Research Article

Association between End-Stage Renal Disease and Abdominal Aortic Aneurysm: A Nationwide Population-Based Cohort Study

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Abstract

Background

Abdominal aortic aneurysm (AAA) and end-stage renal disease (ESRD), defined by need for chronic renal replacement therapy, have similar epidemiological profiles and pathogenic mechanisms. However, studies testing for a connection between these two illnesses are rare. In this research, we tested the hypothesis that there is an association between AAA and ESRD.

Materials and Methods

Data from 2009 to 2015 were extracted from the Korean National Health Insurance Service database for this investigation. The study encompassed 16,671 individuals who had received a new AAA diagnosis. To form a control group, 50,013 participants without the diseases were selected using propensity score matching based on age and sex. The primary endpoint of this study was newly diagnosed ESRD.

Results

The hazard ratio (HR) of ESRD incidence in the AAA group was 2.5 (95% CI 2.0-3.2); in addition, when the AAA group was divided into surgical and non-surgical groups, the HR of the non-surgical group was 2.0 (95% CI 1.5-2.6). When AAA, chronic kidney disease (CKD), and proteinuria co-occurred, the HR of ESRD incidence increased to 128.7 compared to the cases without AAA. There were interactions of diabetes mellitus (DM), CKD, and proteinuria with incidence of ESRD (p < 0.05). In the absence of these comorbidities, the HR for ESRD was higher in the presence of AAA [1.6 vs. 3.8 (DM), 2.3 vs. 3.4 (CKD), and 1.8 vs. 3.0 (proteinuria)].

Conclusions

Our findings revealed a significant correlation between AAA and ESRD even after adjusting for several health conditions. This discovery suggests the need for regular monitoring of AAA patients. This proactive approach can aid in promptly identifying signs of ESRD and addressing modifiable risk factors at an early stage through timely interventions. **Keywords:** aortic aneurysm; abdominal; end-stage kidney disease; association

Introduction

Chronic kidney disease (CKD) is defined as an abnormality of kidney function, present for > 3 months, with negative effects on health. Glomerular filtration rate (GFR) is often used as an indicator of renal function. CKD is the diagnosis when the GFR is < 60 ml/min/1.73m2,

and CKD stage 5 is the diagnosis when the GFR is < 15 ml/min/1.73m2.1 Also, end-stage renal disease (ESRD) is defined as uremia with need for chronic renal replacement therapy; however, this definition is not

universally accepted.2 In 2018, the incidence of ESRD in the United States was 390.2 per million, and the prevalence was 242 per million.3

An abdominal aortic aneurysm (AAA) refers to a persistent dilatation of the abdominal aorta that surpasses the standard diameter by 50% or more than 3 cm. In Western populations, the average yearly occurrence of new AAA diagnoses is 0.4-0.67%.4 The current guidelines recommend considering surgical intervention for symptomatic and large asymptomatic fusiform AAAs. In this context, large is defined as a maximum diameter \geq 55 mm in men and \geq 50 mm in women.5 However, most asymptomatic AAAs are discovered through screening or incidentally during the diagnosis of other conditions.6 When discovered through screening, the majority of AAA are 4.5 cm or less.7

Oliver-Williams et al.8 determined an AAA mean growth rate of 0.26 (0.25-0.28) cm/year in the first five years in men, with an initial AAA of 3.0-5.4 cm that increased to 0.80 (0.73-0.86) cm/year after 15-19 years. Therefore, even if patients are under surveillance, the condition may progress to a stage that requires surgical treatment. The odds ratio of mortality for patients receiving chronic renal replacement therapy was 4.0 when undergoing vascular surgery compared to that of patients with normal renal function.9 This trend was also present with endovascular treatment.10,11 Therefore, it is important to identify an association between AAA and ESRD to prevent ESRD.

This research tested the hypothesis that a correlation exists between AAA and ESRD. We used data from the Korean National Health Insurance Service (NHIS) database that spanned seven years.

2.Methods

This study is a parallel study to "Risk of various cancers in adults with abdominal aortic aneurysm" and "The risk of dementia in adults with abdominal aortic aneurysm" by Cho et al.12,13 We used similar study protocols, patient group selection methods, and statistical methods.

