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Long-Term Outcomes of Open Repair of Inflammatory and Atherosclerotic Abdominal Aortic Aneurysms

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Abstract

Background: Abdominal aortic aneurysms (AAA) are a common vascular disease mostly affecting those over the age of 65 years. Open surgical repair (OSR) is considered the gold standard for the treatment of AAA, however long-term mortality and morbidity still remain high in patients with inflammatory AAA, when compared to atherosclerotic AAA. The aim of this study was to evaluate long-term outcomes of both inflammatory and atherosclerotic AAA after OSR.

Methods: Out of 837 aortic interventions, 149 patients were identified as having undergone open surgical repair for AAA between 2003 and 2013. Of the 149 patients, histopathological data was available for 92 patients with open AAA repair. Kaplan-Meier curves were analysed to evaluate probability of survival.

Results: Patients with inflammatory AAA were younger (70 years) by an average of 2 years compared to atherosclerotic AAA (72 years). Morbidity and length of intensive care stay were insignificantly different in both groups. Inflammatory AAA were associated with higher all cause survival rate (82%) compared to atherosclerotic AAA (68%) (P=0.008) after ten years.

Conclusion: There was no difference in clinical outcomes between both atherosclerotic AAA and inflammatory AAA, which is due to the technique used. IAAA were associated with lower mortality rates and improved all cause survival at ten years post open surgical repair.

Keywords: Aorta; Aneurysm; Inflammatory; Atherosclerotic; Open repair

Introduction

Abdominal aortic aneurysms (AAA) usually strike in patients with advanced atherosclerosis [1,2]. The exact cause is poorly understood. General risk factors that predispose AAA development are age, male gender, history of smoking, atherosclerosis, hypertension, chronic obstructive pulmonary disease (COPD), family history and genetic disorders [1,3,4]. The actual causative relationship between atherosclerosis and AAA formation is still undetermined however, a number of studies advocate that atherosclerosis promotes aneurysm formation through mechanical weakening of the aortic wall, with a loss of extra cellular matrix [2,5]. Conversely, other studies have suggested that there may not be a causal relationship between atherosclerosis and aneurysm formation [4]. Previous experimental models have shown that atherosclerosis was found after development of a AAA, suggesting that aneurysm formation preceded atherosclerotic lesion development [6,7].

Inflammatory abdominal aortic aneurysms (IAAA), another subset of AAA, occur in approximately 5 to 10 % of all AAA [8]. When compared with atherosclerotic AAA, IAAA demonstrate abnormalities in serum inflammatory markers [7,8]. IAAA are having a thick, firm, smooth wall that is shiny white in appearance, alongside an increase in wall vascularity with multiple small vessels traversing it. The adjacent dense fibrosis is marked and may involve adjoining tissues and structures [7,9,10-14].

It is well known that open repair is the gold standard for treatment of AAA. Although IAAA are less likely to rupture than atherosclerotic AAA (AAAA), surgical repair of aortic aneurysms is prudent for the treatment of aneurysms to prevent rupture [15-17]. While results of surgical repair have improved, the mortality and morbidity still remain higher for IAAA in comparison to AAAA [9,18].

The purpose of this study was to evaluate and compare long-term outcome between IAAA and AAAA post open surgical repair. The primary endpoint was long-term survival. Secondary endpoints were risk factors associated with both groups, postoperative intensive care unit stay, and postoperative complications.

Methods

This study was a retrospective review of a prospectively maintained vascular database, at a tertiary referral vascular centre, from 1st January 2001 to 1st July 2013. Institutional ethical committee approval was sought. The committee waivered the need for approval due to the retrospective nature of the study.

All patients admitted with a discharge or post-mortem diagnosis of AAA, with a histopathological report, operative details and computerized tomography (CT) scans during the study period were included in this study. Preoperative information collected for analysis included age, gender, and comorbidities (family history, hypertension, ischemic heart disease, atrial fibrillation, congestive cardiac failure, pulmonary disease, hyperlipidaemia hypercoagulability, diabetes mellitus and smoking; Table I). Comorbidity data, preoperative C - reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were

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Table I: Patient demographics and preoperative risk factors.

