Gender Influence on Abdominal Aortic Aneurysm Surgery in a Caribbean Population

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Abstract

Female patients with abdominal aortic aneurysms (AAAs) are usually less common and older than their male counterparts. We report on AAA disease in a Caribbean nation with respect to gender and review their outcomes relative to the male population. Data were collected prospectively and analyzed retrospectively for patients with AAAs who underwent surgery from 2001 to 2018. Sixty patients were diagnosed with AAA with 44 going on to have surgical repair of which 35 were males, aged 61 to 89 (mean age 73.4 years). Nine women ages 44 to 74 years (mean age 60.8 years) had surgical intervention, three being between 40 and 49 years. The size of aneurysms in these patients ranged from 4.3 to 11.0 cm in diameter (average 6.95 cm), female patients having an average diameter of 6.7 cm. Of the 44 patients, 43 underwent open and one endovascular repair. Thirty-three were elective cases and 11 were ruptured with 32 aorto-aortic and 13 aorto-iliac repairs. There were nine fatalities, three elective and six ruptured, with only one being female. Women had similar outcomes to men in all age groups with young patients having good results. Female AAA patients are usually older, undergo less surgical procedures especially if endovascular, and have worse outcomes than their male counterparts. Our study showed that the females were younger but had similar outcomes to the male patients. The female Caribbean patients may present at much younger ages than in continental populations and this may be due to genetic, ethnic, or lifestyle factors.

Keywords
- abdominal aortic aneurysm
- female-gender
- young
- Caribbean

This study is a review of abdominal aortic aneurysms (AAAs) seen at the San Fernando Hospitals on the Caribbean islands of Trinidad and Tobago from 2000 to 2018. The incidence of AAA disease in the English-speaking Caribbean has not been previously documented especially with respect to gender and ethnicity. The population of these islands is comprised of people of mainly Afro-Caribbean and Asian East Indian descent with the remainder made up of Chinese, Middle-East Arabs (Syrian and Lebanese), Caucasians, and Hispanics. Most of this AAA population was of Asian East Indian origin with Afro-Caribbeans making up one-third of the operative AAA population.

The annual incidence of new AAAs is approximately 0.4 to 0.67% in Western populations.[1] In one study, males 65 to 74 had an incidence of 55 per 100,000 rising to 112 per 100,000 person-years for ages 75 to 85 years.[2] Women were found to have a much lower incidence of AAAs and were, on average, older than men.[3] Women have similar risk factors as men but

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in age- and smoking-adjusted models, Africa-descent race was more strongly associated with AAA in women than men.[3]

Women have been shown to experience worse outcomes in both elective and ruptured AAAs in both endovascular and open repair.[4] There is an almost double risk for mortality in women due to the threshold of 5.2 cm in elective open repair suggesting open repair should have a higher limit of 5.5 cm.[5] This study centers on the relation of AAAs and gender within the context of patients presenting for surgical intervention.

Materials

Patient Population

The population of these islands is comprised of people of mainly Afro-Caribbean and Asian East Indian descent with the remainder made up of Chinese, Middle-East Arabs (Syrian and Lebanese), Caucasians, and Hispanics. Most of this AAA population was of Asian East Indian origin with Afro-Caribbeans making up one-third of the operative AAA population.

The study population was derived using convenience sampling. This AAA population includes all patients who were referred with aneurysms in the catchment population (500,000–600,000 patients) irrespective of gender, age, and American Society of Anesthesiologists status. All patients had imaging and presented for consultation.

The exclusion criteria included: Patients with aneurysm size < 5.5 cm in males and < 5.0 cm in females, elderly patients who had severe cardiac disease (myocardial infarct within 3 months), uncorrected arrhythmias, frail or infirm patients, and mainly, people who did not want surgery (the majority). Age was not used as an exclusion criterion. The inclusion criteria were size of aneurysm, symptomatic or ruptured aneurysm, and fitness and consent to surgery. Some patients who may have had aneurysms which did not meet the stipulated size but who were either symptomatic or whose aneurysms were tender on palpation, were also included for surgical intervention.

