascularization. Ann Vasc Surg 2012; 26: 946–56.
30. Mezzetto L, Mastrorilli D, Scorsone L, et al.: Early and midterm outcomes of hybrid first line treatment in patients with chronic limb threatening ischemia. Vascular 2022; 30: 891–901.
31. Mirmehdi I, Rigamer M, Nguyen A, Larson R, Albuquerque F, Levy M: Experience with eversion endarterectomy of the common femoral artery with comparison to standard endarterectomy with patch. Ann Vasc Surg 2020; 63: 204–8.
32. Nishibe T, Maruno K, Iwahori A, et al.: The role of common femoral artery endarterectomy in the endovascular era. Ann Vasc Surg 2015; 29: 1501–7.
33. Perou S, Pirvu A, Morel J, Magne JL, Elie A, Spear R: Femoral bifurcation endarterectomy with transection-eversion of the superficial femoral artery: technique and results. Ann Vasc Surg 2018; 53: 177–83.
34. Peters AS, Meisenbacher K, Weber D, et al.: Isolated femoral artery revascularisation with or without iliac inflow improvement—a less invasive surgical option in critical limb ischemia. Vasa 2021; 50: 217–23.
35. Ray JJ, Eidelson SA, Karcutskie CA, et al.: Hybrid revascularization combining iliofemoral endarterectomy and iliac stent grafting for TransAtlantic Inter-Society Consensus C and D aortoiliac occlusive disease. Ann Vasc Surg 2018; 50: 73–9.
36. Siracuse JJ, Gill HL, Schneider DB, et al.: Assessing the perioperative safety of common femoral endarterectomy in the endovascular era. Vasc Endovascular Surg 2014; 48: 27–33.
37. Soares TR, Amorim P, Manuel V, et al.: A single-center experience in the eversion femoral endarterectomy. Vascular 2020; 28: 348–54.
38. Uhl C, Götzke H, Zeman F, et al.: Long-term outcome of common femoral artery endarterectomy in octogenarians and non-octogenarians. Scand J Surg 2021; 110: 400–6.
39. Woronowicz-Kmiec S, Betz T, Töpel I, Bröckner S, Steinbauer M, Uhl C: Short and long-term outcome after common femoral artery hybrid procedure in patients with intermittent claudication and chronic limb threatening ischemia. Vasa 2021; 50: 363–71.
40. Zavatta M, Mell MW: A national vascular quality initiative database comparison of hybrid and open repair for aortoiliac-femoral occlusive disease. J Vasc Surg 2018; 67: 199–205.e1.

Corresponding author
Dr. med. Carola Marie Hoffmann-Wieker
Klinik für Gefäßchirurgie und Endovaskuläre Chirurgie
Universitätsklinikum Heidelberg
Im Neuenheimer Feld 420, 69120 Heidelberg, Germany
carola.hoffmann-wieker@med.uni-heidelberg.de

Cite this as:
Hoffmann-Wieker CM, Ronellenfitsch U, Rebelo A, Görg N, Schwarzer G, Ballotta E, Gouëffic Y, Böckler D: Open surgical thrombarterectomy versus endovascular treatment in occlusive processes of the femoral artery bifurcation—a systematic review and meta-analysis of aggregate data and individual patient data. Dtsch Arztebl Int 2022; 119: 803–9.
DOI: 10.3238/arztebl.m2022.0331

► **Supplementary material**

eReferences, eMethods, eTables, eFigures, eBox:
www.aerzteblatt-international.de/m2022.0331

Supplementary material to:

Open Surgical Thrombendarterectomy Versus Endovascular Treatment in Occlusive Processes of the Femoral Artery Bifurcation

A Systematic Review and Meta-Analysis of Aggregate Data and Individual Patient Data

by Carola Marie Hoffmann-Wieker*, Ulrich Ronellenfitsch*, Artur Rebelo, Nadine Görg, Guido Schwarzer, Enzo Ballotta, Yann Gouëffic, and Dittmar Böckler

Dtsch Arztebl Int 2022; 119: 803–9. DOI: 10.3238/arztebl.m2022.0331

eReferences

e1. Zou J, Xia Y, Yang H, Ma H, Zhang X: Hybrid endarterectomy and endovascular therapy in multilevel lower extremity arterial disease involving the femoral artery bifurcation. Int Surgy 2012; 97: 56–64.

e2. Böhme T, Romano L, Macharzina RR, et al.: Outcomes of directional atherectomy for common femoral artery disease. EuroIntervention 2021; 17: 260–6.

e3. Cioppa A, Franzese M, Gerardi D, et al.: Three-year outcome of directional atherectomy and drug coated balloon for the treatment of common femoral artery steno-occlusive lesions. Catheter Cardiovasc Interv 2022; 99: 1310–6.

e4. Cotroneo AR, Iezzi R: The role of „cutting" balloon angioplasty for the treatment of short femoral bifurcation steno-obstructive disease. Cardiovasc Intervent Radiol 2010; 33: 921–8.

e5. Davies RSM, Adair W, Bolia A, Fishwick G, Sayers RD, McCarthy MJ: Endovascular treatment of the common femoral artery for limb ischemia. Vasc Endovascular Surg 2013; 47: 639–44.

e6. Imran HM, Hyder ON, Soukas PA: Efficacy and safety of adjunctive drug-coated balloon therapy in endovascular treatment of common femoral artery disease. Cardiovasc Revasc Med 2019; 20: 210–4.

e7. Kronlage M, Erbel C, Lichtenberg M, et al.: Safety and effectiveness of Phoenix atherectomy for endovascular treatment in calcified common femoral artery lesions. Vasa 2021; 50: 378–86.

e8. Lee MS, Heikali D, Mustapha J, Adams G, Mahmud E: Acute procedural outcomes of orbital atherectomy for the treatment of common femoral artery disease: Sub-analysis of the CONFIRM Registries. Vasc Med 2017; 22: 301–6.

e9. Martin R, Vanesa GD, Raleigh JV, et al.: Common femoral artery stenting: computed tomography angiography based long-term patency. Vasc Endovascular Surg 2021; 55: 571–6.

e10. Mehta M, Zhou Y, Paty PS, et al.: Percutaneous common femoral artery interventions using angioplasty, atherectomy, and stenting. J Vasc Surg 2016; 64: 369–79.

e11. Shammas NW, Shammas GA, Karia R, Khalafallah R, Jones-Miller S, Shammas AN: Two-year outcomes of endovascular interventions of the common femoral artery: a retrospective analysis from two medical centers. Cardiovasc Revasc Med 2021; 24: 72–6.

