

Gender based differences in Abdominal Aortic Aneurysm (AAA) rupture : A retrospective study

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Abstract

Introduction: Annually, 5% of sudden deaths are due to Abdominal Aortic Aneurysm (AAA) rupture. AAA ruptures have worse outcomes in females than males and occur at a smaller size in females. USPSTF recommends a one-time ultrasound screening for males aged 65-75 years who ever smoked. There is insufficient evidence to screen females aged 65-75 years who ever smoked in spite of the available evidence. The objective of this study is to compare the characters, mortality and morbidity of ruptured AAAs in females and males. **Methods:** This is a retrospective review of 117 patients from two teaching institutions over a period of six years. A total of 39 parameters were compared between males and females including demographic characters, co-morbidities like hypertension, dyslipidemia, diabetes mellitus, cardiovascular diseases; previous history of AAA; medications, characters of aneurysm, type of surgery and its outcome; post-operative complications and long term survival. **Results:** The incidence of AAA rupture was higher in males (68%) than in females (32%). Females had a later age of death from AAA rupture. There was a significant difference in the size of AAA rupture between females (mean=7.4 cm) and males (mean=8.2 cm); $p = 0.04$. The probability to undergo surgery for ruptured AAA was significantly lower for females as compared to males ($p=0.03$). Females had higher overall mortality ($p=0.001$) and post-operative mortality after surgical repair ($p=0.02$) from AAA. Female gender was an independent predictor of higher length of ICU stay, incidence of postoperative complications, use of vasopressors and use of ventilator. **Conclusion:** Using a similar threshold of size of AAA for elective surgery for both males and females might not be appropriate. AAA screening might be warranted for high risk females owing to the higher morbidity and mortality.

What is already known about the topic?

AAA rupture is more common in males than females and current guidelines from USPSTF recommend screening only for males who have ever smoked and are more than 65 year old. There is no enough evidence to suggest routine screening for females.

What does this article add?

This study is a multi-center retrospective cohort study proving that female patients admitted with AAA rupture had a higher overall mortality and post-operative mortality than males, though the size of aneurysm is smaller in females at the time of rupture. They had a longer length of ICU stay, higher incidence of postoperative complications, use of vasopressors and ventilator. Routine screening might be warranted for females considering the worse outcomes.

Introduction :

Abdominal aortic aneurysms (AAA) affect males to females at the ratio of 4:1 but females are known to have worse outcomes.¹ Available literature suggests that ruptured aneurysms occur in females more frequently and

also at smaller diameters compared to males.¹ The prevalence of AAAs with diameter larger than 2.9 cm in males ranges from 1.9 to 18.5% which is much higher than females (0 to 4.2%).² Females with AAAs usually present late, grow rapidly than males, and also have a four-time higher risk of rupture at a diameter 5.0-5.9 cm than males.³ The average annual risk of rupture of AAA with [?] 6 cm is 14.1% in males and 22.3% in females. The mortality of AAA rupture is about 50%.⁴

In 2017, total deaths due to AAA were about 9928 which was up from 2600 in 2013.^{5,6} Surgical intervention either by endo-vascular repair (EVAR) or open repair is offered for aneurysms [?]5.5cm in both males and females. Rupture of AAA is a medical emergency and is associated with a very high pre-hospitalization mortality.⁷ Some reports also suggest that females who received EVAR or open repair were more likely to have a higher postoperative mortality than males. Differences in diagnosis and treatment rates or inherent anatomical dissimilarities and lack of screening for females seem to be the reasons for higher mortality rate in females.⁵

Ultrasound has 90% sensitivity and 100% specificity to diagnose AAA and has been the standard screening tool for AAA. The 2019 United States Preventive Services Task Force (USPSTF) guidelines recommend one-time screening with ultrasonography in males aged 65-75 years who had ever smoked. When it comes to screening guidelines in females, USPSTF concludes that there is insufficient evidence to screen females aged 65-75 years who had ever smoked.⁸ These recommendations have been consistent for many years even after multiple studies suggesting higher mortality in females as illustrated above. With this study, we attempted to specifically study the characters of ruptured AAAs in an attempt to study the outcomes in females as compared to males.

Methods:

Objectives :

The objective of the study was to compare the outcomes of ruptured AAAs between males and females. We also compared the characters of the patients presenting with the ruptured AAAs, the characteristics of the aneurysms itself and post-operative course between males and females.

