Aus der Klinik für Gefäß- und Endovaskularchirurgie

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# Inflammatory abdominal aortic aneurysm and postoperative outcomes after open-surgery: a 10-year single-center experience

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## Abstract

Inflammatory abdominal aortic aneurysms (IAAAs) are rare clinical entities with an exaggerated inflammatory component. The aim of this study is to report outcomes of a single-centre 10-years experience in open surgical management of IAAA and to compare the results with non-inflammatory, atherosclerotic abdominal aortic aneurysms (non-IAAAs).

We retrospectively reviewed the medical records of 18 patients with IAAA selected out of patients with AAA who underwent open surgery in the Department of Vascular and Endovascular Surgery at the University Hospital Dusseldorf from January 2006 to December 2015. These patients were matched with controls, selected from a prospectively retained database of 1002 patients with AAA undergoing open surgery during the study period. A 1:2 case control match regarding age, gender and year of treatment was performed. We analyzed both groups for preoperative parameters, intraoperative findings and early postoperative outcomes.

The two groups showed considerable similarities with no significant (NS) differences in the clinical features. Both groups outlined comparable aneurysm size (62mm vs. 56mm): however, the mean preoperative CRP was found to be significantly elevated in the study group (mean value 2.6 mg/dl vs. 0.9 mg/dl, $p<0.05$). Most patients were operated using a standard transperitoneal median laparotomy approach; only one patient of each group was operated using a left retroperitoneal approach. There was no significant difference in operation time (190 min vs. 194 min) and 30-day mortality 0%. The in-hospital mortality was 11% in the study group and 0% in the control group. We found a significant higher complication rate in the study group 10(56%) vs. 12(33%). The major complications were also more frequent in the study group 4(22%) vs. 6(16.7%). IAAAs showed a statistically significant longer length of intensive care unit and hospital stay when compared with non-IAAAs (7 and 20 days vs. 2 and 14 days, $p<0.05$). IAAAs outlined a significantly greater transfusion requirement for erythrocytes and fresh frozen plasma than non-IAAAs.

Open surgical treatment of IAAA guarantees a regression of the inflammatory process in most patients, which was detected through ultrasound in follow-up examination, although the approach to the surgical site is highly demanding. IAAA exhibits clear gender predominance and is associated with significantly higher transfusion requirement, early morbidity and length of stay.

## Zusammenfassung

Die inflammatorische Aneurysmen der Aorta abdominalis (IAAA) sind seltene klinische Entitäten mit einer deutlichen entzündlichen Komponente.

Das Ziel dieser Studie ist es, die Ergebnisse der 10-jährigen Erfahrung im offenen chirurgischen Management von IAAA zu analysieren und sie mit denen von den nicht-inflammatorischen, arteriosklerotischen abdominalen Aortenaneurysmen (nicht-IAAA) zu vergleichen.

Wir haben retrospektiv die medizinischen Akten von 18 Patienten mit IAAA aus allen Patienten mit Aneurysmen der Aorta abdominalis (AAA) ausgewählt, die eine offene chirurgische Behandlung in der Abteilung für Gefäß- und Endovaskularchirurgie am Universitätsklinikum Düsseldorf von Januar 2006 bis Dezember 2015 erhalten haben. Diese Patienten wurden mit Kontrollen, ausgewählt aus 1002 Patienten mit AAA, die sich während des Studienzeitraums einer offenen chirurgischen Behandlung unterzogen haben, verglichen.

Ein 1:2 Fallkontrolle Match in Bezug auf Alter, Geschlecht und Jahr der Behandlung wurde durchgeführt. Wir analysierten beide Gruppen für präoperative Parameter, intraoperative Befunde und frühe postoperative Ergebnisse.

Die beiden Gruppen zeigten erhebliche Ähnlichkeiten ohne signifikante (NS) Unterschiede in den klinischen Merkmalen. Beide Gruppen zeigten eine vergleichbare Aneurysma-Größe (62 mm vs. 56 mm). Allerdings wurde festgestellt, dass der mittlere präoperative CRP-Wert (C-reaktiv Protein) in der Studiengruppe signifikant erhöht war (Mittelwert 2,6 mg/dl vs. 0,9 mg/dl, $p < 0,05$). Die meisten Patienten wurden durch einem standardmäßigen transperitonealen medianen Laparotomie-Zugang operiert; nur ein Patient jeder Gruppe wurde durch einem linken retroperitonealen Zugang operiert. Es gab keinen signifikanten Unterschied in der Operationszeit (190 min vs. 194 min) und die 30-Tage-Mortalität lag bei 0%. Die Krankenhaus-Mortalität betrug 11% in der Studiengruppe und 0% in der Kontrollgruppe. Wir fanden eine signifikant höhere Komplikationsrate in der Studiengruppe 56% (n=10) gegenüber 33% (n=12). Die schwerwiegende Komplikationen waren auch in der Studiengruppe mit 22% (n=4) gegenüber 16,7% (n=6) häufiger. Die IAAA zeigten einen statistisch signifikanten längeren Intensivstationsaufenthalt und Krankenhausaufenthalt im Vergleich zu den nicht-IAAA (7 und 20 Tage vs. 2 und 14 Tage, $p < 0,05$). Zusätzlich zeigten die IAAA ein signifikant

größeren Transfusionsbedarf für Erythrozytenkonzentrate und Plasmen als die nicht-IAAA.

Die offene chirurgische Behandlung von IAAA garantiert eine Regression des Entzündungsprozesses bei den meisten Patienten, die durch Ultraschalluntersuchung bei der Nachuntersuchung nachgewiesen wurde, obwohl der Ansatz für die chirurgische Therapie sehr anspruchsvoll ist.

Das IAAA zeigt eine klare geschlechtsspezifische Prävalenz und ist mit einem signifikant höheren Transfusionsbedarf, einer frühen Morbidität und einem längeren Krankenhausaufenthalt verbunden.

## Abbreviations

| | |
|---|---|
| 18F-FDG | 18-fluorodeoxyglucose |
| AAA | abdominal aortic aneruysm |
| ANOVA | analysis of variance |
| ASA | american society of anesthesiologists |
| BMI | body mass index |
| CRP | C-reactive protein |
| CT | computed tomography |
| ESR | erythrocyte sedimentation rate |
| EVAR | endovascular aneurysm repair (or endovascular aortic repair) |
| IAAA | inflammatory abdominal aortic aneurysm |
| ICU | intensive care unit stay |
| IgG4-RSD | IgG4-related systemic disease |
| iNOS | inducible nitric oxide synthase |
| INR | international normalized ratio |
| LOS | length of stay |
| MRA | magnetic resonance angiography |
| non-IAAA | non inflammatory abdominal aortic aneurysm |

| | |
|---|---|
| NS | not significant |
| OSR | open surgical repair |
| PAF | periaortal fibrosis |
| PAI | periaortic inflammation |
| PET | positron emission tomography |
| PLT | platelet |
| PTT | partial thromboplastin time |
| TGF-ß | transforming growth factor-beta |
| US | ultrasonography |
| WBC | white blood cell count |