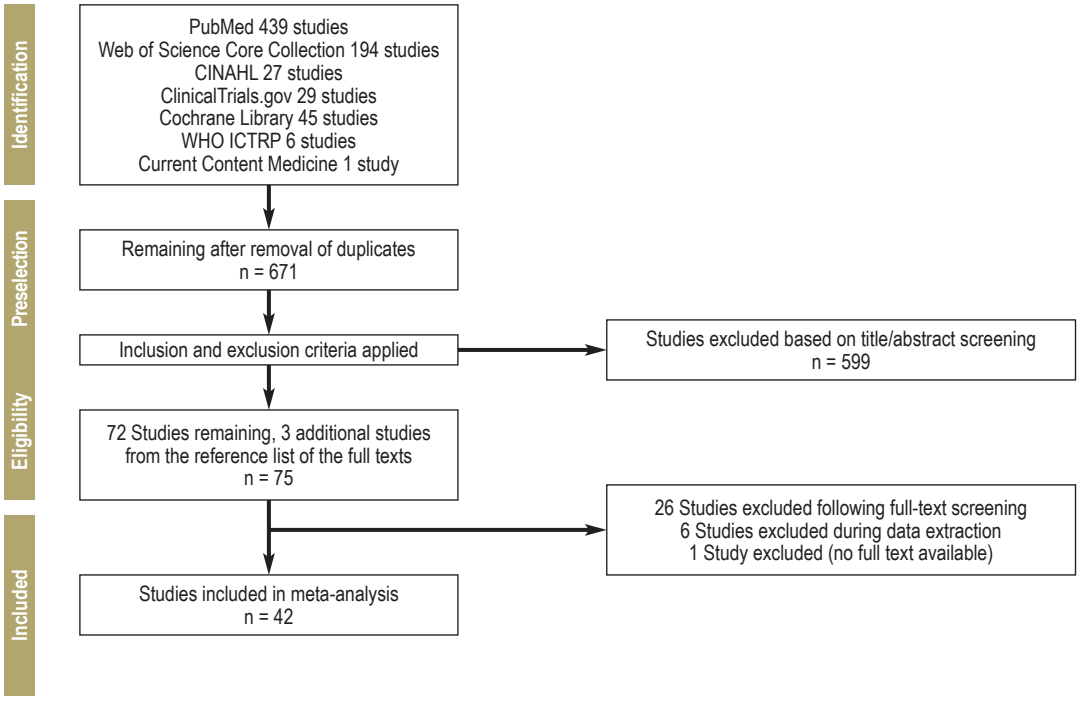
e12. Stavroulakis K, Schwindt A, Torsello G, et al.: Directional atherectomy with antirestenotic therapy vs drug-coated balloon angioplasty alone for common femoral artery atherosclerotic disease. J Endovasc Ther 2018; 25: 92–9.

e13. Kuo TT, Chen PL, Huang CY, Lee CY, Shih CC, Chen IM: Outcome of drug-eluting balloon angioplasty versus endarterectomy in common femoral artery occlusive disease. J Vasc Surg 2019; 69: 141–7.

e14. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G: Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. Res Synth Methods 2019; 10: 476–83.

e15. Balduzzi S, Rücker G, Schwarzer G: How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 2019; 22: 153–60.

eFIGURE 1



PRISMA diagram

Flowchart showing the different phases of the systematic review and the number of studies included and excluded in the various phases

eBOX

Search strategy

Search period: 11/1965–02/2022

Determining the relevant aspects of the topic

P
Peripheral arterial occlusive disease (PAOD) in the region of the inguinal/ femoral artery

I
Thrombendarterectomy (TEA)

C
Endovascular treatment

Strategy

1 P
2 I
3 C
4 1 AND 2 AND 3

Databases searched and number of hits per database

PubMed: 439
Cochrane Library: 45
Web of Science Core Collection: 194
CINAHL: 27
Current Content Medicine CCMed (via LIVIVO): 1
ClinicalTrials.gov (study registry): 29
WHO ICTRP (study registry): 6

Reporting of results

The results were saved in EndNote™ and deduplicated according to the Wichor Bramer method. To this end, the following settings were used: "Author," "Year," "Title," "Secondary Title/ Author, Year, Title," "Pages/ Title/ Author, Year." Some articles may nevertheless appear multiple times.

Hits were sorted in EndNote™ according to database. The PubMed hits were the first to be exported to EndNote™. As such, they are favored in the deduplication, that is to say that in the case of duplicates, entries from other databases are removed first.

The number of hits in each database in this report refers to status prior to deduplication in EndNote™.

Example:

PubMed

No. of hits	**Date**
323 + 116	17 July 2017 and 15 February 2022

1. P (29,831)
(("Arterial Occlusive Diseases"[Mesh] OR
Arterial Occlusive Disease*[tw] OR
Arterial Obstructive Disease*[tw])
AND
("Femoral Artery"[Mesh] OR
femoral arter*[tw] OR
inguinal arter*[tw]))
OR
"Peripheral Arterial Disease"[Mesh] OR
peripheral artery disease*[tw] OR
peripheral Arterial Disease*[tw]

2. I (21,476)
"Endarterectomy"[Mesh] OR
thrombendarterectom*[tw] OR
endarterectom*[tw]

3. C (303,688)
"Endovascular Procedures"[Mesh] OR
intravascular*[tw] OR
endovascular*[tw] OR
angioplast*[tw] OR
stent*[tw]

4. (445)
1 AND 2 AND 3

eMETHODS SECTION

Methods

The study was conducted according to the PRISMA Guidelines *(eFigure 1)* and prospectively registered (PROSPERO: CRD42018091539). The PubMed, EMBASE, Cochrane Library, Web of Science, ClinicalTrials.gov, and ICTRP databases were searched using a predefined search strategy *(eBox)* for the period 11/1965–2/2022 by independent reviewers (NG/AR, UR/CHW). Identified abstracts were read by the reviewers and checked for inclusion criteria. For TEA, these were studies on patients with femoral artery bifurcation lesions that received open surgical treatment involving opening of the vessel lumen, thrombendartectomy, and reconstruction with or without patch plasty. For ENDO, studies of endovascular procedures (atherectomy, PTA, or stenting) on femoral artery bifurcation lesions were included. For both techniques, studies were also included in which there was additional endovascular treatment of central or peripheral vascular lesions in the same intervention but no simultaneous open surgical treatment of other arterial vascular lesions or bypass implantation. With the exception of case reports, all study designs were taken into consideration. Based on the full text, the reviewers made a final appraisal regarding inclusion. The risk of bias of the individual studies was assessed on the basis of the following specified domains: selection bias, performance bias, attrition bias, detection bias, and reporting bias. The overall risk of bias was classified as 'low' if there was no risk of bias in any of these domains, as 'moderate' if there was a risk of bias in two domains, and as 'high' if there was a risk of bias in three or more domains.

Individual patient data (IPD) were requested for all included studies. If these were not available, aggregate data (AD) were extracted from the respective publication.

The following endpoints were defined for the meta-analyses.

Primary endpoint

- Primary patency (PP): Time from procedure to occurrence of a clinically relevant reocclusion process at the femoral artery bifurcation, as defined in the respective study

Secondary endpoints

- Freedom from interventions: Time from procedure to reintervention at the treated femoral artery bifurcation
- Secondary patency (SP): Time from procedure to definitive occlusion of the femoral artery bifurcation
- Limb preservation: Time from procedure to ipsilateral major amputation
- Duration of inpatient hospital stay
- Perioperative morbidity, mortality, and need for revision within 30 days
- Overall survival: Time from procedure to death, irrespective of cause of death
- Pre- to postinterventional change in ankle-brachial index (using the last measurement at follow-up in each case)
- Duration of the procedure in minutes

Statistical methods

Data on the duration of the procedure and the inpatient hospital stay were presented as mean values. Incidences were calculated for perioperative morbidity, need for revision, and perioperative mortality. In a second step, a comparison of the two collectives was performed. To this end, meta-analyses with random effects models were conducted, first only for randomized (primary analysis) and then for all directly comparative studies. In the meta-analyses, the probabilities were first transformed using

the log function. The inverse variance method was used to combine the individual probabilities. To estimate the variance between studies, the Paule–Mandel method was employed in the random effects model, and the "metaprop" function in the R package meta was used (e15). In the meta-analysis that included the individual TEA and ENDO arms from nonrandomized trials, no formal statistical comparison of the two groups was carried out since these included heterogeneous populations, thus the risk of bias in the comparison would have been unreasonably high. Hazard ratios were calculated for time-dependent endpoints (primary/secondary patency, freedom from interventions, limb preservation, overall survival). The duration of inpatient hospital stay was presented as weighted mean difference. The dichotomous endpoints of perioperative morbidity, need for revision, and perioperative mortality were evaluated using risk ratios. For all endpoints, 95% confidence intervals (CI) were calculated and reported.