Sample:

The study was nested as a multi-center retrospective study and the sample was obtained from two community-based sister hospitals located in a metro city in Western New York. Over a period of 6 years, all the patient charts admitted with a diagnosis of Abdominal Aortic Aneurysm in the two hospitals were reviewed. The data was collected through a retrospective review of paper charts and electronic medical records. Approval was obtained from the Institution's Review Board (IRB) of the hospital system.

The inclusion criteria for the study were the patients who presented with a rupture of the aneurysm. The patients who were admitted for elective repair, endo-vascular leak or endo-vascular repair were excluded.

Variables:

Demographic characters like age and gender, patient's comorbidities (hypertension, dyslipidemia, diabetes mellitus, cardiovascular diseases), previous history of AAA (size at previous diagnosis, previous attempt to repair and history of rupture), current use of cardio-protective medications (statins, aspirin, clopidogrel and beta-blockers), the characters of aneurysm (size, involvement of iliac arteries) were noted and compared between males and females. They were labeled as smokers if they smoked at least 100 cigarettes in their lifetime. The hospital course including length of stay in ICU and hospital, incidence and type of surgery, immediate post-operative complications like ventilator dependent respiratory failure, hypovolemic shock, acute renal failure, myocardial infarction were reviewed. The immediate post-operative mortality and overall mortality with or without surgery were noted. The long-term survival of the discharged patients was identified using the SSN database. Patients discharged alive were followed for a period of 2 years. Date of death was procured from <https://ladmf.ntis.gov> (SSN database).

A total of 39 parameters were compared between males and females. The patient data was kept confidential and the only primary investigators had access to the data through a personal access key.

Statistical analysis:

SPSS version 26 was used for analysis of the study. We analyzed between-group differences on demographic and baseline characteristics by using chi-square tests for categorical variables and t-tests for continuous variables. The predictors of mortality were projected based on a logistic regression model, adjusting for age, hypertension, major comorbidities, smoking status and use of preventive medications. We took the p-value as less than 0.05 for statistical significance. Kaplan-Meier survival curve analysis was used to analyze the long-term survival of these patients (2-year mortality).

Results:

A total of 1538 patients were hospitalized to either hospital with a diagnosis of AAA. About 92% of the sample (1417 patients) were excluded and 117 patients were included for final analysis (figure 1) as the sample was restricted to ruptured aneurysms only. Out of the 117 patients, 79 were male (67.6%) and 38 were female patients (32.4%) admitted with a AAA rupture.

Table 1 demonstrates the demographic characters of the sample. 100% of the sample were Caucasian. Obesity was more prevalent in the male patients with a significant statistical difference ($p=0.02$) but there was no difference in the distribution of tobacco use, hypertension, other major cardiovascular co-morbidities or use of any cardio-protective medications.

Gender was identified as an independent predictor of age of rupture after adjusting the effects of hypertension, co-morbidities, smoking, use of medications and previous history of aneurysms ($p=0.005$). The mean age of rupture in males was 75.8 years (S.D.=10) and in females, it was 82.4 years (S.D.=8.6). We evaluated the age specific incidence of the aneurysm ruptures and it was noted that 65.8% of the male patients were under 85 years age and 65.7% of the female patients were over 85 years old (figure 2).

Table 2 describes the characteristics of the ruptured aneurysms in male and female patients. There was no difference in the pattern of the location of the rupture, whether they are supra-renal, infra-renal or both, whether they are located on the left, right or both sides. There were 75 males (94.9%) and 34 females (89.5%) with an infra-renal aneurysm. However, there was a significant difference in the size of the aneurysm rupture between the two groups. Female patients tend to have a significantly smaller size of aneurysm at the time of rupture (mean=7.46 cm, S.D.=2.09) as compared to the males (mean=8.23 cm, S.D. 1.84), $p=0.04$. About 58% of the male patients had a known previous diagnosis of AAA and 29% of them had their aneurysms repaired on an elective basis. In the female patients, AAA was a known diagnosis in only 50% of the cases and surgical repair was performed only in 10.5% of the cases. At their previous diagnosis, the mean size of the aneurysm was significantly smaller in males (4.0 cm, S.D. 3.3), as compared to the females (5.0 cm, S.D. 2.6), $p=0.03$. The AAA was found in either routine screening or as an incidental finding.