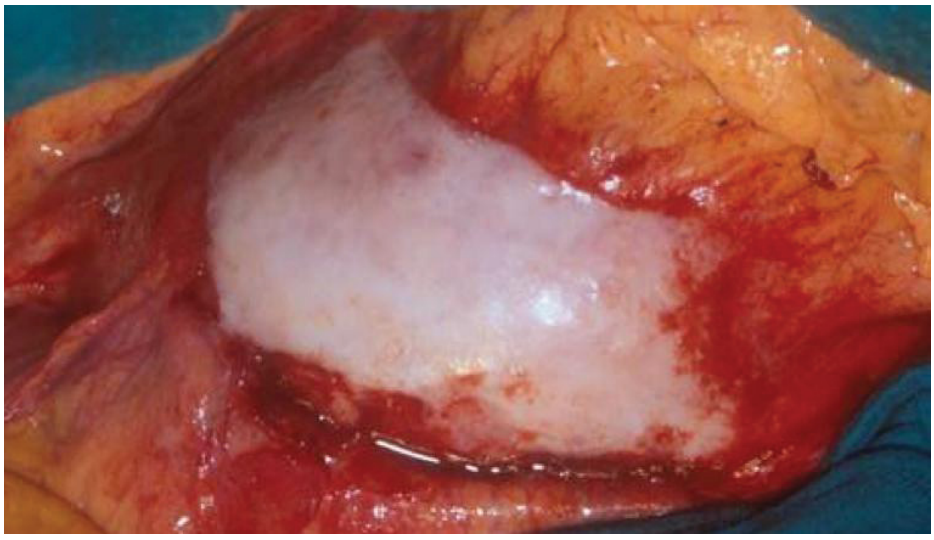
# Table of Contents

# 1. Introduction

## 1.1. Definition

An inflammatory aneurysm represents a special form of aneurysm with an exaggerated inflammatory component. It is characterised by marked fibrotic thickening of the aortic wall, extensive perianeurysmal, retroperitoneal fibrosis and dense adhesions to adjacent abdominal organs such as ureters, duodenum or sigmoid colon. Frequently, the aortic wall is found to be infiltrated by lymphocytes and plasma cells.[1]

The first morphologic description of the inflammatory aneurysm belongs to Walker, who in 1972 used the term to characterize a group of 19 patients, whose aneurysms showed a ‘thick, firm, smooth wall with a shiny white appearance’ and where the ‘dense fibrosis extended to involve adjacent structures’.[2]



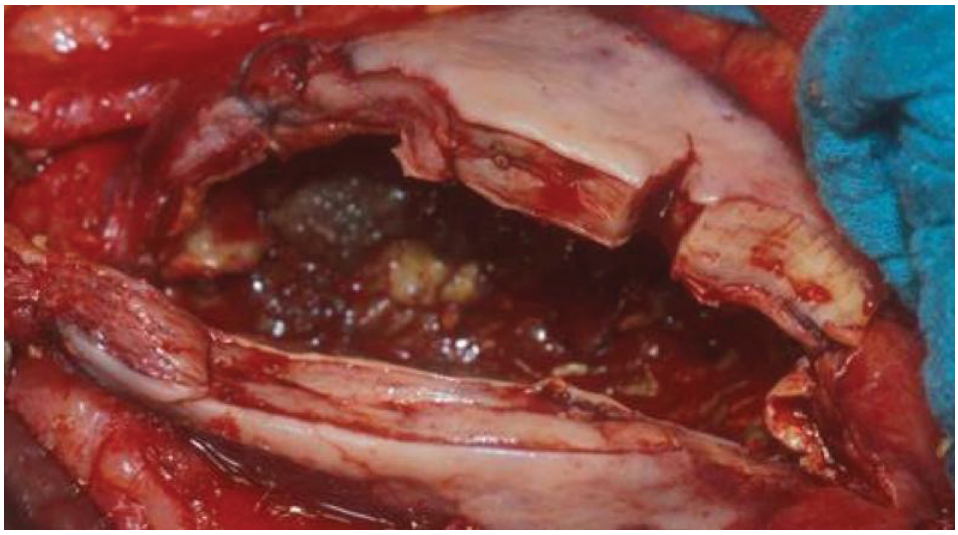


***Figure 1.*** *Intraoperative photos of an IAAA*

According to other authors the first inflammatory aneurysm description, dates back to 1935 and is attributed to James. James reported a fatal case of uraemia secondary to ureteral obstruction as a result of fibrosis surrounding a large aneurysm of the abdominal aorta.[3]

## 1.2. Epidemiology and Natural Course

The incidence of inflammatory abdominal aortic aneurysm (IAAA) at autopsy ranges from 2,5 to 10%. IAAA is considered to be a variant of abdominal aortic aneurysm (AAA) and counts for 2 - 14% of all AAAs.[4]

The prevalence of newly diagnosed abdominal aortic aneurysm was reported as 65 per 100,000 individuals/annually. Given that 2–14% of all AAAs might be IAAAs, the prevalence of inflammatory aortic aneurysm might be comparable or slightly

higher than that of idiopathic retroperitoneal fibrosis, which has been reported to have an incidence of 0.1 per 100,000 individuals/annually.[5]

The risk of rupture of an inflammatory aneurysm in the natural course is reported to range from 15% to 25%, which is apparently not greater than the probability of rupture of non-inflammatory aneurysms.[6, 7] There is no correlation found between maximal inflammatory aneurysm diameter and rupture risk due to the lack of evidence. Even though a variety of alternate parameters have been proposed as more sensitve predictors of rupture risk including AAA expansion rate, increase in intraluminal thrombus thickness, wall stiffness, wall tension, and peak AAA wall stress, a maximal diameter ≥ 5.5 cm remains a strong recommendation to treat in asymptomatic patients.[8] The recommendations in the therapy of the IAAAs are not distinguished from these of AAAs.