eTABLE 1

Characteristics of the included studies

Study	Procedure	Type of data	Period	Publication year	Study design	Follow-up period (months)	Number of patients	Number of interventions
Ballotta (1)	TEA	IPD	2000–2007	2009	Prospective	50	117	121
Kang (3)	TEA	AD	2002–2005	2008	Retrospective	27	58	65
Kuma (27)	TEA	AD	1998–2014	2016	Retrospective, multicentric	33	111	118
Siracuse (36)	TEA	AD	2007–2010	2013	Retrospective	-	1513	1513
Dufranc (23)	TEA	AD	2010–2012	2014	Prospective	16	121	147
Zou (e1)	TEA	AD	2007–2009	2012	Retrospective	12	40	41
Kechagias (4)	TEA	AD	1983–2006	2007	Retrospective	71	90	111
Mukherjee (18)	TEA	AD	1969–1987	1989	Retrospective	86	29	29
Nishibe (32)	TEA	AD	2010–2014	2015	Retrospective	14	34	38
Wieker (7)	TEA	IPD	2006–2012	2016	Retrospective, bicentric	59	655	713
Malgor (29)	TEA	AD	1997–2008	2012	Retrospective	75	145	169
Siracuse (17)	ENDO	AD	2010–2015	2017	Retrospective	5	1014	–
Davies (e5)	ENDO	AD	2006–2012	2013	Retrospective	27	115	121
Cotroneo (e4)	ENDO	AD	2005–2007	2010	Retrospective	9	18	27
Lee (e8)	ENDO	AD	2009–2011	2017	Retrospective	-	147	200
Mehta (e10)	ENDO	AD	2006–2013	2016	Retrospective	43	167	167
Linni (20)	TEA ENDO	AD	2011–2013	2014	RCT	11 9	80	80
Gouëffic (19)	TEA ENDO	IPD IPD	2011–2013	2017	RCT	24	103	103
Berchiolli (21)	TEA	AD	2008–2011	2019	Retrospective	42	43	43
Böhme (e2)	ENDO	AD	2009–2017	2021	Retrospective	31	250	250
Cioppa (e3)	ENDO	AD	2012–2016	2021	Register	36	78	80
DeCarlo (22)	TEA	AD	2012–2017	2021	Retrospective	-	1537	–
Elbadawy (9)	TEA	AD	2015–2017	2020	Prospective	32	159	159
Elsherif (24)	TEA	AD	2002–2015	2018	Retrospective	24	40	45
Esposito (25)	TEA	AD	2014–2016	2019	Retrospective	22	31	32
Imran (e6)	ENDO	AD	2010–2014	2018	Retrospective	-	70	80
Jorshery (26)	TEA	AD	2012–2015	2018	Retrospective	1	509	–
Kronlage (e7)	ENDO	AD	2018–2020	2020	Prospective	11	56	61
Kuo (e13)	TEA ENDO	AD AD	2013–2016	2018	Retrospective	24	40 60	40 60
Langenberg (28)	TEA	AD	2013–2016	2018	Retrospective	-	229	229
Martin (e9)	ENDO	AD	2012–2017	2021	Retrospective	32	33	35
Mezzetto (30)	TEA	AD	2016–2018	2021	Retrospective	32	132	132
Mirmehdi (31)	TEA	AD	2007–2018	2020	Retrospective	-	142	142
Perou (33)	TEA	AD	2006–2015	2018	Retrospective	-	129	143
Peters (34)	TEA	AD	2013–2014	2021	Retrospective	16	95	95
Ray (35)	TEA	AD	2000–2007	2017	Retrospective	23	36	41
Shammas (e11)	ENDO	AD	2012–2017	2021	Retrospective	-	89	116
Soares (37)	TEA	AD	2016–2019	2020	Retrospective	6	19	19
Stavroulakis 1 (e12) Stavroulakis 2 (e12)	ENDO ENDO	AD	2011–2016	2018	Retrospective	16 17	26 21	26 21

Uhl (38)	TEA	AD	2007–2018	2021	Retrospective	54	863	977
Woronowicz-Kmie 1 (39) Woronowicz-Kmie 2 (39)	TEA TEA	AD	2007–2018	2021	Retrospective	84 84	267 160	267 160
Zavatta (40)	TEA	AD	2009–2015	2018	Retrospective	9	879	879

AD, aggregate data; ENDO, endovascular treatment; IPD, individual patient data; RCT, randomized controlled trial; TEA, thrombendarterectomy

eTABLE 2

Main findings of the included studies

Study	Primary patency[1]	Secondary patency	Freedom from intervention	Limb preservation	Overall survival	30-Day morbidity	30-Day mortality
	1 Y (%)	1 Y (%)	1 Y (%)	1 Y (%)	1 Y (%)	(%)	(%)
Ballotta (1)	100	-	100	100	100	6.6	0
Kang (3)	93	-	82	100	89	5	0
Kuma (27)	98.1	-	99	97.4	86.8	16	-
Siracuse (36)	-	-	-	-	-	7.9	1.5
Dufranc (23)	93.2	98.6	-	96.5	89.2	8.2	-
Zou (e1)	64	78	-	86.4	-	24.4	-
Kechagias (4)	-	-	-	-	-	5.4	1.8
Mukherjee (18)	100	-	-	100	-	3.4	0
Nishibe (32)	90	-	94.7	97	97	11	0
Wieker (7)	96.5	99.1	-	-	93.9	16.3	-
Malgor (29)	96	100	90.2	92	88	16	0.7
Siracuse (17)	83	-	85.3	93.5	92.9	9.9	1.6
Davies (e5)	-	-	77	97	87	19	2.5
Cotroneo (e4)	57.9	79.6	-	88.9	77.8	0	0
Lee (e8)	-	-	-	-	-	24	-
Mehta (e10)	-	-	-	-	-	3	0.6
Linni (20) TEA	100	100	100	100	90	17.5	0
Linni (20) ENDO	86	82	75	97.5	88	0	2.5
Gouëffic (19) TEA	87	-	-	-	95	21	0
Gouëffic (19) ENDO	82	-	-	-	98	7	0
Berchiolli (21)	85.3	90.3	-	95.2	88.4	11.6	2.3
Böhme (e2)	-	-	-	-	-	10.4	0.4
Cioppa (e3)	-	-	-	-	-	-	-
DeCarlo (22)	-	-	-	-	-	34.7	0.8
Elbadawy (9)	-	-	-	-	-	14	2
Elsherif (24) TEA/hybrid	-	-	-	-	-	-	2.9
Elsherif (24) TEA	-	-	-	-	-	-	10
Esposito (25)	-	-	-	-	-	15	0
Imran (e6)	94	-	-	-	-	-	-
Jorshery (26)	-	-	-	-	-	23.8	2.8
Kronlage (e7)	-	-	-	-	96.4	0	0
Kuo (e13) ENDO	75	97.5	75	90	-	7.5	-
Kuo (e13) TEA	96.7	98.3	96.7	96.7	-	11.7	-
Langenberg (28)	-	-	-	-	-	-	2.1
Martin (e9)	88.9	96.3	-	-	-	-	-
Mezzetto (30)	96	-	-	-	-	5	1
Mirmehdi (31)	-	-	-	-	-	-	-
Perou (33)	96.3	-	-	-	93.8	18.8	0.7
Peters (34)	-	-	-	-	-	25.3	4.2
Ray (35)	-	-	-	-	-	31	2.7
Shammas (e11)	-	-	77.9	99.1	94.4	-	-
Soares (37)	87.5	100	-	-	-	10.5	5.3