	Atherosclerotic AAA (n=80)	Inflammatory AAA (n=12)	*p* value
Gender (% M:F)	71:29:00	67:33:00	0.74*
Male n (%)	57 (71%)	8 (67%)	
Mean Age (yrs±SD)	72 (±34.2)	70 (±29.7)	0.83**
Family history	7	0	0.5*
Hypertension	54	9	0.03*
Ischemic heart disease	18	2	1.00*
Atrial fibrillation	6	0	1.00*
Congestive cardiac failure	5	0	1.00*
Pulmonary disease	15	2	1.00*
Hyperlipidemia	51	9	0.04*
Hypercoagulability	0	1	0.1*
Diabetes mellitus	8	0	0.59*
Smoking	50	9	0.52*

*p value is Chi-Square; **p value is independent sample t-test

collected to establish risk factors associated with both types of AAA, if any.

Post-operative data collected for analysis included histopathology, major adverse clinical events (MACE), and length of postoperative survival. Cardiac, pulmonary and cerebrovascular events, renal insufficiency, deep vein thrombosis, pulmonary embolism, coagulopathy and bowel ischemia were classified as MACE.

Categorization

Diagnosis of aneurysm type was made by collectively reviewing the preoperative CT scans, operative findings and histopathological data. The IAAA radiological spot diagnosis is defined as AAA with an inflammatory rim surrounding the aorta on a CT abdomen (Figure 1A, Figure 1B), [18]. IAAA were categorized intraoperatively by thickening of the adventitia due to marked inflammation with or without involvement of adjacent structures, fibrosis and adhesion. AAAA were defined by severe atherosclerosis i.e. atheroma resulting in weakening of the aortic wall on CT (Figure 2A, Figure 2B).

Surgical technique

A laparotomy and transperitoneal transaortic approach was used in all cases with mid-line incisions. Ligating the left gonadal vein and the descending lumbar tributary of the left renal vein allowed full mobilisation of left renal vein, facilitating exposure of the proximal aortic neck. Both common iliac arteries were exposed, the aorta clamped and sac opened at the left anterolateral aspect.

In case of IAAA, minimal dissection was performed to avoid the phlegm of tissue and enterotomies of the duodenum or jejunum. Dissection around the juxtarenal area was performed to allow the Crawford clamp to slide in vertically, with two multipurpose clamps placed at the level of common iliac artery bifurcation, which is a safer way to avoid iliac vein injury. The IAAA sac was opened at the left postromedial surface in order to utilize the aortic sac as a cushion retractor for the adhered bowel. In the case of AAAA, the left renal vein was divided close to the inferior vena cava, saving the adrenal and gonadal branches. The proximal aortic clamp was placed obliquely in an inter-renal position, preserving blood supply to the highest renal artery. No perfusion shunting was performed [16].

Tissue sampling

Tissue samples were collected from the anterior aneurysm wall by opening the aneurysm sac with a longitudinal ellipse-shaped full thickness biopsy including intraluminal thrombus (ILT) for histological analysis. Tissue samples were cut in 5 mm segments that were preserved in 4% formaldehyde solution, embedded in paraffin and cut in 4 µm thick sections. Sections were mounted on adhesive Starfrost slides and dried for 48 hours at 37°C, before light microscopy. Routine haematoxylin and eosin staining was performed for nuclei and cytoplasm exposure. Sections were also stained for macrophages, lymphocytes, smooth muscle cell, endothelial cells, elastin fibrin and collagen.

Statistical analysis

Statistical analysis was used to assess risk factors, and performed using Minitab 16 (Minitab Inc. PA, USA) and SPSS statistical software (SPSS version 20.0, SPSS Inc., IL, USA). Continuous variables were reported as the mean, the median and the range. Missing responses were treated as "no" for specific diseases. All-cause death was estimated using the Kaplan-Meier test. Linear logistic regression models were used for multivariate analysis. Analysis of covariance was used to analyse continuous variables. p values less than 0.05 were considered as statistically significant.