## 1.3. Risk Factors

Patients usually present at a younger age than those with atherosclerotic aortic aneurysm, demonstrating mean ages from 62 to 68 years, 5 to 10 years younger than the mean age of patients with non-IAAAs.[9] Male gender and smoking are the main risk factors that are strongly associated with aortic aneurysm formation. These two factors are even more prevalent in patients with IAAA, than in patients with AAA. A genetic risk factor could also be mapped in patients with inflammatory AAAs. Rasmussen's et al. suggest that gene association with IAAA is located in the HLA-DR B1 locus. This association suggests a critical contribution of antigen binding in the pathogenesis of this form of AAA.[10] Large-vessels vasculitis, such as giant cell arteritis and Takayasu arteritis, could also cause IAAA.[11]

## 1.4. Etiopathogenesis

The etiology and pathogenesis of inflammatory aneurysm in spite of the increasing number of observations reported in recent years is yet obscure. Some authors attribute IAAA to an autoimmune reaction and others to a severe inflammatory reaction secondary to arteriosclerosis. The inflammatory process can be triggered by syphilitic arterial disease, tuberculosis, giant cell arteritis, Salmonella infection but in most cases no etiology cant be established.[12]

An immune reaction against some antigen components in the aneurysm wall may lead to the exaggerated inflammatory response, that is characteristic of IAAAs.[13]

Elevated inflammatory markers, such as erythrocyte sedimentation rate, white blood cell count, and C reactive protein, are commonly observed.[14] Autoimmunity may have a role in the formation of IAAA as suggests the observation of positiv anti-nuclear antibodies and IgG4 elevation.[14-16]

IgG4-related systemic disease is a newly recognized disorder that may manifest as inflammatory abdominal aortic aneurysm or retroperitoneal fibrosis;[17] therefore, elevation of serum IgG4 levels and/or infiltration of IgG4-positive plasma cells in the periaortic tissues may aid IAAA diagnosis.

On the other hand, Kasashima et al. found a IgG4 relation in only about 50 percent of inflammatory aortic aneurysm cases; however, the clinical picture does not seem to differ substantially between IgG4-related and non-IgG4-related inflammatory aortic aneurysms.[15] These findings indicate that the presence of this entity cannot be determined solely on IgG4 positivity. It may be a heterogeneous disease. Stone et al conclude that identification of IgG4+ plasma cells does not necessarily indicate

involvement by IgG4-related systemic disease (IgG4-RSD). They suggest a 50/50 rule for the pathologic diagnosis of IgG4-related aortitis/periaortitis.[17] In presence of an overall histology that is consistent with an aortitis or periaortitis and that is not readily explained by another process such as atherosclerosis, an IAAA diagnosis require at least 50% of the plasma cells stain for IgG4 as well as at least 50 IgG4+ plasma cells per 400x high-power field, counting at least three fields.

Tan et al (2013) stated that SMAD3 deficiency promotes inflammatory aortic aneurysms in angiotensin II–infused mice via activation of iNOS.[18] Two years later, found Dai et al. that SMAD3 deficiency promotes vessel wall remodeling, collagen fiber reorganization and leukocyte infiltration in an inflammatory abdominal aortic aneurysm mouse model.[1] SMAD3 is a key component of TGF-β canonical signal pathways. TGF-β signaling activation in the pathogenesis of aortic aneurysms is controversial. Inhibiting the TGF-β signaling, ameliorates Marfan syndrome (MFS)-associated aneurysms.[19] but on the other hand, such inhibition exacerbates angiotensin II infusion-induced AAA, which is protective against IAAA progression.[20]

The existing literature provides strong in vivo evidence supporting the important role of SMAD3 in protecting vessel wall integrity and suppressing inflammation in AAA pathogenesis. More than one study demonstrate that, under stress condition, disrupting SMAD3 expression activates SMAD-mediated TGF-β canonical pathway as well as SMAD-independent pathways, including ERK1/2 and NF-kB signal pathways.[21-23] The increased inflammation and the SMAD3 mutation-induced immune defects, promote vessel wall remodeling and aortic aneurysm formation.

Although important steps have been reached in the explanation of the etiopathogenesis of IAAA, further investigation is needed.

## 1.5. Diagnostics

### 1.5.1. Clinical signs

The patient with AAA that comes with abdominal or back pain, weight loss and raised erythrocyte sedimentation or elevated C-reactive protein levels, is highly suspect to have an inflammatory AAA.[9] This classical triad is not always present. Other signs such as anaemia, low-grade fever, probably due to deterioration, fatigue of obstuctive uropathy can be also present. Clinical signs alone cannot establish the diagnosis. Until the advent of modern radiologic imaging modalities, inflammatory aneurysms were often discovered at the time of surgery.

### 1.5.2. Imaging

Nowadays once a clinical suspicion of an IAAA is raised, an ultrasonography (US) of the abdomen can quickly confirm the existence of an inflammatory aneurysm, but with the cost of low sensitivity (13,5 %).[24]

Computed tomography (CT) scan with contrast enhancement is a reliable imaging modality for the diagnosis of IAAA.[25] Magnetic resonance angiography (MRA) is also useful for diagnosis and follow-up. These modalities provide adequate information for the diagnosis and allow for surgical treatment planning. Once the diagnosis is established, it is important to obtain imaging of the entire aorta with an appropriate modality like CT or magnetic resonance angiography to rule out

inflammatory changes of the thoracic aorta.[26] IAAA characteristics can be identified on computed tomography (CT) scans, with the typical ´mantle sign´.[2] CT scan has a sensivity of up to 90% and is considered the gold standard.[27] Perianeurysmal adhesions that involve the duodenum, the inferior vena cava, left renal vein, the ureter or the sigmoid colon vary. The most common adhesions are with the duodenum and are present to up to 70% of the patients. An ureteral obstruction is observed in up to 20% of IAAA patients.[9]

Aortic ultrasound is relatively unreliable in inflammatory aneurysms, and CT or MRA are the diagnostic modalities of choice, with MRA being slightly more accurate in delineating the level of aortic involvement.[28]

Contrast enhanced ultrasonography improves differentiation between covered aortic rupture and inflammatory aneurysm and is recommended as an additional tool in the characterisation of suspected IAAA. [29]

In patients with IAAA, a correlation between periaortic 18-fluorodeoxyglucose (18F-FDG) uptake and intensity of inflammatory was found. This can cause pathological findings in 18F-FDG positron emission tomography (PET).[30] The process seems to depend on the release of matrix metalloproteinases focally produced and/or activated by inflammatory cells, leading to degradation of elastin and collagen in the aneurysm wall. Increased metabolic activity of the IAAA wall on PET scan reflects increased rupture risk better than aneurysm size.[31, 32] Xu et al described in 2010 a potential link between high wall stress and accelerated metabolism in aortic aneurysm wall.[33]

18F-FDG-PET CT might be a new diagnostic instrument to improve rupture prediction in patients with IAAA.

### 1.5.3. Macroscopic Histology findings

The porcelaneous appearance, excessive thickening of the aortic wall (greater than 0,5 cm in most cases) and perianeurysmal adhesions are the main macroscopic characteristics of inflammatory aneurysms. These aneurysms are covered on their anterior and lateral sides with thick, white fibrous tissue.

The histological features of the IAAAs are those of the atherosclerotic aneurysms with the addition of large amounts of hyaline periaortic fibrous tissue within which are large number of plasma cells and often lymphoid follicle with germinal centres. The fibrous tissue may be very cellular in areas with a whorled pattern.[34]

## 1.6. Treatment

The indications for treatment are the same as for abdominal aneurysm repair. Although the inflammation is in most cases limited to the infrarenal segment of the aorta, the dense adherence of local structures, such as ureters or duodenum, frequently requires suprarenal or supraceliac aortic clamping to protect the structure from injuries by the surgery. [35, 36]

### 1.6.1. Conservative

There are some reports indicating that steroid therapy alone can be successful in controlling the inflammatory process and the symptoms.[37-39] However, due to the risk of rupture and the lack of time to wait until the steroid therapy reduces inflammation, surgery is considered the method of choice.