Stavroulakis 1 (e12)	68	81	75	88	–	–	–
Stavroulakis 2 (e12)	88	100	89	80	–	–	–
Uhl (38)	-	-	-	-	–	–	2.7
Woronowicz-Kmie 1 (39)	87	-	-	99	93	–	1.4
Woronowicz-Kmie 2 (39)	82	-	-	88	74	–	1.4
Zavatta (40)	81	-	-	97.1	95.7	–	3.4

ENDO, endovascular treatment; Y, year; RCT, randomized controlled trial; TEA, thrombendarterectomy

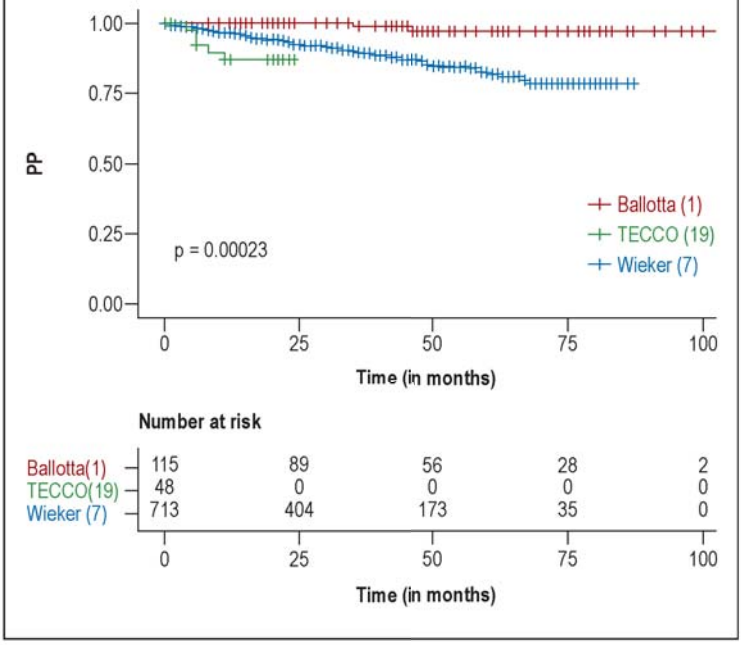
eTABLE 3

Main characteristics of the study populations of all studies included in the meta-analyses

Parameter	Mean	Percentage
Age	70.1 Y	
Males		70.2
Females		29.8
Diabetes mellitus		51.5
Smokers		53.3
Coronary heart disease		46.9
Arterial hypertension		80.9
Hyperlipidemia		68.5
Chronic renal failure		21.4

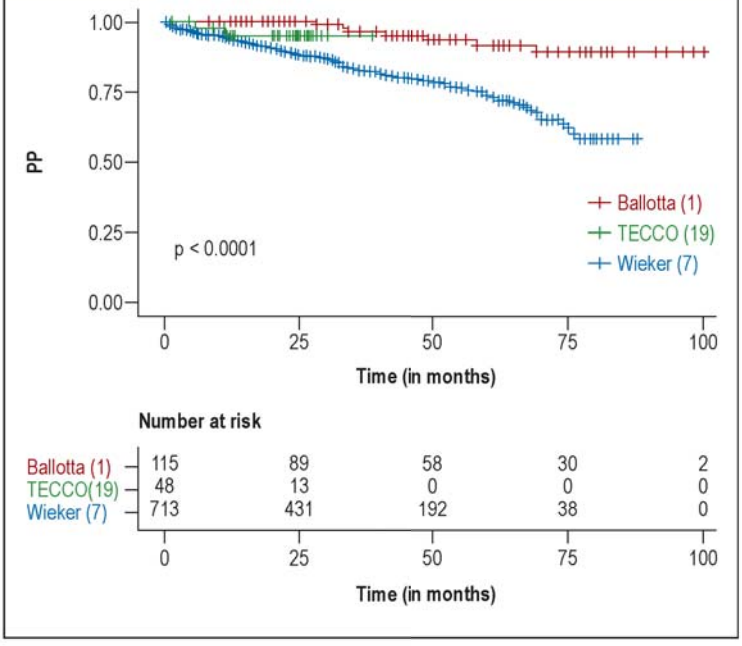
Y, years

eFIGURE 2



Kaplan–Meier curve of primary patency (PP) following thrombendarterectomy (TEA), based on individual patient data (IPD)

eFIGURE 3



Kaplan–Meier curve for overall survival following thrombendarterectomy (TEA), based on individual patient data (IPD)

eTABLE 4

Evaluation of the risk of bias of the individual studies included in the meta-analyses

	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Overall risk of bias
Ballotta (1)	+	+	+	–	–	High
Berchiolli (21)	+	+	+	–	–	High
Böhme (e2)	+	+	+	–	–	High
Cioppa (e3)	+	+	+	+	–	High
Cotroneo (e4)	+	+	+	–	–	High
Davies (e5)	+	+	+	–	–	High
DeCarlo (22)	+	+	+	–	–	High
Dufranc (23)	+	+	+	+	–	High
Elbadawy (9)	+	+	+	–	–	High
Elsherif (24)	+	+	+	+	–	High
Esposito (25)	+	+	+	+	–	High
Gouëffic (19)	–	+	+	–	–	Medium
Imran (e6)	+	+	+	+	–	High
Jorshery (26)	+	+	+	–	–	High
Kang (3)	+	+	+	+	–	High
Kechagias (4)	+	+	+	–	–	High
Kronlage (e7)	+	+	+	–	–	High
Kuma (27)	+	+	+	–	–	High
Kuo (e13)	+	+	+	–	–	High
Langenberg (28)	+	+	+	–	–	High
Lee (e8)	+	+	+	+	–	High
Linni (20)	–	–	+	–	–	Medium
Malgor (29)	+	+	+	–	–	High
Martin (e9)	+	+	+	+	–	High
Mehta (e10)	+	+	+	–	–	High
Mezzetto (30)	+	+	+	+	–	High
Mirmehdi (31)	+	+	+	–	–	High
Mukherjee (18)	+	+	+	–	–	High
Nishibe (32)	+	+	+	–	–	High
Perou (33)	+	+	+	+	–	High
Peters (34)	+	+	+	–	–	High
Ray (35)	+	+	+	+	–	High
Shammas (e11)	+	+	+	–	–	High
Siracuse (36)	+	+	+	+	–	High
Siracuse (17)	+	+	+	–	–	High
Soares (37)	+	+	+	+	–	High
Stavroulakis (e12)	+	+	+	–	–	High
Uhl (38)	+	+	+	–	–	High
Wieker (7)	+	+	+	–	–	High
Woronowicz (39)	+	+	+	+	–	High
Zavatta (40)	+	+	+	+	–	High
Zou (e1)	+	+	+	–	–	High

+, Risk of bias present in the respective category; –, no risk of bias present in the respective category

Comparison of percutaneous and cutdown access-related minor complications after endovascular aortic repair