Patient Demographics

Demographic data were collected prospectively for patients with AAAs who underwent surgery between 2001 and 2018 which was then retrospectively analyzed. AAAs who underwent surgery from 2001 to 2018 were also analyzed retrospectively. There were 60 patients with AAAs who were referred for consultation. There were 44 patients, 35 males with age range of 61 to 89 (median = 73.4) years and 9 females with a median age of 60.8 years who required surgery either due to the size (male: diameter AAA $\geq$ 5.5 cm, females: 5.0 cm) or due to symptomatic or ruptured status. Of the 9 females only 2 were above the age of 68 years and 5 were 65 years and less.

In the study were three young female patients (ages 44, 47, and 48 years), which was quite unusual since all other patients were above 60 years of age. None of these patients had any family history of aneurysmal disease, nor were they positive for connective tissue disorders. None had a history of Ehlers-Danlos or Marfan's syndrome although a 44-year-old patient had a Marfanoid habitus. She is currently undergoing clinical investigation and genetic testing. All three were considered for genetic testing but costs proved prohibitive at that time being only available in the private sector. Each will be tested once available since all young patients with AAA should be referred for genetic testing and mosaic screening.

Imaging, Surgical Approach

Two imaging modalities were used to diagnose patients either a computerized tomography (CT) or ultrasound. All patients had CT scans prior to surgical intervention but a few had an ultrasound scan (USS) in addition to CT. The average size of aneurysms for male patients ranged from 4.0 to 13.2 cm (mean 6.95 cm) and for female patients ranged from 5.0 to 10.0 cm (mean of 6.7 cm). Thirty-three (75%) cases were initially diagnosed by USS but all patients had CT scans prior to surgical intervention.

Endovascular aneurysm repair (EVAR) is not currently widely available at the public hospitals because of the cost. Most patients (43) underwent open repair and one endovascular surgery. Several patients in the cohort had multiple contributory factors. Twenty-five (56.8%) patients were hypertensive, 20 (45.5%) were current or recent ex-smokers, 9 (20.5%) had ischemic heart disease, and 9 (20.5%) suffered from hyperlipidemias (►**Table 1**).

Three male patients with small aneurysms (4.2–4.5 cm) underwent surgical intervention. Two presented with very mild pain and were listed as asymptomatic but aneurysms were tender on palpation and underwent elective repair. The other (4.5 cm aneurysm) was symptomatic.

Results

There were 35 male and 9 female patients who underwent surgical intervention, 43 were open procedures (►**Fig. 1**) and one EVAR. When divided into groups, male and female unruptured and ruptured, the numbers were (►**Tables 1** and **2**) 26 versus 9 and 7 versus 2, respectively, when the division between the ethnic groups was made, and then grouped into mean age according racial groups and gender. When considering the aneurysm status at presentation, the unruptured-to-ruptured ratio was 33:11 or 3.0, meaning one-third of all AAAs in the series were ruptured. This ratio in the male population (unruptured: ruptured) was 2.9 and 3.5 in the female subgroup. In a comparison between male and female subgroups, unruptured was 3.7 and ruptured was 4.5 (►**Fig. 2**). The overall ratio of male to female patients was (35/9) 3.88.

Percentage of the males who were unruptured was 74% and in females it was 78%, but overall the largest of these subgroups was unruptured (►**Fig. 3**).

►**Table 2** shows that 20% of patients were female and the largest subset of patients were the male elective (or unruptured) group. The mean age of the female subset was far lower (60.9 years) than the male population (73.4 years).