Total number of patients

Data source

The NHIS serves as the sole public medical insurance system in South Korea, providing coverage to approximately 97% of the country's 50 million citizens. The remaining 3% receive coverage through Medical Aid.14 As part of its services, the NHIS offers a health examination program every two years for all insured individuals aged 40 and above and for employee subscribers aged 20 and older. Additionally, the NHIS maintains an extensive dataset of medical records in Korea. These records include patient demographics, medical treatments, procedures, and disease diagnoses following the 10th edition of the International Classification of Diseases (ICD-10). For this study, data from the NHIS database spanning the years 2009 to 2015 were collected.

Study population

Between January 2009 and December 2015, a total of 45,767 individuals was diagnosed with AAA using the appropriate ICD-10 code. Cases of AAA were determined by identifying individuals with multiple instances of AAA diagnosis codes I71.3-I71.6, I71.8, and I71.9 within the previous year at outpatient departments, those who had experienced repeated hospitalizations with these codes, or individuals who had undergone aneurysm repair such as open surgical aneurysmal repair (OSAR) or endovascular aneurysmal repair (EVAR). These surgical repair procedures are indicated by ICD-10 codes of O0223, O0224, O0234, M6611, or M6612. Exclusions were applied to patients who had not undergone a health examination within two years before the diagnosis of AAA (n = 26,123), those aged under 20 years (n = 195), or those with incomplete data (n = 219). Although we intended to exclude patients who had been diagnosed with ESRD prior to their AAA diagnosis, no such cases were found. From the remaining patients, a subset of individuals with greater than one year between the diagnosis of AAA and ESRD was chosen. Therefore, the analysis included 16,671 AAA patients who were matched with 50,013 controls (1:3 ratio) using propensity score matching based on age and sex (Figure 1). The observation period concluded in December 2019. The primary objective of this study was to identify newly diagnosed cases of ESRD. This study was conducted with approval from the Institutional Review Board of The Catholic University of Korea, Eunpyeong St. Mary's Hospital, Seoul, Korea (PC24ZASI0037).



AAA: abdominal aortic aneurysm, ESRD: end-stage renal disease



AAA: abdominal aortic aneurysm, ESRD: end-stage renal disease

Figure 2: Kaplan-Meier plot for incidence of ESRD in patients with AAA.

The upper graph illustrates the incidence of ESRD between the AAA group and the control group. The lower graph shows the incidence of ESRD divided among the control group, the group that underwent surgery for AAA, and the group that received non-surgical treatment.

Definitions of ESRD and other covariates

ESRD patients were identified using rare incurable disease codes of V001 (hemodialysis), V003 (peritoneal dialysis), and V005 (kidney transplantation). For CKD, the criterion was the scientifically appropriate estimated GFR measured during routine health examinations. The estimated GFR is calculated using the Modification of Diet in Renal Disease (MDRD) equation; the threshold was defined as less than 60.

Smoking status was categorized as non-smoker, ex-smoker, or current smoker. Alcohol consumption status was categorized as non-drinker, mild-to-moderate drinker (average consumption < 30 g/day), and heavy drinker (average consumption \geq 30 g/day). Regular exercise was defined as engaging in strenuous activity for \geq 20 minutes on \geq three days per week or moderate-level activity for \geq 30 minutes on \geq five days per week. The sedentary group encompassed all others. Household income was divided into two categories. The low-income group was composed of those in the lowest 20% income bracket or those receiving Medical Aid.

Diabetes was defined as a fasting blood glucose (FBG) ≥ 126 mg/dL or receiving a prescription for antidiabetic medication under the ICD-10 code E11–14. Presence of hypertension was defined as a systolic blood pressure (BP) ≥ 140 mmHg, a diastolic BP ≥ 90 mmHg, or receiving a prescription for antihypertensive medication under the ICD-10 codes I10–13 and I15]. Dyslipidemia was defined as a total cholesterol ≥ 240 mg/dL or prescription for lipid-lowering medication under the ICD-10 code E78. CVD was defined by the codes for cerebrovascular disease I60-64 and cardiovascular disease I20-25.

Statistical analysis

For comparing baseline characteristics, Student's t-tests were employed for continuous variables, and chi-square or Fisher's exact tests were used for categorical variables. The incidence rates of ESRD are presented per 1,000 person-years. Multivariate Cox proportional hazard regression analyses were performed to evaluate the association between ESRD and AAA.