### 1.6.2. Surgical

#### 1.6.2.1. Conventional

Aortic replacement with a tube graft or bifurcation Y graft is the most common choice. The operation is considered difficult due to periaortic fibrosis. The primary surgical challenge associated with these lesions is the safe dissection of surrounding structures during open repair of these lesions. Complications associated with conventional open surgery have included duodenal perforation and ureteral injury.

A standard, midline transperitoneal approach is most commonly utilized for aneurysm resection and grafting. Such an approach, reduces the risk for duodenal and left renal vein injury, as well as inferior vena cava injury, and is more safe to gain proximal control of the aorta.[40]

However, the retroperitoneal approach may have advantages over the transabdominal approach for the following reasons:

(1) The posterolateral aspect of the aorta is not significantly involved by the inflammatory process, unlike the anterior one;

(2) The duodenum does not need to be dissected away from the aorta and, in fact, is not to be seen;

(3) The left renal vein moves up off the neck of the aneurysm with forward mobilization of the kidney, facilitating proximal contro1.[41]

Several tools can resolve hydronephrosis, such as preoperative nephrostomy, ureteral catheter placement, or ureteral stenting, as well as intraoperative ureterolysis.[6]

Yusuf et al compared postoperative outcomes after open surgical repair between patients with inflammatory aneurysm and patients with atherosclerotic aneurysm. This study showed that patients with inflammatory aneurysms were at an increased risk for postoperative renal failure. Postoperative computed tomographic evaluation revealed that, despite surgical treatment, the fibrotic process did not resolve or even progress in some cases. The study concludes that surgical repair of an inflammatory aneurysm may not result in a complete resolution of the inflammatory process.[40] Another research group reported similar findings, stating that a complete resolution was present in slightly more than half of patients.[13] This ongoing inflammatory process is an important factor and has its impact on late postoperative outcomes. This process, according to Yusuf et al, is strongly associated with the risk of death in patients undergoing surgery for an inflammatory AAA.

Yin et al in 2010 concluded that despite having more symptoms, larger size and longer operation time, patients with IAAA can be treated with approaches that have low morbidity and mortality, similar to patients with non-IAAA. They observed no difference on long-term outcome of IAAA patients from patients with atherosclerotic aneurysms.[42]

The fact that open surgical repair does not always resolve the inflammatory process led the researchers to propose an endovascular repair of inflammatory AAA in order to minimize the operative trauma. Nevertheless, effect of endograft placement on perianeurysmal inflammation is not clearly defined.

#### 1.6.2.2. Endovascular

Endovascular grafting offers an alternative approach to the treatment of potentially high-risk patients with typical atherosclerotic AAAs because it decreases morbidity

and mortality associated with extensive retroperitoneal dissection and prolonged aortic cross-clamping.[43]

In 2015 the Cochrane Collaboration made an effort to compare the open repair versus endovascular repair for inflammatory abdominal aortic aneurysms. However the lack of high-quality studies evaluating the treatment for inflammatory abdominal aneurysm didn't allow reliable conclusions to be drawn.[44] Such a review is important, because the treatment of IAAA poses a special challenge to the surgeon due to the risk of iatrogenic injury in open repair or, on the other hand, due to the potentially increased inflammatory response after stent graft implantation.

The most recent study from Kakkos et al in 2015 regarding outcomes, found endovascular IAAA repair to be associated with a shorter operative time, reduced transfusion needs, and hospitalization. These findings reflect a smoother postoperative course compared to open surgical repair (OSR) and explain the reduced morbidity and mortality with EVAR.[45] The authors also suggest that further prospective trials should focus on the role of EVAR for IAAAs by confirming the results of comparative studies and by providing long-term results, including the course of periaortic fibrosis (PAF), hydronephrosis, aneurysm-related mortality and all-cause mortality.

Paravastu et al suggested in 2009 that based on patient suitability either OSR or EVAR may be considered in the treatment of IAAA. The former may be preferred in those patients who have hydronephrosis and are deemed low risk, whereas the latter is associated with lower 1-year mortality.[24]

# 2. Aim of the study

## 2.1. Project Plan

We retrospectively reviewed the medical records of patients with IAAA selected out of 1002 patients with AAA who underwent open surgery in the Department of Vascular and Endovascular Surgery at the University Hospital Dusseldorf from January 2006 to December 2015. These patients were matched with controls, selected from a prospectively retained database. A 1:2 case control match regarding age, gender and year of treatment was made. We analysed both groups for preoperative parameters, intra-operative findings and early postoperative outcomes.

## 2.2. Questions

In our study, the outcomes of the therapy of the inflammatory aortic aneurysm are analyzed and compared with the results of patients of comparable demographic and clinical parameters with non-inflammatory aortic aneurysm. The optimal therapy is evaluated within the framework of the study. The following questions were answered:

- What are the perioperative mortality and morbidity rates for open therapy in IAAA and non-IAAA group?
- Are there differences between groups in terms of morbidity and mortality?

- Is there an increased frequency of aortoenteral fistulae in short-term or long-term course of patients with inflammatory aneurysms?
- Are there other specific long-term complications related to the inflammatory component?

## 2.3. Study Design

All patients with inflammatory aneurysm of the abdominal aorta, which underwent an open surgical treatment in our Department of Vascular and Endovascular surgery, from July 2006 to July 2015, are included. Control group form patients with non-IAAAs, which have the same demographic (age, gender) and clinical (e.g., BMI, ASA, comorbidity) characteristics with the study group. Then we compared the two groups in terms of outcomes. The following parameters were examined: duration of operation, extent of the findings (intraop.), transfusion requirement, reoperation rate, intensive care period, total length of stay, 30-day mortality rate and long-term complications. The study was approved by the Ethics Committee of the University of Dusseldorf and adhered to the principles of Declaration of Helsinki (Study Nr: 5415R, Register ID: 2016014917).

# 3. Material and Methods

## 3.1. Patient data

We retrospectively reviewed and analyzed the medical records of patients with IAAA who underwent open surgery in the Department of Vascular and Endovascular Surgery at the University Hospital Dusseldorf from January 1, 2006 to December 31, 2015. The study was approved by the Ethics Committee of the University of Dusseldorf and adhered to the principles of Declaration of Helsinki (Study-Nr: 5415R, Register ID: 2016014917).