ARTUR REBELO, PATRICK VOSS, ULRICH RONELLENFITSCH, CARSTEN SEKULLA and JÖRG UKKAT

Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle (Saale), Martin-Luther-University Halle-Wittenberg, D-06120 Halle (Saale), Germany

Received May 9, 2022; Accepted July 8, 2022

DOI: 10.3892/etm.2022.11563

Abstract. The aim of the present study was to compare the open surgical and percutaneous access for thoracic/endovascular aortic repair (T/EVAR) regarding in-hospital and post-hospital minor-complications. Percutaneous (pEVAR) and cutdown (cEVAR) techniques for femoral vessel access for T/EVAR were compared regarding their minor complications. The basic population of this retrospective cohort study consisted of 44 percutaneous and 215 cutdown accesses for endovascular aortic repair (T/EVAR-procedure) conducted between August 2008 and October 2019. The primary outcome consisted of conservatively treatable minor complications until hospital discharge and during follow up. Secondary outcomes comprised postoperative pain and complications requiring invasive treatment. Minor complications were observed in 11.4% (pEVAR) vs. 9% (cEVAR) of cases throughout index hospital stay and 10 vs. 13.7% during follow-up. No significant differences were noticed regarding overall complication rate between pEVAR and cEVAR. Only bleedings treatable through compression occurred significantly more often in the pEVAR-group (6.8 vs. 0.5%; P=0.02). In conclusions, the percutaneous technique represents a safe and quickly executable alternative to cutdown access. A significant difference in overall minor complications could not be observed. In both techniques, complications may occur even months after surgery. In order to demonstrate the superiority of the percutaneous technique compared with cutdown access, possible predictors for the use of the percutaneous technique should be defined in the future.

Correspondence to: Dr Artur Rebelo, Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle (Saale), Martin-Luther-University Halle-Wittenberg, Ernst-Grube-Str. 40, D-06120 Halle (Saale), Germany
E-mail: artur.rebelo@uk-halle.de

Key words: groin access, thoracic/endovascular aortic repair, complications, percutaneous, cutdown, life quality

Introduction

Treatment of aortic pathologies changed fundamentally during the last two decades: endovascular treatments and especially the use of stentgrafts have become more and more frequent (1). Treatment of the abdominal aorta is commonly referred to as endovascular aortic repair (EVAR), and that of the thoracic aorta as thoracic endovascular aortic repair (TEVAR) (1). With the establishment of thoracic/endovascular aortic repair (T/EVAR), during which stentgrafts are deployed minimally invasive through an arterial access vessel, risky open aortic repair (OAR) can mostly be circumvented. Potential benefits of T/EVAR vs. OAR include reduced perioperative and 1-year mortality, shortening of hospital stay and less periprocedural complications (2-5).

To establish large-bore vessel access in T/EVAR either classic cutdown or percutaneous technique may be performed. cEVAR consists of a skin incision and surgical preparation of the access vessel. In pEVAR, the access vessel is punctured through the skin. After puncture, a suture mediated closure device (SMCD) is used to prepare the sutures for closure of the puncture site (5). Commonly used SMCDs are the systems Perclose ProGlide or Prostar XL (both by Abbott Vascular) (6).

Both access techniques have been compared to a limited extent regarding different parameters (7). A meta-analysis from 2017 comparing both techniques analyzed two randomized controlled trials with 181 patients and suggested equivalence of pEVAR and cEVAR (7). Analyzed parameters included bleeding complications, wound infections and major vessel complications (7). Especially access-related major complications like thrombosis and access-vessel injury were rarely observed in both techniques throughout different studies (8,9).

Current evidence clearly shows a reduction of operation time in pEVAR (10-12). Also technical success rates of more than 90% imply good feasibility of the percutaneous technique (11,13,14). Achieving high success rates presupposes preoperative evaluation of the access vessel, usually the Common Femoral Artery (CFA). Particularly diameter, anterior calcification and possible kinking of the vessel are relevant (15,16). The impact of the CFA calcification level remains uncertain. Starnes *et al* (17) postulate safe feasibility of pEVAR even in calcified vessels, other studies suggest different results (18,19). Furthermore, routine ultrasound

guidance for pEVAR-access seems to reduce incidence of access-site complications, especially hematomas and injuries of the femoral nerve (20,21).

Complications of both techniques frequently have been recorded only for short term outcomes. A randomized controlled trial from 2019 shows no superiority for either approach with wound infection rates between 0 and 1.5% but a reduction of postoperative pain after pEVAR (22). Other studies also included access-related complications, however only until one month after surgery (11,13) or without comparing them to cEVAR (14,23). Nevertheless, overall acquired data shows a clear trend towards reduced access-related complication rates when using the percutaneous technique (9)

The aim of this study was to compare the incidence of short- and long-term minor complications after percutaneous and cutdown groin vessel access for T/EVAR. Because of several previous studies implying a rather low incidence of access-related major complications (8,9), those complications were not considered in the present study.

Materials and methods

Definitions. In this retrospective cohort study minor complications after groin vessel access were compared between pEVAR and cEVAR. As the term 'minor complication' is not subject to a specific definition it was defined as a conservatively treatable complication. In the 'Classification of Surgical Complications' by Dindo *et al* (24), this corresponds to severity degrees I and II. Thus, the following primary endpoints have been chosen: Secondary wound healing, wound infection, lymphocele, lymphorrhea, bleeding, hematoma, femoral neuropathy.

Every event chosen as a primary endpoint was defined to be conservatively treatable (e.g. through cooling and analgesia). Complications requiring invasive treatment, such as hematomas requiring surgical intervention, were not considered as primary endpoints. Bleeding was defined as a failure of vascular closure manageable by manual compression. Hematomas were defined as a collection of blood in the vessel access area. Femoral neuropathy was defined as sensomotoric symptoms relating to the femoral nerve caused by direct affection in the vessel access area. There were no events of neuropathy being generated by other complications such as retroperitoneal or intraspinal hematoma.

Complications were stratified into those occurring during the index hospital stay and early (0-1 months postoperative), medium (2-6 months postoperative) and late (>6 months postoperative) during follow-up, based on their first documentation.

Postoperative pain was chosen as a secondary endpoint. Patients were asked to assess their pain on a scale from 0 (no pain) to 10 (highest imaginable pain). Given that many of the patients were in the intensive care unit (ICU) on the first postoperative day, the second postoperative day was selected for recording of patients' pain level.

Additionally, the relatively frequent complications hematomata and lymphoceles requiring revision were defined as secondary endpoints.

Study design and population. This study retrospectively evaluates data from all patients who received a single T/EVAR at our institution between August 2008 and October 2019. The minimum follow-up of the latest included patients was three months.

Overall, 269 patients had an operation during the previously mentioned period. Out of this cohort, 110 patients were not eligible for this study. Exclusion criteria are displayed in Table I. Only two of the 12 exclusions because of periprocedural major complications were caused by access-related events (aneurysm of the CFA and bleeding from the access vessel requiring open patching).

Data of 159 patients with 259 femoral access sites were included in the study. Results were analyzed per patient (e.g. pain level) or per access site (e.g. complication), as appropriate. 47 percutaneous accesses were conducted initially, in which 3 needed conversions to cutdown due to technical failure. For vessel access in pEVAR, ultrasound guidance was not routinely used. For closure of the percutaneous vessel access site, SMCD's Perclose ProGlide, Prostar XL (both by Abbott Vascular) or AngioSeal (Terumo) were used. Technical failure of percutaneous access was caused by a failure of the SMCD's in all 3 cases. Thus 44 percutaneous and 215 cutdown accesses (31 patients vs. 128 patients) were included into the analysis of postoperative complications. The first eligible cEVAR patient underwent surgery in November 2008, the first included pEVAR patient was operated on in January 2017. Each involved surgeon had conducted at least 350 percutaneous accesses for different interventions before performing the first pEVAR.