Results

Clinical characteristics

Out of 837 aortic interventions, 149 patients were identified who underwent open surgical repair of AAA between 2003 and 2013; of the 149 patients, histopathological data was available for 92 patients with either an infra-, juxta- or supra-renal aortic aneurysms. Both aneurysm types were of similar ages. The mean age of AAAA was 72 years, while IAAA had a mean age of 70 years (p=0.23). Men predominated in both aneurysm groups, although the proportion of women tended to be higher in the IAAA group (p=0.01).

Mean preoperative CRP and ESR were elevated in both the IAAA (39 mg/L & 31 mm/hr) and AAAA (29.18 mg/L & 23.20 mm/hr) groups. There were insignificant changes in the post-operative CRP and ESR levels (p=0.118). Blood cultures were negative in all patients with IAAAs. Mean maximum diameter was 70.1 mm and 80.0 mm for AAAA and IAAA, respectively (p=0.196).

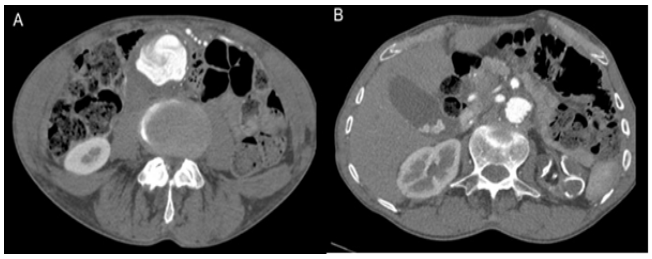


Figure 1A: Inflammatory AAA showing the phlegmon of tissue surround the aortic sac wall with no distinction from right psoas muscle, this finding was labelled as a contained leak of AAA, but open surgery demonstrated IAAA typical appearance; **Figure 1B:** Inflammatory AAA with involvement of adjacent structures and adhesions.

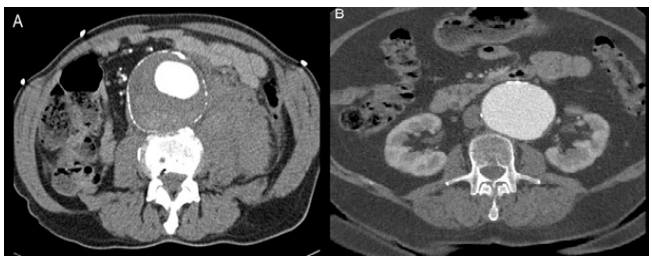


Figure 2A: CT of a 7.62 cm atherosclerotic AAA with thrombus; **Figure 2B:** CT scan of a 6 cm atherosclerotic AAA without thrombus with calcification in the anterior aortic sac wall.

Binary logistic regression

Binary logistic modelling was performed to assess any significant risk factors associated with aneurysm formation, and showed that hypertension and hyperlipidaemia were the only risk factors that were statistical significant in the development of AAAA, with *p* values of 0.03 and 0.04.

Histopathology

An independent observer performed histopathological examination, which revealed two definitive and distinct categories of AAA: inflammatory and atherosclerotic. Twenty-seven patients out of 80 (33.8%) with AAAA were classified with severe atherosclerotic plaque of the aortic wall containing cholesterol clefts, fibrosis as well as dystrophic calcification. Thirty-six patients out of 80 (45%) and 3 patients out of 12 (25%) with AAAA and IAAA, respectively, were classified with acute inflammation without thrombus. Inflammatory aggregates were composed of lymphocytes and macrophages. Seventeen patients out of 80 (21.3%) with AAAA were associated with degenerative atheroma with the presence of thrombus. Nine IAAA patients (75%) were classified with chronic inflammation of the media and adventitia, without underlying atherosclerotic plaque or atheroma.