A total of 1002 patients with AAA during the study period were recruited. Twenty patients with IAAA were identified. Two of them were excluded because they had an endovascular repair. The diagnosis was set in most cases radiologically prior to operation and confirmed morphologically and histologically. In two cases the diagnosis was made by the surgeon and was further histologically confirmed. Exclusion criteria were: age younger than 18, necessity of suprarenal repair, emergency operation, prior, concomitant connective tissue disorders (i.e. Marfan syndrome, Ehler-Danlos syndrome etc.), aortic dissections, prior vascular or endovascular aortic repairs, vasculitis and infected aneurysms. A 1:2 case-control matching was applied for age (±1 year), gender and year of treatment to analyze outcomes. The controls were selected from a prospectively pool of patients undergoing surgery on non-IAAA. We analyzed both groups for preoperative parameters, intraoperative findings and early postoperative outcomes.

Preoperative parameters included body mass index (BMI), smoking habits, history of abdominal pain, coronary heart disease, hyperlipidemia, renal impairment, hypertension, diabetes mellitus and peripheral artery disease were assessed. Overall perioperative risk was classified according to the American Society of Anesthesiologists' physical status classification system (ASA).[46] Since patients who required urgent or emergency surgery were excluded, we used the ASA score to categorized patients in groups of ≤II, or ≥III, to consider comorbidity.

Prior to operation, patients were screened for C-reactive protein (CRP), white blood cell count (WBC), platelet (PLT) count, creatinine levels, partial thromboplastin

time (PTT) and international normalized ratio (INR). After operation the same parameters were examined.

End points of this study were surgery time (from incision to suture), intraoperative blood loss, transfusion requirement for the entire in hospital stay, complications requiring re-operation or re-intervention, length of stay (LOS), length of intensive care unit stay (ICU) and 30-day mortality. Early morbidity was assessed using the Dindo–Clavien classification. [47]

| Grade | Definition |
|---|---|
| I | Any deviation from normal postoperative course |
| II | Requiring pharmacological treatment |
| III | Requiring surgical, endoscopic or radiological intervention |
| IIIa | Intervention not under general anesthesia |
| IIIb | Intervention under general anesthesia |
| IV | Life-threating complication |
| IVa | Single organ dysfunction (including dialysis) |
| IVb | Multiorgan dysfunction |
| V | Death of a patient |

***Table 1.*** *The Dindo-Clavien classification of postoperative complications, used in our study.* [47]

## 3.2. Statistical analysis

Data are presented as median with full data range. Categorical variables are stated as frequency distribution and were analyzed using Fischer's exact test. The t-test was applied to compare continuous variables. A p-value $<0.05$ was considered to be statistically significant. Data analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

# 4. Results

A total of 1002 patients who underwent surgery for AAA were recruited within the period of investigation. Of these, 20 patients (2%) had an IAAA. Two patients of the IAAA group were offered endovascular treatment (excluded from the study). On clinical examination (6/18) 33.3% of the patients presented with symptoms. Among these, back pain and hydronephrosis being the most common symptoms (11% each), whereas abdominal pain was the most uncommon symptom (6%). There was no documented weight loss. The remaining 18 patients were matched with 36 patients who underwent open surgery for non-IAAA in the same period. Compared to the IAAA group, we observed less symptomatic patients in the non-IAAA group, 5/36 (14%). Median follow-up was 19.6 months [3-81 months]. Six patients were lost during the follow-up.

## 4.1. Demographic data and preoperative parameters

As patients were matched for age, gender and year of operation, no demographic differences were observed between the two study groups. Median age was 70.5 years [57-83] for the IAAA group and 71 [57-84] for the non-IAAA group. Male-to-female ratio was 9:1 in both groups.

We also observed no differences in WBCs, PLTs and creatinine levels prior to surgery in both study groups (Table 2). CRP level was slightly higher in IAAA patients (1.35mg/dl [0-18.5], vs. 0.4 [0-5.9] in the non-IAAA group), however data failed statistical significance (p=0.16).

Preoperative parameters such as BMI, comorbidity, smoking habits and preoperative ASA score showed no significant differences. (Tables 2, 3).

| Preoperative parameter | IAAA (N=18) | non-IAAA (N=36) | p-value |
|---|---|---|---|
| Age in years (range) | 70.5 (57-83) | 71 (57-84) | -* |
| Sex: Male (percentage) | 16 (89%) | 32 (89%) | -* |
| BMI (kg/m$^2$) | 26.2 (3.2) | 28.3 (3.8) | 0.063 |
| WBCs (x1000/nL) | 8.3 (2.6) | 7.6 (1.6) | 0.223 |
| PLTs (x1000/nL) | 260 (109) | 214 (70) | 0.068 |
| Creatinine (mg/dL) | 1.06 (0.2) | 1.18 (0.5) | 0.340 |
| CRP (mg/dL) | 2.6 (4.3) | 0.9 (1.3) | ***0.038*** |
| Diameter (mm) | 62 (17.4) | 56.6 (13.2) | 0.202 |
| Max. Diameter (mm) | 100 | 102 | |
| Juxtrarenal expansion | 7 (38.9%) | 12 (33.3%) | |

***Table 2.*** *Characteristics of patients with IAAA and non-IAAA. Age is expressed in median years and range, sex in absolute and percentage frequencies, the rest parameters in mean-deviation form. * p value was not expressed for matched variables. Statistical significance: p<0.05. (62)*

| Comorbidity | IAAA (N=18) | non-IAAA (N=36) | p-value |
|---|---|---|---|
| Hypertension | 14 (78%) | 32 (89%) | 0.42 |
| COPD | 2 (11%) | 9 (25%) | 0.3 |
| Coronary heart disease | 9 (50%) | 20 (56%) | 0.77 |
| Dyslipidemia | 5 (28%) | 17 (47%) | 0.24 |
| Diabetes mellitus | 1 (6%) | 10 (28%) | 0.08 |
| Chronic renal failure | 5 (28%) | 4 (11%) | 0.14 |
| Active smoker | 6 (33%) | 7 (19%) | 0.32 |
| Cerebrovascular disease | 0 | 4 (11%) | 0.29 |
| Peripheral arterial occlusive disease | 3 (17%) | 5 (14%) | 1 |

***Table 3****. Comorbidities in the two groups. Variables are expressed in absolute and percentage frequencies. Statistical significance: p<0.05. (62)*

## 4.2. Perioperative parameters

Median laparotomy was the standard approach in all patients. Only 1 patient of each group was operated using a left retroperitoneal approach. We observed no significant difference between the study groups with regard to total operation time (191 minutes in IAAA group vs. 196 minutes in non-IAAA group). In the IAAA group, 61% of the patients received a tube graft (vs. 58% non-IAAA group) and 39% (vs. 42% non-IAAA group) had a bifurcated graft. Eight patients of the study group (44%) and 11 controls (23%) required suprarenal clamping.

We found significant higher transfusion rates in the IAAA group. Blood loss was substituted with 5.2 red cell concentrates (vs. 1.4 non-IAAA group, p=0.016) and 5.1 fresh frozen plasmas (vs. 2.1 in non-IAAA group, p=0.038). There was no difference in platelet units transfusion (0.4 in IAAA group vs. 0.5 in non-IAAA group, p=0.91). Postoperatively, no special medical therapy/steroid was given.