Follow-Up at the study site is conducted regularly one, three and six months after surgery and from then on in an annual cycle. It includes clinical examination of the access site and a CT angiogram of the aorta, iliac arteries, and access vessels or, if contraindicated, ultrasound examination of the access vessels. 97 patients presented for follow-up. 30 percutaneous and 131 cutdown access sites (19 patients vs. 78 patients) were eligible for analysis of follow-up complications. The main reasons for follow-up interruptions were lack of understanding regarding the necessity of follow-up, unawareness of appointment schedule and follow-up performed in another hospital as we are a tertiary referral hospital. Table II gives an overview of included patients and access sites.

Statistical analysis. Data were retrospectively collected with Excel (Version 2019, Microsoft, Redmond) and analyzed using SPSS (Statistics subscription, Build 1.0.0.1347; IBM Corp.). For descriptive statistics, the absolute number and percentage or, if appropriate, mean value and standard deviation (MV ± SD) were reported. Nominal variables were compared by Fisher's exact test and an unpaired t-test was used for comparison of metric variables. Statistical significance was defined as $P<0.05$.

Ethical approval. The study was approved by the ethics committee of the University Hospital Halle (Saale), Germany (ID 2019-037).

Results

Baseline characteristics and comorbidities. Table III shows baseline characteristics and comorbidities of both groups. No significant differences occurred, the pEVAR- and cEVAR-group were well balanced. Regarding comorbidities,

Table I. Exclusion criteria.

Criteria	No. of patients (%)
Overall excluded cases	110 (41)
Missing/incomplete data	57 (21.4)
Concomitant open procedure[a]	7 (2.6)
Rare indication[b]	15 (5.5)
Major complication	12 (4.4)
Previous femoral access[c]	15 (5.5)
'Learning curve' for percutaneous technique[d]	4 (1.5)

[a]Simultaneous treatment of two aortic segments: One by T/EVAR, another one by open aortic repair. [b]Indication for T/EVAR in less than 5 patients each: Contains atherosclerosis of common iliac artery, iatrogenic damage, revision after therapy at other hospital, thrombus, malignoma and transection. [c]Previous large-bore access (e.g., for endovascular aortic valve replacement) led to exclusion, previous small-bore access up to 6 French (e.g., for coronary intervention) was not an exclusion criterion. [d]Quantifying the learning curve with percutaneous technique is discussed controversially in the literature: A study published in 2013 describes an amount of 30 cases to reach 90% technical success for the percutaneous technique (26). Nelson *et al* (11) assess this number critically because of the initially low success rate of 45% and suggest a far lower number of cases, whereas a third study highlights the importance of ultrasound guidance for achieving high technical success rates (19). As the involved surgeons had each conducted at least 350 percutaneous accesses for different interventions before performing the first percutaneous endovascular aortic repair, only the first 5 percutaneous T/EVAR-accesses (corresponds to n=4 patients) were excluded. T/EVAR, thoracic/endovascular aortic repair.

Table II. Number of included patients and access sites.

Analysis	pEVAR, n	cEVAR, n
Postoperative analysis		
Patients	31	128
Femoral access sites	44	215
Follow-Up analysis		
Patients	19	78
Femoral access sites	30	131

cEVAR, cutdown endovascular aortic repair; pEVAR, percutaneous endovascular aortic repair.

hypertension occurred in a high number of patients in both cohorts (pEVAR: 87.1%, cEVAR, 75%).

Indications for surgery. Indications for T/EVAR included abdominal (AAA), thoracic (TAA) and thoracoabdominal aortic aneurysms (TAAA) as well as penetrating aortic ulcers (PAU) and aortic dissections (AD). For cEVAR, AAA-patients made up the largest part of the cohort (67.2%). This contrasts with the pEVAR-subgroup in which the proportion was minor with 32.3%. Emergency indication for surgery made up a remarkable part in both groups (pEVAR: 22.6%, cEVAR: 16%) (Table IV). However, no significant correlation between emergent procedures and complications could be observed in a subgroup analysis.

Perioperative parameters. Table V summarizes recorded perioperative parameters. Patients receiving pEVAR got local anesthesia in 64.5% of cases compared to 25% of patients in the cEVAR-group (P=<0.01). After cEVAR, a significantly more frequent use of local hemostyptic agents could be observed. Mean duration of surgery differed by 24.7 min in favor of pEVAR (79.7 min vs. 104.4 min, P=0.03).

Primary endpoints. Regarding minor complications until postoperative hospital discharge (Table VI) no significant overall difference could be observed between both techniques. The overall incidence of complications was at a similar level (11.4 vs. 9%, P=0.78). Only conservatively treatable bleedings occurred significantly more often after pEVAR (6.8 vs. <1%, P=0.02).

Likewise, complications recorded during follow-up (Table VII) had a similar incidence (10 vs. 13.7%, P=0.77) with no significant difference in any complication. Table VIII depicts temporal distribution of first appearance of follow-up complications. Persisting of complications was not registered.

Secondary endpoints. Regarding secondary endpoints, subjective pain levels were different among the two groups with mean values of 0.9 (pEVAR) and 1.3 (cEVAR) (P=0.02). Furthermore, hematomas needing invasive revision occurred significantly more often in the pEVAR-group (pEVAR: 4.5%, cEVAR: 1%, P=0.03) (Table IX).

Discussion

This study suggests equivalence of percutaneous and cutdown technique for vessel access in T/EVAR regarding minor complications after surgery. Neither postoperative nor follow-up complications occurred significantly more often overall. Nevertheless, the results of the study suggest that despite ongoing development of improved closure systems, the percutaneous access technique does not reach superiority over cutdown access concerning minor complications. Although several studies reported a reduction of single types of complications, a consistent benefit for patients did not become apparent (7-9).

In contrast to complication rates, clearer advantages of percutaneous technique emerged elsewhere: Besides a reduction in the duration of surgery, which was consistently observed in past research, also a significant reduction of postoperative pain is remarkable. Additionally, the possibility of a more frequent use of local compared to general anesthesia represents an important alternative for patients who are limited in undergoing intubation anesthesia because of their multimorbidity. Even though cutdown access is theoretically also possible in local anesthesia, especially for obese and non-compliant patients it is often not feasible.

As complications during follow-up emerge in approximately the same number of cases as during hospital stay, clinical examination of the access site should always be conducted and properly documented on follow-up appointments. Future

Table III. Baseline characteristics and comorbidities.

Variables	pEVAR (n=31 patients)	cEVAR (n=128 patients)	P-value
Female, n (%)	10 (32.3)	24 (19.0)	0.14[a]
Male, n (%)	21 (67.7)	104 (81.0)	
Age, years (MV ± SD)	71 (9.9)	71.6 (10.0)	0.91[b]
Hypertension, n (%)	27 (87.1)	96 (75.0)	0.23[a]
Diabetes Mellitus Type I, n (%)	1 (3.2)	2 (2.0)	0.48[a]
Diabetes Mellitus Type II, n (%)	5 (16.1)	21 (16.0)	0.19[a]
COPD, n (%)	7 (22.6)	21 (16.0)	0.44[a]
Marfan-Syndrome, N (%)	1 (3.2)	2 (2.0)	0.48[a]
BMI, kg/m2 (MV ± SD)	27.2 (4.9)	27.3 (5.1)	0.92[b]
ASA-levels 2 and 3, n (%)	26 (83.9)	96 (75.0)	0.47[a]
ASA-levels 4 and 5, n (%)	5 (16.1)	29 (23.0)	

[a]P-value determined by Fisher's exact test. [b]P-value determined by t-test. Results are presented as the absolute number (percentage of cohort patient number) unless indicated otherwise. MV ± SD, mean value ± standard deviation; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiology; cEVAR, cutdown endovascular aortic repair; pEVAR, percutaneous endovascular aortic repair.