►**Table 3** shows the number, causes, and timing of deaths from AAA surgery in our island community. Nine of the 44

Table 1 Abdominal aortic aneurysms: distribution by age, gender, race, risk factors, presentation, status, aneurysm size, anatomical location, time to surgery, and outcomes

No.	Age	Gender	Race	↑ Lipids	↑BP	IHD	Smoker	Presentation	Status	Size	Anatomy	Time to surgery	Outcome
1	73	M	A		Yes	Yes		Asymptomatic	Elective	7.5 cm	Aorto-iliac	2 weeks	Myocardial infarct 5 days p/op
2	82	M	A	Yes	Yes			Asymptomatic	Elective	7.5 cm	Aorto-iliac	2 weeks	Died age 92 age-related illness
3	67	M	EI	Yes	Yes	Yes		Pulsatile mass	Elective	10.0 cm	Aorto- iliac	2 weeks	Died from renal failure p/op
4	66	F	EI		Yes			Abd pain	Elective	6.0 cm	Aortic	2 weeks	Fatal brain tumor 5 years p/op
5	83	M	A					Asymptomatic	Elective	6.0 cm	Aorto-iliac	2 weeks	Died of CVA age 91
6	74	F	A		Yes		Yes	Asymptomatic	Elective	9.0 cm	Aortic	2 weeks	Died of CVA age 81
7	84	M	EI	Yes		Yes	Yes	Asymptomatic	Elective	4.2 cm	Aortic	2 weeks	Died age-related illness
8	74	M	A		Yes		Yes	Abd pain	Elective	5.0 cm	Aortic	2 weeks	Alive 16 years p/op
9	69	M	EI		Yes		Yes	Pulsatile mass	Elective	10.7 cm	Aortic	2 weeks	Alive 16 years p/op
10	63	F	Hisp			Yes	Yes	Asymptomatic	Elective	5.8 cm	Aortic	2 weeks	Fatal lung malignancy
11	72	M	EI			Yes	Yes	Asymptomatic	Elective	4.5 cm	Aortic	24 weeks	Fatal arrhythmias post/op
12	80	M	EI					Asymptomatic	Elective	6.5 cm	Aortic	2 weeks	Lost to follow-up
13	79	M	EI					Abd pain	Elective	5.0 cm	Aortic	2 weeks	Lost to follow-up
14	76	M	EI		Yes		Yes	Asymptomatic	Elective	7.1 cm	Aorto-iliac	2 weeks	Alive 15 years p/op
15	68	F	EI		Yes			Asymptomatic	Elective	10.0 cm	Aortic	4 weeks	Alive 15 years p/op
16	76	M	A		Yes			Asymptomatic	Elective	7.5 cm	Aorto-iliac	2 weeks	Died of age-related illness
17	71	M	EI	Yes	Yes	Yes	Yes	Abd pain	Elective	8.3 cm	Aortic	2 weeks	Alive 14 years p/op
18	70	M	A		Yes			Abd pain	Elective	7.0 cm	Aortic	2 weeks	Alive 14 years p/op
19	70	M	Mx				Yes	Abd pain	Elective	6.0 cm	Aortic	2 weeks	Alive 12 years p/op
20	69	M	EI	Yes		Yes	Yes	Pulsatile mass	Elective	6.0 cm	Aortic	2 weeks	Alive 12 years p/op
21	69	M	EI		Yes		Yes	Flank pain	Rupture	11.0 cm	Aortic	Emergent	Alive 11 years post/op
22	73	M	EI		Yes			Abd pain	Elective	6.8 cm	Aortic	1 week	Died from age-related illness
23	89	M	EI		Yes		Yes	Abd pain	Rupture	6.5 cm	Aorto-iliac	Emergent	Died 3 months postsurgery-unrelated
24	75	M	EI					Hypotension	Rupture	7.0 cm	Aorto-iliac	Emergent	Died on table, repair completed
25	71	M	Cau					Asymptomatic	Elective	13.0 cm	Aorto-iliac	2 weeks	Alive 10 years p/op
26	73	M	EI	Yes	Yes		Yes	Abd pain	Rupture	3.0 cm	Aortic	Emergent	Alive 10 years p/op
27	67	M	A	Yes			Yes	Abd pain	Rupture	8.5 cm	Aortic	Emergent	