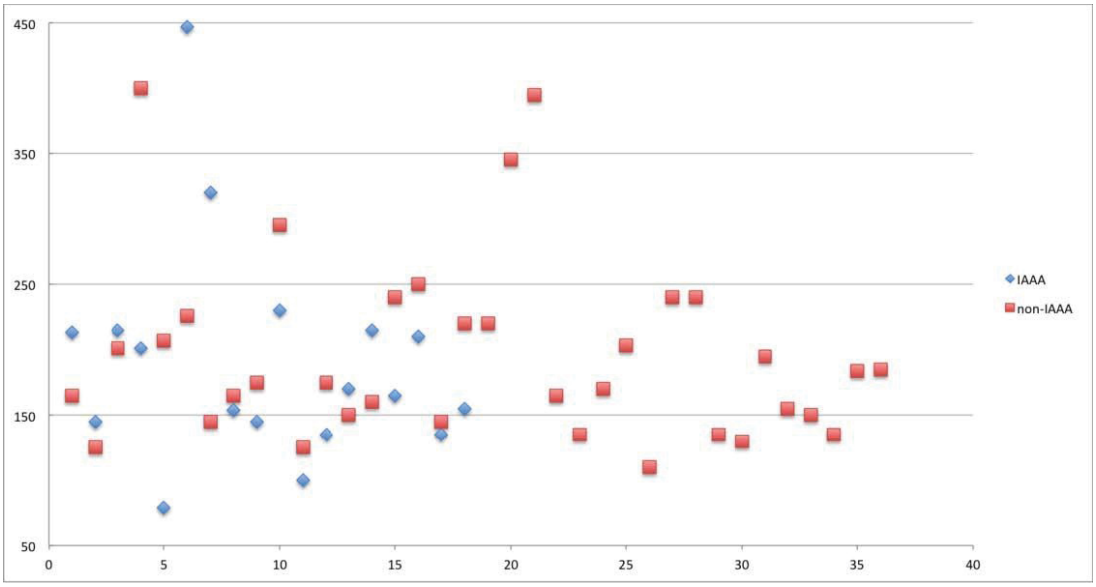



***Figure 1.*** *Duration of surgery, comparable in both groups. (62)*

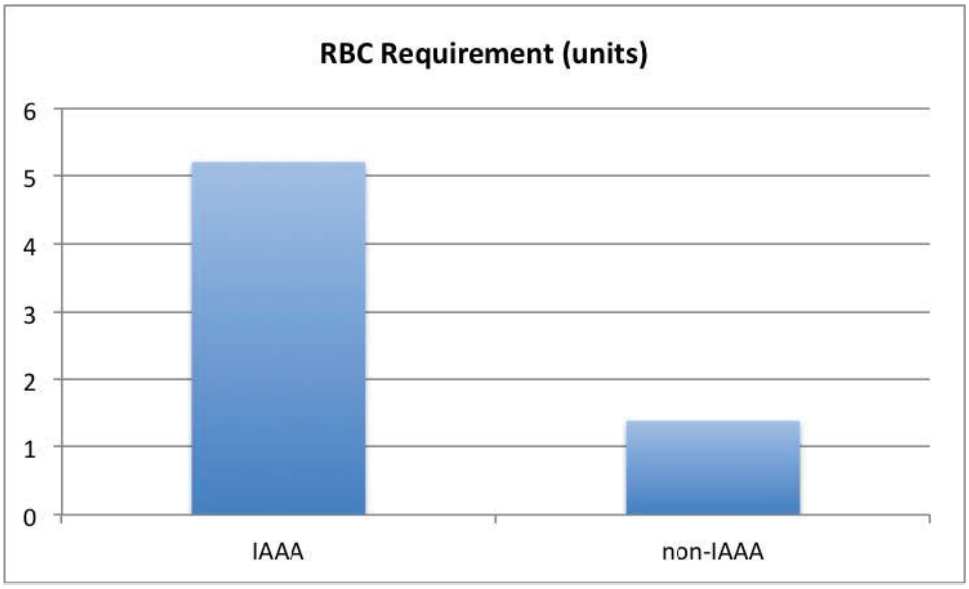



***Figure 2.*** *Significant higher transfusion requirement in the IAAA group. (62)*

## 4.3. Postoperative outcomes

The need for ICU management and the length of overall hospital stay were significantly higher in the study group ($p<0.05$) (Table 4, Figure 3).

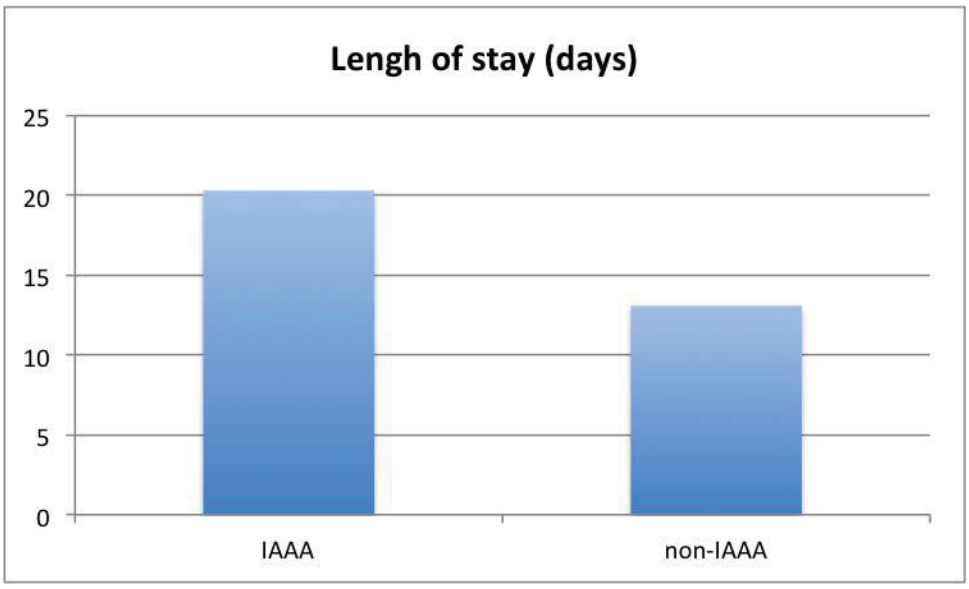



***Figure 3.*** *Overall Length of Stay was significantly longer in the IAAA group. (62)*

Complication rate was in 10/18 (56 %) vs. 12/36 (33%) in the non-IAAA group ($p<0.05$) (Table 5). Suprarenal clamping needed in eight patients with IAAA (44.4%) and in 11 patients with non-IAAA (30.5%) In the study group 5 out of 8 (62.5%) patients with suprarenal clamping suffered one or more complications and the two of them died three months after the operation. In the control group 6 out of 36 (16.7%) suffered one or more complications. Postoperative WBCs, PLTs and creatinine levels outlined no difference for both groups (Table 4). We observed a 30-day mortality rate of 0% for both groups. Two patients with IAAA died after the surgery in-hospital. One patient died of sepsis due to development of intestinal ischemia 2 months after the operation and 1 patient died 3 months after surgery due to respiratory insufficiency. Both these patients required a suprarenal clamping.