Table IV. Indications for surgery.

Indications for surgery	pEVAR, n (%) (n=31 patients)	cEVAR, n (%) (n=128 patients)
AAA	10 (32.3)	86 (67.0)
TAA	6 (19.4)	3 (2.0)
TAAA	3 (9.7)	6 (5.0)
PAU	6 (19.4)	13 (10.0)
AD	6 (19.4)	20 (16.0)
Emergency	7 (22.6)	20 (16.0)

AAA, abdominal aortic aneurysm; TAA, thoracic aortic aneurysm; TAAA, thoracoabdominal aortic aneurysm; PAU, penetrating aortic ulcers; AD, aortic dissection; cEVAR, cutdown endovascular aortic repair; pEVAR, percutaneous endovascular aortic repair.

Table V. Perioperative parameters.

Parameters	pEVAR (n=31 patients)	cEVAR (n=128 patients)	P-value
Local anesthesia[a], n (%)	20 (64.5)	32 (25.0)	<0.01[c]
Use of hemostyptic agents[b], n (%)	1 (3.2)	52 (41.0)	<0.01[c]
Duration of surgery, min (MV ± SD)	79.7±59.1	104.4±53.9	0.03[d]
Blood transfusion (red cell concentrates), n (%)	1 (3.2)	4 (3.0)	0.42[c]
ICU stay, days (MV ± SD)	1.4±1.5	1.3±1.2	0.83[d]
Hospital stay, days (MV ± SD)	8.7±6.9	7.9±4.8	0.56[d]
Start of physiotherapy, days (MV ± SD)	1.9±1.4	2.1±2.3	0.59[d]

[a]Without additional sedation. [b]Includes hemostyptic products Tabotamp (Johnson & Johnson), Tachosil (Takeda Pharmaceutical Company, Ltd.) and Cellistypt (B. Braun Melsungen AG). [c]P-value determined by Fisher's exact test. [d]P-value determined by t-test. Results are presented as the absolute number (percentage of cohort patient number) unless indicated otherwise. ICU, intensive care unit; MV ± SD, mean value ± standard deviation; cEVAR, cutdown endovascular aortic repair; pEVAR, percutaneous endovascular aortic repair.

studies might quantify the period in which access-related complications might be able to appear after T/EVAR.

Besides the retrospective design implying possible selection bias regarding the chosen technique for vessel access, the limitations of this study include a low cohort size mainly in the pEVAR group. The main reason for this lies in incompletely accessible data especially from older cases. Moreover, the fact that ultrasound guidance was not routinely used for

Table VI. Primary endpoints until hospital discharge.

Complication	pEVAR, n (%) (n=44 access sites)	cEVAR, n (%) (n=215 access sites)	P-value[a]
Secondary wound healing	0	5 (2.0)	0.59
Wound infection	0	1 (<1)	>0.99
Lymphocele	0	0	-
Lymphorrhea	0	6 (3.0)	0.59
Bleeding	3 (6.8)	1 (<1)	0.02
Hematoma	1 (2.3)	5 (2.0)	>0.99
Femoral neuropathy	1 (2.3)	2 (1.0)	0.43
Overall	5 (11.4)	20 (9.0)	0.78

[a]P-value determined by Fisher's exact test. Results are presented as the absolute number of events (percentage of cohort groin access number). cEVAR, cutdown endovascular aortic repair; pEVAR, percutaneous endovascular aortic repair.

Table VII. Primary endpoints during follow-up.

Complication	pEVAR (n=30 access sites)	cEVAR (n=131 access sites)	P-value[a]
Secondary wound healing, n (%)	0	3 (2.0)	>0.99
Wound infection, n (%)	0	5 (4.0)	0.56
Lymphocele, n (%)	1 (3.3)	2 (2.0)	0.46
Lymphorrhea, n (%)	0	4 (3.0)	>0.99
Hematoma, n (%)	1 (3.3)	0	0.19
Femoral neuropathy, n (%)	1 (3.3)	4 (3.0)	>0.99
Overall, n (%) (mean ± SD)	3 (10) (2.3±1.2)	18 (13.7) (4.3±4.6)	0.77

[a]P-value determined by Fisher's exact test. Results are presented as the absolute number of events (percentage of cohort groin access number) or as absolute number of events (percentage of cohort groin access number) (mean value ± standard deviation of months after surgery until first documentation of complication). cEVAR, cutdown endovascular aortic repair; pEVAR, percutaneous endovascular aortic repair.

Table VIII. Time of first documentation of complications during follow-up.

Months after surgery	pEVAR, n (%) (n=3 complications)	cEVAR, n (%) (n=18 complications)
Early (0-1 months)	1 (33.3)	4 (22.2)
Medium (2-6 months)	2 (66.6)	10 (55.5)
Late (>6 months)	0 (0.0)	4 (22.2)

cEVAR, cutdown endovascular aortic repair; pEVAR, percutaneous endovascular aortic repair.

Table IX. Secondary endpoints.

Secondary endpoints	pEVAR	cEVAR	P-value[a]
Complications until hospital discharge	n=44 access sites	n=215 access sites	
Pain level (MV ± SD)	0.9±1.0	1.3±0.9	0.02
Hematoma requiring invasive therapy, n (%)	2 (4.5)	3 (1.0)	0.03
Lymphocele requiring invasive therapy, n (%)	0	0	-
Complications during follow-up	n=30 access sites	n=131 access sites	
Hematoma requiring invasive therapy, n (%)	0	0	-
Lymphocele requiring invasive therapy, n (%)	0	3 (2.0)	>0.99

[a]P-value determined by t-test (pain level) and Fisher's exact test (hematoma and lymphocele). Results are presented as the absolute number of events (percentage of cohort groin access number) or as the MV ± SD. MV ± SD, mean value ± standard deviation; cEVAR, cutdown endovascular aortic repair; pEVAR, percutaneous endovascular aortic repair.

vessel access in pEVAR might have had a negative impact on the technical success and complication rates of this subgroup. Lastly, albeit excluding the first five percutaneous accesses to account for possible effects of a learning curve, a lack of experience of the operating surgeons with pT/EVAR might have had a negative impact on the results observed for the technique (25). Further prospective studies are needed to identify which group of patients who may profit from each technique.

As of today, the individual surgeon's decision regarding the vessel access technique is mainly based on own preference and expected technical success. The current German guidelines for treatment of AAA suggest only the degree of calcification of the access vessel and the respective surgeon's experience as factors for the decision (26). Prospectively, this decision process should be complemented by evidence-based data for complication rate of access techniques and the related improvement of patient's quality of life. Factors which are associated with percutaneous access with few complications and high technical success should be investigated and defined in the future. By doing so, the technique for vessel access that potentially achieves the best outcome could be chosen more individually.