Table 1 (*Continued*)

No.	Age	Gender	Race	↑ Lipids	↑BP	IHD	Smoker	Presentation	Status	Size	Anatomy	Time to surgery	Outcome
													Died 45 days p/op, ischemic bowel, ? hernia
28	75	M	A		Yes			Abd pain	Elective	4.5 cm	Aortic	4 weeks	Alive 9 years p/op
29	82	M	Cau		Yes	Yes	Yes	Asymptomatic	Elective	6.0 cm	Aortic	2 weeks	Alive 9 years p/op
30	74	M	EI					Abd pain	Elective	6.0 cm	Aortic	1 weeks	Died of age-related illness
31	65	F	Mx					Asymptomatic	Elective	6.0 cm	Aortic	4 weeks	Alive 9 years p/op
32	48	F	A			Yes	Yes	Abd pain + Fibroid	Rupture	5.0 cm	Aorto-iliac	Emergent	Alive 8 years p/op
33	61	M	EI	Yes	Yes	Yes	Yes	Asymptomatic	Elective	6.0 cm	Aortic	2 weeks	Alive 7 years p/op
34	83	M	A	Yes	Yes			Syncope	Rupture	8.5 cm	Aortic	Emergent	Died day 4 p/op
35	73	F	EI	Yes		Yes	Ex	Bk pain/ hypotension	Rupture	6.0 cm	Aortic	Emergent	Died day 3 p/op
36	44	F	A		Yes		Yes	Umbilical hernia	Symptomatic	6.0 cm	Aortic	1 week	Alive 6 years p/op
37	72	M	A		Yes			Asymptomatic	Elective	7.5 cm	Aortic	2 weeks	Alive 6 years p/op
38	47	F	A		Yes			Abd pain	Elective	6.5 cm	Aorto-iliac	2 weeks	Alive-isolated dissection-for aortic repair
39	68	M	EI		Yes			Hypotension	Rupture	6.0 cm	Aortic	Emergent	Died on table, repair completed
40	67	M	EI		Yes		Ex	Asymptomatic	Symptomatic	7.0 cm	Aorto-iliac	2 weeks	Alive 5 years p/op
41	68	M	EI		Yes			Hypotension	Rupture	6.0 cm	Aorto-iliac	Emergent	Myocardial infarct day 3 p/op
42	69	M	EI		Yes		Yes	Asymptomatic	Elective	7.6 cm	Aortic	4 weeks	Fatal Aorto-enteric fistula 2 years p/op
43	75	M	EI		Yes		Yes	Hypotension	Rupture	7.5 cm	Aortic	Emergent	Myocardial infarct day 3 p/op
44	65	M	EI	Yes	Yes			Asymptomatic	EVAR	7.5 cm	Aortic	2 weeks	Alive, CT scans yearly

Abbreviations: ↑BP, hypertension; ↑Lipids, hyperlipidemia; A, Afro-Caribbean; Abd, abdominal; Bk, back; Cau, Caucasian; CT, computerized tomography; CVA, cerebrovascular accident; EI, Asian East Indian; EVAR, endovascular aneurysm repair; F, female; Hisp, Hispanic; IHD, ischemic heart disease; M, male; Mx, mixed race; p/op, postoperative.
Note: Yellow highlight: three patients below the age of 50 years.

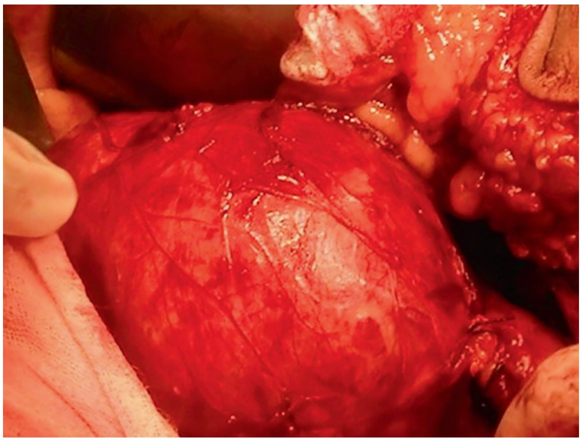

Fig. 1 Infrarenal abdominal aortic aneurysm.