The median follow-up was 19.6 months. Five patients were lost to follow-up direct after the operation and 5 were lost 6 months later. Follow-up included physical examination and duplexsonography. No graft complications were detected. Only two complications were in total detected in the study group, one patient with erection dysfunction and one with peripheral angiopathy. Complications in both groups are summarized in Table 5.

| **Outcome** | **IAAA** | **non-IAAA** | **p-value** |
|---|---|---|---|
| OP length (min) | 191 (84) | 196 (71) | 0.806 |
| Suprarenal clamping | 8/18 (44.4%) | 11/36 (30.5%) | 0.37 |
| Blood loss (ml) | 908 (581) | 755 (760) | 0.46 |
| RBC (units) | 5.2 (8) | 1.4 (3.1) | ***0.016*** |
| FFP (units) | 5.1 (5.7) | 2.1 (4.3) | ***0.038*** |
| TK (units) | 0.4 (0.9) | 0.4 (1) | 0.918 |

| | | | |
|---|---|---|---|
| LOS (days) | 20.3 (12.7) | 13.1 (4.9) | ***0.04*** |
| ICU (days) | 7 (11.5) | 2 (1.7) | ***0.013*** |
| Suprarenal clamping + complications | 5/8 (62.5%) | 6/11 (54.5%) | 1 |
| Postop. CRP (mg/dL) | 6.3 (4.9) | 7.4 (6.6) | 0.565 |
| Postop. WBCs (x1000/nL) | 8.8 (2.5) | 8.3 (2.2) | 0.403 |
| Postop. PLTs (x1000/nL) | 296 (127) | 289 (124) | 0.84 |
| Postop. Creatinine (mg/dL) | 1.04 (0.3) | 1.26 (0.8) | 0.29 |

***Table 4.*** *Perioperative findings and postoperative outcomes in mean-deviation form. Statistical significance: $p<0.05$. (62)*

| **Complication** | **Study Group (N=18)** | | **Control Group (N=36)** | |
|---|---|---|---|---|
| Grade I | 1 | edema | 0 | |
| Grade II | 7 | pneumonia, arrhythmia, acute renal failure, urinary infection, scrotal edema, diarrhea | 6 | respiratory insufficiency, prostatitis, delirium, leg ischemia, hematuria, acute renal failure |
| Grade IIIa | 0 | | 2 | myocardial infarction, stress ulcer |
| Grade IIIb | 2 | sigmoidal ischemia, occlusion inferior mesenteric artery, respiratory failure | 3 | bleeding, occlusion of y-prosthesis |
| Grade IVa | 0 | | 1 | acute renal failure leading to hemodialysis |
| Grade V | 2 | Sepsis, respiratory insufficiency | 0 | |
| **Major, ≥ IIIb** | **4 (22%)** | | **4 (11%)** | |
| **Total** | **12 (67%)** | | **12 (33%)** | |

***Table 5.*** *Postoperative complications classified according to Dindo[5]. By Grade ≥ IIIa an intervention is necessary and Grade V means the death of a patient. (62)*

# 5. Discussion

We retrospectively analyzed 18 patients with IAAA, in terms of outcomes after open surgical repair and compared the results to 36 controls with non-IAAA and similar demographical characteristics, treated at the same time. The prevalence of IAAA in our population was 2%, which is lower compared to previous findings in the literature, 9%-10%.[2, 45, 48] As these studies did not distinguish between ruptured and the non-ruptured neither between infected and inflammatory aneurysms our results seem closer to reality. We excluded all aneurysms with a positive microbiological examination of the aneurysm. The male-to-female ratio and the mean age reported in these studies are comparable with our findings.[48]

IAAAs have been reported to be more frequently symptomatic on clinical presentation compared to non-IAAAs. Although authors stated that the proportion of symptomatic IAAA might vary, the average lies by 63.9%.[2, 4, 24, 27, 40, 42, 45, 49-51] In this study we found a proportion of symptomatic IAAA patients of 33.3%. With the advent of broadly available in room imaging modalities, an increase in incidentally found IAAA patients of up to 58% could be recently observed.[48] The fact that more and more IAAA are currently detected before they become symptomatic through the extensive use of CT scans, could offer an explanation for this finding. In general, there is a reduction of symptomatic IAAA patients on admission from 47% in 1972[2] to 42% in 2008. This downward trend fits well together with the findings of this study.

The pulsing mass, weight loss and elevated erythrocyte sedimentation rate (ESR) have been considered as a classical triad of IAAA.[42] As the use of modern imaging technologies leads to improved image quality and reduced radiation doses, IAAA can be diagnosed quicker and more accurately. As a consequence, the triad becomes less important as an IAAA diagnostic tool. The utility of ESR was unclear from the previous literature, because ESR is an unspecific marker.[51, 52] The use of early imaging in the diagnosis of IAAA could be confirmed from our study Most of the patients were present in emergency.[45] The triad is losing its significance due to prompt diagnosis of IAAA, a tendency that was confirmed from our study.[51] Besides new approaches to the diagnosis periaortic inflammation (PAI) seems to be responsible for typical symptoms such as abdominal and back pain, ureteral obstruction and consecutive hydronephrosis.

PAI is usually depicted in CTA scans as thickness of the aortal wall. Especially after endovascular approach the regression of PAI is used as evaluation tool to conclude weather a relief from obstructive symptoms seems likely. Although of high interest for surgeons, CTA scan after open repair cannot be ethically justified. The incidence of hydronephosis, as one of the most frequent obstructive complications, is as high as 20% according to previous studies.[53] In our series, there was a 28% incidence of chronic renal failure prior to the operation. One patient had a unilateral radiological revealed ureteral stenosis without clinical signs of obstructive uropathy. Indicator of surgical quality might be the operative time, complication rates and transfusion requirements.

Prifti et al. reported an operative time of 278 minutes and Nuellari et al. stated a blood loss of 1700 ml during open surgical repair of IAAA.[4, 54] Compared to our data operative time was longer and blood loss was higher. These discrepancies

seems reasonable as our patients were operated in a planned basis where these parameters are more easy to control than in emergency situations. A transperitoneal approach reduces the risk for duodenal and left renal vein injury and allows for a more safe proximal control.[40] Surgical complications from the adherent organs occur in 4.5-15% of cases.[6] Although in many of our cases, the duodenum was adherent on aneurysm wall, a clean preparation without considerable injury was performed. In the early years, an extensive adhesiolysis was routinely performed which led to major complications, such as vein or duodenal injury (Pennell et al, 1985).[27] It has previously been described that about 44% of patients had undergone a bifurcated grafting operation.[45] As in our study around half of the patients received either a tube graft or a bifurcated graft. We believe that the use of bifurcated graft should be limited to severe disease that includes iliac arteries to reduce the risk of graft infection and long-term complications. Suprarenal clamping is considered a marker of excessive disease and has been associated with worse postoperative outcomes. Our study confirmed this finding. More patients with IAAA required a suprarenal clamping and in this subgroup two deaths were observed in the late postoperative course. Suprarenal clamping alone, even if not combined with suprarenal repair, as in our study, serve as a factor/marker of complicated course. However, this finding could also mean that IAAA has a much more aggressive pathology, compared to non-IAAA.