The hazard ratio (HR) was not adjusted in model 1. Model 2 was adjusted for age; sex; income level; and presence of diabetes, hypertension, and dyslipidemia. In model 3, additional variables of smoking status, alcohol consumption, exercise habits, and BMI were incorporated and adjusted.

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Model 4 additionally adjusted for a history of CVD and the presence of CKD. Statistical significance was set at p < 0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and the R Project for Statistical Computing version 3.3 (Vienna, Austria)

3.Results

Baseline characteristic

Dyslipidemia and hypertension are recognized as key risk factors for AAA, and these conditions were more commonly observed in the AAA

group. Additionally, the AAA group exhibited a higher proportion of smokers and those with elevated BMI and greater waist circumference. Physical activity was notably lower among members of the AAA group, and their alcohol consumption was relatively lower. The proportion of low-income participants in this group was relatively lower. Within the AAA group, there was a greater incidence of patients with DM and individuals with a history of CVD. Significantly more patients with CKD were observed in the AAA group; this corresponded to a reduced eGFR (Table 1).

		1	
Variable	No	Yes	p-value
	50,013	16,671	
Age (years)	65.87±11.37	65.87±11.37	1
Sex (male)	32,175 (64.33)	10,725 (64.33)	1
Smoking status			< 0.001
Non	29,611 (59.21)	8,495 (50.96)	
Ex	11,786 (23.57)	3,892 (23.35)	
Current	8,616 (17.23)	4,284 (25.7)	
Alcohol consumption			< 0.001
None	31,419 (62.82)	11,207 (67.22)	
Mild to moderate	15,463 (30.92)	4,434 (26.6)	
Heavy	3,131 (6.26)	1,030 (6.18)	
Regular exercise	11,089 (22.17)	3,350 (20.09)	< 0.001
Diabetes mellitus	9,710 (19.41)	3,475 (20.84)	< 0.001
Hypertension	26,765 (53.52)	13,141 (78.83)	< 0.001
Dyslipidemia	16,343 (32.68)	9,492 (56.94)	< 0.001
Income level, low (1st quartile)	9,457 (18.91)	3,036 (18.21)	0.046
History of cerebrovascular disease	2,907 (5.81)	2,896 (17.37)	< 0.001
History of cardiovascular disease	6,260 (12.52)	8,358 (50.13)	< 0.001
CKD (eGFR < 60)	7,625 (15.25)	3,766 (22.59)	< 0.001
BMI (kg/m ²)	23.92±3.11	24.03±3.22	< 0.001
Waist circumference (cm)	83.05±8.59	84.02±8.91	< 0.001
SBP (mmHg)	127.38±15.46	128.56±16.73	< 0.001
DBP (mmHg)	77.38±9.81	78.48±10.84	< 0.001
Glucose (mmol/L)	103.51±26.64	102.05±25.65	< 0.001
Cholesterol (mmol/L)	193.46±42.03	193.61±43.53	0.712
eGFR (mL/min/1.73 m ²)	79.51±39.85	75.39±32.25	< 0.001

 Table 1: Clinical characteristics of control and abdominal aortic aneurysm (AAA) patients.

ESRD risk according to AAA

In a study population of 66,684 participants, 379 (0.56%) developed ESRD. Compared to the control group, the AAA group had a higher risk of ESRD in the unadjusted model, with HR 4.33 (95% CI 3.53-5.31), and also in the fully-adjusted model with HR 2.51 (95% CI 2.0-3.16). In the AAA group, when divided into surgical and non-surgical subgroups, the surgical subgroup had a significantly higher HR (Table 2-1). These results

were easily confirmed through the Kaplan-Meier plot, in which the AAA group showed significantly higher incidence probability of ESRD than the control group (Figure 2). This difference was significant as the p-value was less than 0.05 (p-value <0.001).