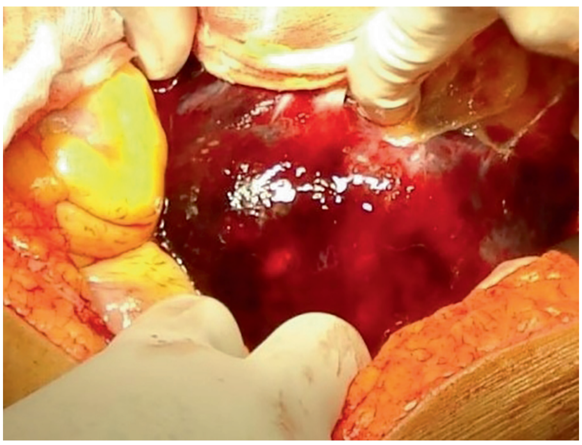

Fig. 2 Contained retroperitoneal rupture of an abdominal aortic aneurysm.

Fig. 3 Gray Turner's sign: usually seen in ruptured abdominal aortic aneurysms (AAAs), here after elective aneurysm repair.

Table 2 Ethnicity, status by gender and age by population subsets

Ethnicity	No. of patients	Percentage
Asian East Indian	25	57
Afro-Caribbean	14	32
Mixed race	2	5
Caucasian	2	5
Hispanic	1	2
Total	44	100
Gender	**No. of patients**	**Percentage**
Male Unruptured	26	59
Male ruptured	9	20.50
Female unruptured	7	16
Female ruptured	2	4.50
Total	44	100
Population subsets	**No. of patients**	**Mean age**
Male	35	73.4
Female	9	60.9
Asian East Indian	25	72
Afro-Caribbean	14	69.1
Other	5	70.2
Male Asian East Indian	22	72.4
Male Afro-Caribbean	10	75.5
Female Asian East Indian	3	69
Female Afro-Caribbean	4	53.3

Table 3 Survival and death analyses

Survival, deaths	No. of patients	Percentage	Cumulative percentage
Alive	30	68.20	68.20
Myocardial infarct	5	11.40	79.60
Hypotension	2	4.50	84.10
Renal failure	1	2.30	86.40
Arrhythmia	1	2.30	88.70
Tumors	2	4.50	93.20
Age-related	2	4.50	97.70
Aorto–enteric fistula	1	2.30	100
Total	44	100	100

deaths (9/44, 21%) occurred during, immediately after, or within the first week of surgery (early deaths), with postoperative myocardial infarcts comprising the majority of deaths (5/9, 56%). The survival at 2 years was 32/44 (73%) and 30/44 (68%) at 5 years, but 32/35 (91%) of patients who had surgery and survived were alive at 2 years postsurgery and 30/35 (86%) reached the 5-year mark. Age, unrelated illnesses, and malignant disease accounted for late deaths (11% of patients). Survival analyses (►**Table 4**) showed the distribution of the patients who were alive at 5 years postsurgery but the distribution is hampered by the small numbers while the

Table 4 Cause and timing of deaths: intraoperative, immediate, early, late deaths, and patient survival

Function	Early deaths				Late deaths
Time	Overall	Intraoperative	Immediate postoperative	Postoperative	> 2 years
Cause		Hypotension 2	Fatal arrhythmias 1	Myocardial infarcts-5	Aorto-enteric fistula 1
				Acute renal failure 1	Age-related 2
Deaths	9	2	1	6	3
Death ratio	9 of 44	2 of 44	1 of 44	6 of 44	3 of 44
Percentage	21%	4%	2%	14%	7%
No. surviving surgery					
% surviving surgery					

distribution of deaths with the average (and standard deviation from this number) are as expected from the survival table.