Survival analysis

At 10 years the cumulative aneurysm related survival rate was 75 % and 76 % (Figure 3), and cumulative all cause survival rate was 82%, and 68% (Figure 4) for IAAA and AAAA, respectively (p= 0.008 Log rank). At 1 year, aneurysm related survival was 91% for patients with IAAA and 87% for patients with AAAA treated with open surgical repair. There were 14 deaths in the AAAA group and 3 deaths in the IAAA group. The main cause of death was a ruptured aneurysm, which was reported in four patients within the atherosclerotic AAA group. Cardiac arrest was the reported cause of death in two patients with AAAA and one patient in the IAAA group. One patient died of multiple organ failure due to septicaemia in the IAAA group. One patient died of cerebral infarction in the AAAA group. The cause of death was unknown for seven patients in AAAA group and one patient in the IAAA group.

Major adverse clinical events

Atherosclerotic AAA had an insignificant higher incidence of MACE postoperatively in comparison to IAAA. There was no statistical significance of MACE between both aneurysm groups (Table II).

Intensive care unit stay

The mean length of intensive care unit (ICU) stay was 5.8 days for atherosclerotic AAA, and 6 days for IAAA (t-test: p=0.884, 95% CI 1.713 to 2.086). Median postoperative follow-up was 42.8 months (range 0-120 months) and 37.7 months (range 0-108 months) for IAAA and atherosclerotic AAA, respectively.

Discussion

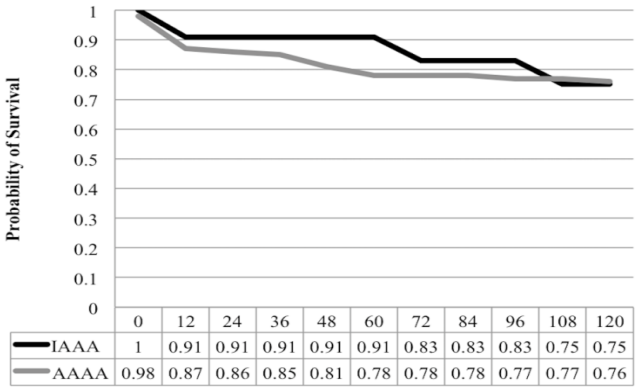
Between the 1st of January 2003 and 1st of July 2013, there were 837 aortic interventions, of which 149 patients had open repair, but only 92 patients had histopathological data available. This highlights the paradigm shift towards endovascular intervention, while histopathology may not be routinely carried out during any open surgical AAA repairs, even in those with a suspected inflammatory or atherosclerotic AAA [19].

Patients with AAAA treated with open repair have a better aneurysm related survival in comparison to those treated for IAAA (76% versus 75%; p=0.09), however, further analysis of all cause survival, showed that patients with AAAA faired worse than those IAAA (68% and 82%; p=0.008) post open surgical repair. Sasaki et al. reported that incidences of perioperative complications were similar in both AAAA and IAAA groups, and 5-year survival was 74.6% and 80.2% for AAAA and IAAA, respectively [10]. Five-year aneurysm related survival was 78% and 91%, and all cause survival was 77% and 89% for patients with AAAA and IAAA, respectively. There has been a shift in the treatment of AAAs to EVAR throughout the years, which is associated to lower morbidity and mortality rates. A meta-analysis carried out by Kakkos et al. reported the outcomes of open versus endovascular repair (EVAR) of IAAA [20,21]. They reported a 0% mortality rate after EVAR in comparison to 3.6 % after open surgical repair (p=1.00). EVAR was also associated with a lower morbidity rate of 11% compared to open surgical repair at 33 %.

There were in-significant differences in postoperative complications post open surgical repair between both AAAA and IAAA groups, indicating patients treated in high volume centres for abdominal aortic aneurysms have better outcomes post-operative. There were no reports of deep vein thrombus between two aneurysm entities; however patients with AAAA had higher rates of pulmonary complications post-operative in comparison to IAAA. Results also showed no significant difference in the length of post-operative ICU stay (p=0.884, 95% CI 1.713 to 2.086), corresponding to results reported previously [9,10].