Additionally, a more detailed subgroup analysis was conducted based on the presence of proteinuria and CKD. In the unadjusted model, the HRs for ESRD onset were 4.79 (95% CI: 1.69-13.54) for those with proteinuria

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only, 11.81 (95% CI: 7.72-18.08) for those with CKD only, and 180.39 (95% CI: 118.36-274.91) for those with both conditions. In the fullyadjusted model, these HRs were 3.15 (95% CI: 1.11-8.93), 86 (95% CI: 5.57-13.26), and 86.64 (95% CI: 55.82-134.5), respectively. Moreover, when AAA was present with these conditions, the incidence of ESRD increased dramatically; the fully adjusted model had an HR of 128.66 (95% CI: 81.58-202.9) (Table 2-2). In studying the onset of ESRD, we identified variables that interact synergistically with AAA. Among various factors, only the presence of diabetes mellitus (DM), chronic kidney disease (CKD), and proteinuria showed significant interactions, all of which were negative. This implies that the combined effect of AAA with any of these conditions on the risk of developing ESRD is less than would be expected from their individual impacts [1.64 vs. 3.76 (DM), 2.26 vs. 3.39 (CKD), 1.78 vs. 3.01 (proteinuria)] (Table 3) (p-vaule : <0.001, 0.224, 0.304).

Interactions with AAA on occurrence of ESRD

AAA	Ν	Event	Duration	Rate	Model 1	Model 2	Model 3	Model 4	
No	50,013	166	235,023.07	0.70631	1	1 1		1	
Yes	16,671	213	69,842.43	3.04972	4.33(3.53,5.31)	3.26(2.63,4.01)	3.13(2.53,3.87)	2.51(2.0,3.16)	
AAA group divided into surgical and non-surgical groups (Reference : control group)									
No	50,013	166	235,023.07	0.70631	1	1	1	1	
Non-surgical	12,250	112	53,443.82	2.09566	2.98(2.34,3.78)	2.51(1.96,3.21)	2.45(1.91,3.13)	2.01(1.55,2.61)	
Surgical	4,421	101	16,398.62	6.15906	8.79(6.86,11.27)	4.97(3.83,6.44)	4.77(3.66,6.21)	3.65(2.77,4.82)	
AAA group divided into surgical and non-surgical groups (Reference : non-surgical group)									
No	50,013	166	235,023.07	0.70631	0.34(0.26,0.43)	0.4(0.31,0.51)	0.41(0.32,0.52)	0.50(0.38,0.65)	
Non-surgical	12,250	112	53,443.82	2.09566	1	1	1	1	
Surgical	4,421	101	16,398.62	6.15906	2.95(2.26,3.87)	2.0(1.51,2.60)	1.95(1.48,2.57)	1.82(1.38,2.4)	

 Table 2-1. Hazard ratio of AAA for incidence of ESRD.

AAA: abdominal aortic aneurysm, ESRD: end-stage renal disease

Rate: incidence rate per 1,000 person-years

Model 1: non-adjusted. Model 2: adjusts for basic demographics and health conditions, including age; sex; income level; and the presence of diabetes, hypertension, and dyslipidemia. Model 3: includes all factors from Model 2 and further adjusts for lifestyle factors of smoking status,

alcohol consumption, exercise status, and body mass index (BMI). Model 4: builds on Model 3, adding adjustments for a history of cardiovascular disease (CVD) and the presence of chronic kidney disease (CKD).

CKD	UPRO	AAA	N	Event	Model 1	Model 2	Model 3	Model 4	
No	No	No	41,308	32	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	
No	Yes	No	1,080	4	4.79(1.69,13.54)	3.15(1.1,8.83)	3.14(1.11,8.9)	3.15(1.11,8.93)	
Yes	No	No	7,059	63	11.81(7.72,18.08)	8.74(5.67,13.48)	8.65(5.61,13.33)	8.6(5.57,13.26)	
Yes	Yes	No	566	67	180.39(118.36,274.91)	89.79(57.94,139.14)	86.15(55.51,133.70)	86.64(55.82,134.5)	
No	No	Yes	12,391	44	5.04(3.2,7.95)	3.9(2.46,6.19)	3.80(2.39,6.05)	3.48(2.18,5.57)	
No	Yes	Yes	514	12	33.86(17.44,65.75)	19.56(10.0,38.28)	19.17(9.77,37.61)	17.6(8.93,34.7)	
Yes	No	Yes	3,369	95	45.89(30.73,68.51)	28.99(19.17,43.85)	27.89(18.41,42.26)	25.49(16.68,38.96)	
Yes	Yes	Yes	397	62	288.95(188.49,442.97)	146.16(93.78,227.78)	139.87(89.52,218.54)	128.66(81.58,202.9)	