There is a high surgical mortality, due most likely to poor patient selection since those with substantial comorbidities did not fare well. After the initial 3 to 4 years of surgery all elective patients survived as well as those with leaking AAAs. However, six patients with ruptures did not survive due mainly to lack of blood and blood products on an emergency basis since most ruptures came in at night when resources are limited. Late presentation of several patients also added to this figure.

Statistical Analyses

Statistical analysis showed a positive association between age and size of AAA as well as size of AAA and outcome (►**Table 5**). The former was a positive association with the size noted to increase as the age of patient increased. The size, however, had a negative association with outcome such that as the size increased the outcome decreased or was worse as expected. There was no association between age and outcome.

Univariate analysis showed significance for AAA size (21.967) and ethnicity (3.200). However, one-way analysis of variance tests found none of the factors were statistically significant despite the close associations (►**Table 6**).

Using binomial testing, a relationship between the variables like elevated lipids and ischemic heart disease is seen with a significance of 0.002, and elevated blood pressure was also significant at 0.50.

Table 5 Pearson's two-tailed test correlations statistical analysis of age, aneurysm size, and outcome

	Age	Size	Outcome
Pearson's correlation	1	0.046	0.329[a]
Significance (two-tailed)		0.766	0.029
N	44	44	44
Pearson's correlation	0.046	1	−0.101
Significance (two-tailed)	0.766		0.514
N	44	44	44
Pearson's correlation	0.329[a]	-0.101	1
Significance (two-tailed)	0.029	0.514	
N	44	44	44

[a]Correlation is significant at the 0.05 level (two-tailed).

Discussion

AAA disease is uncommon in younger age groups, especially in women, who typically present at an older age than men.[3] This is borne out in many large series of AAA patients where women were generally older and had a greater chance of hypertension, smoking, and dyslipidemia.[6] In our small series the results have shown that women had a lower mean age (60.9 years) compared with men (73.4 years).

Looking at the factors influencing AAA disease, women who smoke have a higher incidence of developing AAAs than

Table 6 One-way ANOVA test

ANOVA						
		Sum of squares	df	Mean square	*F*	Significance
Size measurement	Between groups	0.425	4	0.106	0.758	0.559
	Within groups	5.462	39	0.140		
	Total	5.886	43			
Outcome	Between groups	14.855	4	3.714	1.515	0.217
	Within groups	95.577	39	2.451		
	Total	110.432	43			

Abbreviations: ANOVA, analysis of variance; df, degree of freedom.

men who had not smoked,[7] and prevalence rates of AAA were 0.03% in never smokers, 0.4% in former smokers, and 2.1% in current smokers.[8] An increased prevalence of AAAs in women was also found where there was a history of stroke, transient ischemic attack, hypertension, smoking, as well as atrial fibrillation, ankle brachial index < 0.9, and internal carotid artery stenosis ($\geq 50\%$).[9] Aneurysms in women were found to be rare below the age of 66 years in those screened for AAA disease.[8]

In our series, the mean age was less than observed in developed countries and the common related factors of hypertension, hyperlipidemias, and ischemic heart disease were positively related (statistical analyses: one-sample binomial testing) (►**Table 6**).

The comparative surgical risks for women and men undergoing AAA surgery and outcomes were observed. In one series, 50% of women and 59% of men had hospital admissions but only 37% of females underwent surgery compared with 67% men.[10] Male patients were more likely to have their AAA treated surgically, both electively ($\times 1.8$) and if ruptured ($\times 1.4$)[10] and overall mortality was quoted as 76% in men but 90% for women.[5] The women who presented as emergencies were less likely to undergo repair than men.[11] A female who had surgery was 1.4 times more at risk of dying compared with a man, and this increased if the AAA was ruptured, so that women who had intact or ruptured AAAs were less likely to undergo surgery,[12] and less likely to survive surgery, especially if young.[13] In our series, women appeared to fare just as well (11.1% deaths) not worse than men (22.8% deaths) after undergoing surgery and the younger patients had good outcomes despite other significant morbidities (►**Tables 1**, **3**, and **4**). Though worse outcomes in women have been previously published, women do not have increased perioperative mortality risks when endovascular treatment is used, even in ruptured AAAs.[14]