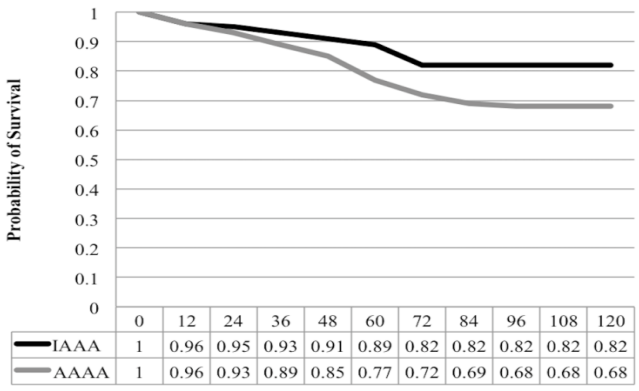
Risk factors

Patient presentation and medical history did not necessarily lead to a diagnosis of either AAAA or IAAA. Results did show that patients with hypertension or hyperlipidaemia were predisposed to the development of an AAAA. Diabetes did not have a significant effect on the development of IAAA or AAAA. This negative association between diabetes and both types of AAA was demonstrated in previous studies, and even diabetes mellitus may be protective against collagen



	0	12	24	36	48	60	72	84	96	108	120
IAAA	1	0.91	0.91	0.91	0.91	0.91	0.83	0.83	0.83	0.75	0.75
AAAA	0.98	0.87	0.86	0.85	0.81	0.78	0.78	0.78	0.77	0.77	0.76

Figure 3: Kaplan Meier curve showing 10-year aneurysm related survival.



	0	12	24	36	48	60	72	84	96	108	120
IAAA	1	0.96	0.95	0.93	0.91	0.89	0.82	0.82	0.82	0.82	0.82
AAAA	1	0.96	0.93	0.89	0.85	0.77	0.72	0.69	0.68	0.68	0.68

Figure 4: Kaplan Meier curve showing 10-year survival (p=0.008 (log rank).

Table II: Postoperative complications.

	Atherosclerotic AAA (n=80)	Inflammatory AAA (n=12)	*p*-value
Cardiac	21 (26.25%)	5 (41.66%)	NS
Pulmonary	13 (16.25%)	1 (8.33%)	NS
Renal insufficiency	18 (22.5%)	6 (50%)	NS
Cerebrovascular	1 (1.25%)	0	NS
Deep vein thrombosis	0	0	NS
Pulmonary Embolism	1 (1.25%)	0	NS
Coagulopathy	7 (8.75%)	0	NS
Bowel ischemia	1 (1.25%)	0	NS

degradation and aneurysm expansion [1,17]. Forsdahl et al. associated high serum total cholesterol and low HDL (high-density lipoprotein) cholesterol as significant risk factors for the development of AAAA [3].

Family history of AAA was insignificant in determining development of any particular type of AAA. There was also no association between smoking and family history and the prediction of either AAAA or IAAA. These findings are possibly due to small cohort size, and modest significance. A number of previous studies have shown that both smoking and family histories are major risk factors in the development of AAA. Kent et al. [4,17] reported findings in which well-known risk factors including male gender, age, family history, and cardiovascular disease were reiterated in AAA development. There was no difference in maximum diameter between both groups, 70.1 mm for AAAA versus 80.0 mm for IAAA.

Patient blood cultures were negative for infection. There was no evidence to support the theory that Endovascular AAA are instigated by infection. This leads us to believe that IAAA are a genetic abnormality, which may be determined via cell mapping. Both Ehrenfeld et al. and Rasmussen et al. mapped HLA-DR B1 locus and the alleles B1*15 and B1*0404 in patients with IAAA. Results demonstrated a genetic predisposition to the development of IAAA [22,23].

Conclusion

In spite of the complexity in repair of IAAA, results do show an encouraging long-term survival rate coupled with low postoperative complications for patients with IAAA and AAAA, treated by open surgical repair in high volume centres. IAAA could not be linked directly to any definitive risk factors, while hypertension and hyperlipidaemia were associated with AAAA. Furthermore, there was no link found between infection and the development of IAAA. Further work is required to determine definitive genetic risk factors. Analysis of larger cohorts of patients is also required to identify the exact cause of these two aortic diseases.

Conflict of interest

None of the authors have any financial arrangement or other relationship that could be construed as a conflict of interest.

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