In conclusion, the percutaneous technique for vessel access in T/EVAR proved to be a safe and quickly executable alternative to cutdown vessel access. No technique reached superiority in terms of minor complications. For patients being dependent on or wishing for local anesthesia for T/EVAR, the percutaneous technique should be the first choice for groin access if anatomical suitability is given. A thorough clinical examination of the groin access site should not be neglected during follow-up as access-related complications might appear even months after surgery. Future studies and guidelines should aim for investigation and definition of more precise criteria for selection of the individually best fitting access technique.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JU, UR and AR were involved in the conceptualization of the study. CS was involved in the study methodology and in the provision of software. JU and UR were involved in data validation. CS and PV were involved in formal analysis. JU, AR, UR and PV were involved in the investigative aspects of the study, as well as in data curation, study supervision and project administration. AR, PV and UR were involved in the provision of resources, in the writing of the original draft, in the reviewing and editing of the manuscript. AR, PV, CS, UR and JU confirm the authenticity of all the raw data and all authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study retrospectively evaluates data from all patients who received a single T/EVAR at our institution between August 2008 and October 2019. Ethical approval for this study was gained from the ethics committee of the University Hospital Halle (Saale) [Halle (Saale), Germany; ID 2019-037]. As all data were processed anonymously, no patient consent was required by the ethics committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Calero A and Illig KA: Overview of aortic aneurysm management in the endovascular era. Semin Vasc Surg 29: 3-17, 2016.
2. Brown LC, Powell JT, Thompson SG, Epstein DM, Sculpher MJ and Greenhalgh RM: The UK endovascular aneurysm repair (EVAR) trials: Randomised trials of EVAR versus standard therapy. Heal Technol Assess 16: 1-218, 2012.
3. Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG and EVAR trial participants: Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: Randomised controlled trial. Lancet 364: 843-848, 2004.
4. Patel R, Sweeting MJ, Powell JT, Greenhalgh RM and EVAR trial investigators: Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): A randomised controlled trial. Lancet 388: 2366-2374, 2016.
5. Hogg ME and Kibbe MR: Percutaneous thoracic and abdominal aortic aneurysm repair: Techniques and outcomes. Vascular 14: 270-281, 2006.
6. Van Wiechen MP, Ligthart JM and Van Mieghem NM: Large-bore vascular closure: New devices and techniques. Interv Cardiol 14: 17-21, 2019.
7. Gimzewska M, Jackson AI, Yeoh SE and Clarke M: Totally percutaneous versus surgical cut-down femoral artery access for elective bifurcated abdominal endovascular aneurysm repair (review) summary of the findings for the main comaprison. Cochrane Database Syst Rev: Feb 21, 2017 (Epub ahead of print).
8. Hajibandeh S, Hajibandeh S, Antoniou SA, Child E, Torella F and Antoniou GA: Percutaneous access for endovascular aortic aneurysm repair: A systematic review and meta-analysis. Vascular 24: 638-648, 2016.
9. Yang L, Liu J and Li Y: Femoral artery closure versus surgical cutdown for endovascular aortic repair: A single-center experience. Med Sci Monit 24: 92-99, 2018.
10. Lee WA, Brown MP, Nelson PR and Huber TS: Total percutaneous access for endovascular aortic aneurysm repair ('Preclose' technique). J Vasc Surg 45: 1095-1101, 2007.
11. Nelson PR, Kracjer Z, Kansal N, Rao V, Bianchi C, Hashemi H, Jones P and Bacharach JM: A multicenter, randomized, controlled trial of totally percutaneous access versus open femoral exposure for endovascular aortic aneurysm repair (the PEVAR trial). J Vasc Surg 59: 1181-1193, 2014.
12. Torsello GB, Kasprzak B, Klenk E, Tessarek J, Osada N and Torsello GF: Endovascular suture versus cutdown for endovascular aneurysm repair: A prospective randomized pilot study. J Vasc Surg 38: 78-82, 2003.
13. Buck DB, Karthaus EG, Soden PA, Ultee KH, van Herwaarden JA, Moll FL and Schermerhorn ML: Percutaneous versus femoral cutdown access for endovascular aneurysm repair. J Vasc Surg 62: 16-21, 2015.

14. Thomas RP, Kowald T, Schmuck B, Eldergash O, Klausen A, Dikov V, Easo J and Chavan A: Retrospective evaluation of percutaneous access for TEVAR and EVAR: Time to make it the standard approach? Rofo 189: 347-355, 2017.
15. Barbash IM, Barbanti M, Webb J, Molina-Martin De Nicolas J, Abramowitz Y, Latib A, Nguyen C, Deuschl F, Segev A, Sideris K, *et al*: Comparison of vascular closure devices for access site closure after transfemoral aortic valve implantation. Eur Heart J 36: 3370-3379, 2015.
16. Vatakencherry G, Molloy C, Sheth N, Liao M and Lam CK: Percutaneous access planning, techniques and considerations for endovascular aortic repair (EVAR). Cardiovasc Diagn Ther 8 (Suppl 1): S184-S190, 2018.
17. Starnes BW, O'Donnell SD, Gillespie DL, Goff JM, Rosa P, Parker MV and Chang A: Percutaneous arterial closure in peripheral vascular disease: A prospective randomized evaluation of the Perclose device. J Vasc Surg 38: 263-271, 2003.
18. Manunga JM, Gloviczki P, Oderich GS, Kalra M, Duncan AA, Fleming MD and Bower TC: Femoral artery calcification as a determinant of success for percutaneous access for endovascular abdominal aortic aneurysm repair. J Vasc Surg 58: 1208-1212, 2013.
19. Mousa AY, Campbell JE, Broce M, Abu-Halimah S, Stone PA, Hass SM, AbuRahma AF and Bates M: Predictors of percutaneous access failure requiring open femoral surgical conversion during endovascular aortic aneurysm repair. J Vasc Surg 58: 1213-1219, 2013.
20. Kalish J, Eslami M, Gillespie D, Schermerhorn M, Rybin D, Doros G, Farber A and Vascular Study Group of New England: Routine use of ultrasound guidance in femoral arterial access for peripheral vascular intervention decreases groin hematoma rates. J Vasc Surg 61: 1231-1238, 2015.
21. Kuo F, Park J, Chow K, Chen A and Walsworth MK: Avoiding peripheral nerve injury in arterial interventions. Diagn Interv Radiol 25: 380-391, 2019.
22. Vierhout BP, Pol RA, Ott MA, Pierie ME, van Andringa de Kempenaer TM, Hissink RJ, Wikkeling OR, Bottema JT, Moumni ME and Zeebregts CJ: Randomized multicenter trial on percutaneous versus open access in endovascular aneurysm repair (PiERO). J Vasc Surg 69: 1429-1436, 2019.
23. Dwivedi K, Regi JM, Cleveland TJ, Turner D, Kusuma D, Thomas SM and Goode SD: Long-term evaluation of percutaneous groin access for EVAR. Cardiovasc Intervent Radiol 42: 28-33, 2019.
24. Dindo D, Demartines N and Clavien PA: Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240: 205-213, 2004.
25. Bechara CF, Barshes NR, Pisimisis G, Chen H, Pak T, Lin PH and Kougias P: Predicting the learning curve and failures of total percutaneous endovascular aortic aneurysm repair. J Vasc Surg 57: 72-76, 2013.
26. Debus ES, Heidemann F, Gross-Fengels W, Mahlmann A, Muhl E, Pfister K, Roth S, Stroszczynski Ch, Walther A, Weiss N, *et al*: S3-Leitlinie zu screening, diagnostik, therapie und Nachsorge des Bauchaortenaneurysmas. AWMF online: 262, 2018.