Table 3 explains the characteristics describing hospital course and mortality of the ruptured AAAs and the post-operative complications. The overall mortality (irrespective of surgery or not) was significantly higher in women (68.4%) as compared to men (31.6%), $p<0.001$. The post-operative mortality was also higher in females which is 50% versus 21.2% in males, $p=0.05$. The overall mortality and post-operative mortality were adjusted for tobacco use, age, major co-morbidities and use of cardio-protective medications using a logistic regression model.

Out of the 79 male patients in the sample, 74 of them (93.7%) had an operative management of the ruptured AAA as compared to only 24 of the 38 females (63.2%), $p=0.03$. Endo-vascular repair of the ruptured AAA was performed more frequently in both males and females (72.2% vs 42.1%) than open repair, $p<0.01$. The post-operative complications (ventilator dependent respiratory failure, requirement of vasopressors and other unexpected complications like blood loss, renal failure etc.) tend to happen more frequently in females as compared to males at a statistically significant level ($p<0.001$) even when adjusted for age, comorbidities,

tobacco use and use of medications. The length of stay in the intensive care unit (ICU) was significantly longer in females as compared to males (5.5 days versus 4.1 days) using the same model, $p=0.02$.

Figure 3 shows the long-term survival of the patients discharged alive after the AAA repair. The available sample for this analysis was 27 patients; out of them 21 were male and 6 were female patients. Males survived an average of 11.0 months (S.D.=2.2) as compared to 9.3 months (S.D.=2.9) in females, though not at a significant level (p -value=0.41). The sample available for this analysis was only 27 patients, 21 males and 6 females.

Discussion :

Cardiovascular disease is the number one cause of death for both men and women in the United States.³ Traditionally, all the cardiovascular diseases were considered as “men’s diseases.” Our study concludes that there was a significant effect of gender on the age of death from AAA rupture and there was a significant difference in the size of AAA rupture between males and females. Women tend to present at an advanced age and have a smaller size of the ruptured aneurysm though the overall incidence of AAA rupture was higher in males. The probability of undergoing surgery for ruptured AAA was significantly lower for women. Female gender was also identified as an independent predictor of longer length of ICU stay, higher incidence of postoperative complications, more frequent use of vasopressors and ventilators.

There are a few previous studies which showed the disparities of risks and outcomes of AAAs in males and females and our study adds to the literature that even ruptured aneurysms tend to fare worse in females. Females are usually protected from the development of AAAs, but behave aggressively with faster growth, frequency of rupture, and higher mortality rate.⁵

100% of the patients included in our study were Caucasian. AAAs are commonly seen in Caucasian population and few studies have reported differences in the development of AAA in Caucasians and African-American populations.⁹ Out of 117 patients included in the study, 92 (78.6%) of them have at least smoked 100 cigarettes in their lifetime. Smoking and genetics play a key role in the development of AAA.¹⁰ Among all the cardiovascular diseases, AAA has the strongest association with smoking, precisely current smoking. In a study by Ulug et al on the prevalence of screening-detected AAAs in women, it was found that smoking had a greater impact on prevalence of AAA in females than in males.¹¹ As seen in our study, there is also a strong correlation between obesity with high waist circumference and AAA. This is probably due to the release of adipokines and obesity induced aortic inflammation leading to weakening of the vessel and further aneurysmal formation.¹² We wanted to neutralize the effect of current use of medications on AAA outcomes as there is evidence suggesting that use of cardio-protective medications like aspirin,¹³ clopidogrel,¹⁴ statins¹⁵ and beta blockers¹⁶ have protective effects against AAA. 93% of our sample presented with infrarenal aneurysm which is consistent with the data that 85% of the AAAs are infrarenal.¹⁷ Though estrogen has a protective effect in the development of AAA in females, hormonal replacement therapy increases the risk of AAA development after menopause¹⁸. Overall, the development of AAA, its progression and outcome are a combination of genetic predispositions and environmental factors¹⁰.