In the USA Veteran AAA Screening program,[3] Afro-American patients presenting with AAA disease, peripheral artery disease, and carotid artery disease were likely to be younger and female.[15] Female AAA patients, from evidence in larger continental populations tend to be older and have worse outcomes after surgery.[4,8] In our series, the female AAA population comprised a mixture of ethnic groups (►**Tables 1** and **2**) and though most Caribbean AAA patients were more likely to be male, if female, they presented at much younger age group. In our study, they were much younger, with three < 50 years of age, formed a higher percentage of the AAA population than expected (20%), but had similar outcomes to male AAA patients (►**Table 2**).

The true reason for the poor outcomes in female patients may lie in the anatomical gender anomalies in aortic diameter. Female AAA patients present later, have more comorbidities, and rupture at much smaller diameters.[16] They are therefore possibly treated less commonly by EVAR due to these anatomic limitations. When utilized, endovascular repair shows better outcomes especially in the short term, although women may suffer more from type IA endoleaks than men.[17] However, for open repair, the results are far worse than men, and they have a definite lower survival with ruptured AAAs compared with male counterparts.[16]

More surgical interventions may now be possible with the introduction of new stent graft devices, such as the Ovation Abdominal Stent Graft platform (Endologix, Irving, CA), which appears to conform better to the anatomic variations, especially the atypical proximal neck seen in women. They appear to present with less complications and have good medium-term outcomes.[18] This may be an attempt to offset the observed inequality in surgery, where fewer women with ruptured AAAs undergo surgery[19] and the 30-day mortality is greater than in men. The generally referenced, recent overall decrease in incidence of ruptured AAAs, is especially visible in the male AAA population, not in females.[20] It may be possible to offer women surgery earlier to diminish the incidence of rupture later on, by changing diameter limitations in surgery. In some communities, the threshold for surgery has been reduced due to increased endovascular interventions. For instance, there is a significant difference in the diameter limits for surgery in AAA patients between countries such as Canada and the United States, yet the perioperative and 1-year patient mortalities remain the same.[21]

The Caribbean population may differ because patients may have individual, ethnic, or lifestyles factors involved. Evidence gathered as early as 1994 had characterized AAA disease in younger people as an aggressive and extensive disease,[22] more symptomatic, with very proximal aneurysms (thoracoabdominal, suprarenal, and juxtarenal) in mainly smokers (83%). They were sometimes familial or related to syndromes (e.g., Marfan, Cogan, Takayasu) but the majority (77%) were nonspecific.[22] It may be that there exists a subgroup of younger patients of certain ethnicities who have early aortic pathology and aggressive disease possibly accelerated by smoking.[22] This might partially explain the findings of our study. Further investigation with a much larger population is needed to quantify this young female group of AAA patients more thoroughly.

Conclusion

The current literature supports the view that AAA surgery patients if female, are generally older, less likely to undergo surgery but more likely to have poorer outcomes than male patients. Our study results show that the mean age of women was much lower than expected, with some patients presenting below the age of 50. The female Caribbean AAA patients may therefore appear to present at much younger ages but results were comparable to the male counterparts. They may differ from the larger continental populations due to genetic, ethnic, or lifestyle factors but this will need to be further investigated in the near future, with a much larger cohort of patients.

Consent

Informed consent was obtained from all the patients involved in this series. Institutional Review was conducted and approval granted by the South West Regional Health Authority's/San Fernando Hospitals Bioethics

Committee. This study was conducted in accordance with the Declaration of Helsinki.

Authors' Contributions

All authors contributed to data analysis, drafting, or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosures

The authors report no conflicts of interest in this work.

Conflict of Interest

None declared.

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