The use of steroids perioperative to reduce the retroperitoneal inflammation and in long term the fibrosis is not common praxis. There are reports that suggest that a steroid therapy affects positive the hydronephrosis but no benefit was showed during the follow-up. (52) In our study no steroids were given routinely. The role of

steroids in preventing hydronephrosis needs further examination as complimentary therapy, especially in the endovascular era, where the inflaming tissue is not being removed.

Open surgical repair (OSR) was widely considered to be the gold standard in the management of inflammatory aneurysms; however, there is an remarkable increase in the number of reports which claim endovascular management as first line strategy. More to that, van Bommel et al. reported a significant lower regression of PAI and hydronephrosis after endovascular aortic repair (EVAR), compared to OSR.[55] Endovascular repair was once considered to have a relative contra-indication for IAAA patients, as a reduction of PAI and fibrosis could not been documented to the same extend as for OSR.[56] The latest literature well supports the reduction or at least no aggravation of PAI after OR[57-59], whereas studies dealing with PAI after EVAR are controversial.[45, 51, 56] Despite this fact, EVAR nowadays plays a central role in the IAAA therapy, as it provides a clear benefit for patient in terms of morbidity and mortality.

The outcomes of patients with IAAA are generally comparable to those from patients with non-IAAA. The early postoperative mortality significantly decreased over the time starting with a 30-day mortality rate of 26% in 1972 and reaching 6% in 2015.[2] A further decrease up to 3.6% could be observed if only patient with un-ruptured aneurysms were analyzed.[45] Kakkos et al. outlined an early postoperative morbidity rate of 27.4% after OR compared to 8.3% after EVAR.[45] As we reported a major complication rate of 22% (n=4), we believe that complication rates as low as being found in this study require experience in OSR of IAAA which could

be guaranteed in specialized centers. As there was no 30-day mortality in both the groups.

In-hospital mortality of the study group was 11% (n=2). IAAA takes in most cases a benign course. Nevertheless, the chronic inflammatory process should not be underestimated, as there long-term complications could occur.

Long-term pseudoaneurysm formation after IAAA was well studied in the existing literature. The incidence rate ranges from 0.4% to 14.2%.[4, 60] Another long-term complication after IAAA is aortoenteric fistula formation.[6, 61] There is also a significant difference in the pseudoanerysm formation between IAAA and non-IAAA. Suprarenal clamping zone is a negative indicator as it symbolized a severe disease of the aortic wall with consecutive degeneration in the long-term course. The effect of a suprarenal clamping was clearly shown in our short-term results. However, we did not observe any pseudoaneurysm formation in the long-term course.

In conclusion, open treatment of IAAA guarantees in most cases a regression of the inflammatory process, but the surgical approach can be dangerous and might lead to local structural injuries, i.e. to the small intestine. Early diagnosis of a non-ruptured aneurysm is crucial as elective surgery guarantees the highest benefit for patients. Endovascular repair of IAAA should be considered as reasonable alternative even as fist line treatment.

Most of the points of the study were discussed above. To clarify more the results and to extent the discussion also on parameters that were not direct investigated in our

study we would like to answer the questions set while planning this study and to comment another two points, the use of steroid in the therapy of the IAAA and the endovascular therapeutic approach.

## 5.1. Questions

- ***What are the perioperative mortality und morbidity rates for open therapy in the IAAA and non-IAAA group?***
- ***Are there differences between the groups in terms of morbidity and mortality?***

There was no 30-days mortality in both groups. In the study group two patients died in hospital one due to sepsis following revision for postoperative sigmoidal ischemia and another due to respiratory collapse also after sigmoidal ischemia and revision. These patients survived the 30 days but died in hospital after 50 and 64 days. In the control group there were no deaths.

The morbidity in the study group was 56% (N=10) in total with 11% (N=2) of these complications being major and leading to the death of the patients. In the control group there was a 33% (N=12) total morbidity, with also 11% (N=4) major complications rate, but without deaths. The morbidity in study group is statistically significant increased.

These numbers confirm that IAAA are, as also stated in the discussed literature, prone to complications and to a more complicated course, when comparing with the non-IAAA.

- ***Is there an increased frequency of aortoenteral fistulae in the short-term or long-term course of patients with inflammatory aneurysms?***

We didn't observe any aortoenteral fistulae in the short-term or long-term course of the patients. There were intestinal complications in short-term course of the patients but most of them presented to us in an elective basis and not with an advanced form of the disease.

The follow-up data does not allow us to extract safe conclusion on the subject although we didn't have any documented cases of fistulae.

Our comment on this is that, at least in our Department, the patients with IAAA were always treated from the most experienced surgeon, fact that guarantees, what in the literature also stated, vigilance and "clean" surgical approach and minimise the surgical trauma of the inflammatory region.

- ***Are there other specific long-term complications related to the inflammatory component?***

Long-term pseudoaneurysm formation after IAAA was well studied in the existing literature. The incidence rate ranges from 0.4% to 14.2%. In our population no pseudoaneurysms were detected in a maximal follow-up period of 81 months. Again, our data doesn't allow us, also in this point, to extract a safe conclusion on this matter and is one of our major limitations.

## 5.2. Limitations

The main limitation of our study is its retrospective nature. The surgeon made the diagnosis in 2 cases, due to lack of inflammation signs in the preoperative CT scan. It is difficult to set clear criteria for inflammatory aneurysms retrospectively. Although a histological confirmation was possible, only few cases in the study presented with periaortic inflammation while some others presented with a lack of aneurysm, which showed a classic glistering white appearance of an IAAA. Longer follow-up is preferable for the depiction of surgical outcome results, but it is not clear how these would be affected. Our study was severely limited by follow-up. We cannot therefore draw safety conclusions regarding the formation of periaortic fibrosis followed by the open repair.

# 6. Conclusion

In conclusion, open treatment of IAAA guarantees a regression of the inflammatory process, but surgical preparation can be demanding and can lead to local structural injuries, i.e. to the small intestine. Patients with IAAA are at increased prevalence for pseudo- or aneurysm formation at the anastomotic sites. An early diagnosis and surgical management of a non ruptured inflammatory aneurysm in an elective setting delivers the best results, in terms of early or even long-term postoperative outcomes. The need of a suprarenal clamping, with or without suprarenal repair should serve as an alarm to be vigilant in the early postoperative course as it is often accompanied with complicated course.

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