In our sample, mean diameter at the time of rupture in males is 8.23 cm with (SD 1.84) while that of females is 7.46 cm (SD 2.09). Few authors believe that discrepancy in geometric and biomechanical properties are the reasons for faster growth of AAA and increased rate of rupture than that of males in spite of low prevalence. Females also exhibit higher proportion of aneurysms with high peak wall stress.¹⁹ In males, the average infrarenal diameter of aorta at the age of 65 years or more is 2.02 cm, whereas in females it is 1.75cm.¹¹ The intuitive thought for smaller diameters of AAA in females when compared to males is that females inherently have smaller aortas.¹⁹ These innate differences could call for gender specific guidelines in screening and elective surgical repair of AAAs in females.

AAA is usually asymptomatic and diagnosis is usually made as an incidental finding on imaging for other medical complaints.²⁰ 65 patients (55.5%) in our sample had the previous diagnosis of AAA who were diagnosed as part of routine screening or as an incidental finding on imaging for other medical illnesses. Few studies suggest that non-specific inflammatory markers like D-dimer levels are elevated in patients with

AAA,²¹ but there are no other diagnostic and prognostic markers for the diagnosis of AAA²⁰ and there is also no drug therapy to limit the progression of AAA.²² The only effective way of diagnosis and follow up of a AAA is abdominal ultrasound. No repeat ultrasound is recommended if the AAA is less than 3 cm but if the initial size is 3 to 4 cm, an ultrasound is recommended every 2-3 years and for a AAA sized 4 to 5.5 cm, ultrasound is recommended every 6 months to one year.²⁰

50% of the females in our sample who had a previous diagnosis of AAA had a mean diameter of 5 cm. Considering the worse outcomes in females with higher mortality and delayed age at presentation, a threshold of 5.5 cm might be too high for females though this has been the recommended size of elective repair in males.²³ The current indications for elective AAA repair include diameter of 5.5 cm for a patient with symptomatic AAA (irrespective of the size) and rapid expansion like 1 cm in one year irrespective of the size. Though elective AAA repair is associated with decreased morbidity and mortality, overall operative mortality and long-term survival mainly depends on the patient's age and other risk factors. Hence, the decision to perform an elective AAA repair must weigh the patient's risk of rupture depending on AAA diameter against the individual risk of surgery.²⁴ Endo-vascular repair (72.2% and 42.1%) for ruptured AAA is performed more frequently than open repair (21.5% and 21.1%) in both males and females.²⁵ In spite of advanced ICU and techniques for repair, mortality still remains high following repair of ruptured AAA.⁵ We adjusted our sample for age, cardio-protective medications and comorbidities and still found that the post-operative complications, overall mortality and morbidity remain higher in females.

Post-operative complications tend to happen more commonly in females as compared to males at a statistically significant level ($p < 0.0001$) when adjusted for age, comorbidities, tobacco use and use of medications. Hence, very close post-procedural surveillance and prompt correction of complications are required to avoid fatal outcomes.²⁶ 24 out of 38 female patients had undergone surgical repair, either EVAR or open repair. Of these, 18 (75%) patients required ventilator, 17 (70.8%) required vasopressors and 10 (58.3%) had other unexpected postoperative complications like blood loss, renal failure, etc. Females (12 out of 24, 50%) who received EVAR or open repair have postoperative complications and are more likely to die than males. Differences in diagnosis and treatment rates or inherent anatomical dissimilarities and lack of screening for females are the reasons for high mortality rate in females after EVAR or open repair.⁵ Hence, there is a need to focus on improving ruptured AAA outcomes in females with a repair at a smaller size and earlier age.

Limitations:

Our study is prospective and single centered. It lacks external validity required to support widespread changes in practice. We compared smoking, hypertension and other medications but we missed comparing covariates like family history and age of menopause in the retrospective review. Our findings could be considered hypothesis generating, perhaps serving as the basis for a larger study.

Conclusion:

With the findings from our study, we want to emphasize the importance of screening for AAAs in high risk women and the importance of formulating "sex-specific" management guidelines of AAA. Routine screening in men of age 65 years and over has significantly reduced the mortality from ruptured AAA. Nearly one-third of the patients who present with ruptured AAA are women, and they do have a very high mortality contributing to a large proportion of deaths from AAA.¹¹ In 2017, USPSTF considered a revised draft plan for AAA screening including asymptomatic males and females. If this plan is implemented, it is possible that there may be reduction in mortality disparity between males and females with ruptured AAA.⁵ Because of the fact that there is no effective treatment other than risk factor modification, screening in females and considering elective surgery at a smaller size ($< 5.5\text{cm}$) may reduce mortality in females.

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