Table 2-2. Hazard ratio of AAA for incidence of ESRD. (Further analysis)

AAA: abdominal aortic aneurysm, ESRD: end-stage renal disease, CKD: chronic kidney disease, UPRO: urine protein (≥ 1+ dipstick proteinuria)

Model 1: non-adjusted. Model 2: adjusts for basic demographics and health conditions, including age; sex; income level; and the presence of diabetes, hypertension, and dyslipidemia. Model 3: includes all factors from Model 2 and further adjusts for lifestyle factors of smoking status, alcohol consumption, exercise status, and body mass index (BMI). Model 4: builds on Model 3, adding adjustments for a history of cardiovascular disease (CVD) and the presence of chronic kidney disease (CKD).

Subgroup	AAA	Ν	Event	Duration	Rate	Model	p for interaction
Age			ESRD				
Age < 65	No	20,208	37	99,486.71	0.37191	1(Ref.)	0.2704
	Yes	6,736	49	31,497.54	1.55568	2.19(1.33,3.6)	
Age ≥ 65	No	29,805	129	135,536.36	0.95177	1(Ref.)	
	Yes	9,935	164	38,344.89	4.27697	2.63(2.03,3.4)	
Sex							
Male	No	32,175	137	149,248.2	0.91793	1(Ref.)	0.2871
	Yes	10,725	170	43,348.08	3.92174	2.51(1.95,3.24)	
Female	No	17,838	29	85,774.87	0.33809	1(Ref.)	
	Yes	5,946	43	26,494.36	1.62299	2.38(1.4,4.06)	
Diabetes							
No	No	40,303	65	191,441.38	0.33953	1(Ref.)	0.0004
	Yes	13,196	133	55,683.95	2.38848	3.76(2.7,5.24)	
Yes	No	9,710	101	43,581.7	2.31749	1(Ref.)	
	Yes	3,475	80	14,158.48	5.65032	1.64(1.17,2.28)	
Hypertension							
No	No	23,248	20	111,370.75	0.17958	1(Ref.)	0.2238
	Yes	3,530	5	15,828.52	0.31589	1.13(0.38,3.39)	
Yes	No	26,765	146	123,652.32	1.18073	1(Ref.)	
	Yes	13,141	208	54,013.91	3.85086	2.6(2.05,3.29)	
Dyslipidemia							
No	No	33,670	83	160,633.2	0.51671	1(Ref.)	0.3037
	Yes	7,179	52	31,580.95	1.64656	2.26(1.54,3.33)	
Yes	No	16,343	83	74,389.87	1.11574	1(Ref.)	
	Yes	9,492	161	38,261.48	4.20789	2.72(2.04,3.63)	
CKD							
No	No	42,388	36	200,251.57	0.1798	1(Ref.)	0.0445
	Yes	12,905	56	55,719	1.005	3.39(2.11,5.47)	
Yes	No	7,625	130	34,771.5	3.7387	1(Ref.)	
	Yes	3,766	157	14,123.44	11.1163	2.26(1.74,2.93)	
UPRO							
No	No	48,367	95	227,669.61	0.4173	1(Ref.)	0.0054
	Yes	15,760	139	66,352.93	2.0949	3.01(2.24,4.04)	
Yes	No	1,646	71	7,353.47	9.6553	1(Ref.)	
	Yes	911	74	3,489.5	21.2065	1.78(1.23,2.56)	

Table 3: Subgroup analysis for interactions of AAA and ESRD

AAA: abdominal aortic aneurysm, ESRD: end-stage renal disease, CKD: chronic kidney disease, UPRO: urine protein (\geq 1+ dipstick proteinuria) Rate: Incidence rate per 1000 person years

Model is adjusted for age; sex;fd income level; presence of diabetes, hypertension, and dyslipidemia; smoking status; alcohol consumption; exercise status; BMI; history of CVD; and presence of CKD.

4.Discussion

Most research on the relationship between AAA and renal function has focused on the relationships between treatments for AAA and renal function. For example, OSAR and EVAR were both associated with acute kidney injury (AKI); and the incidence of AKI was higher in the OSAR group.15,16 Factors affecting this relationship included preoperative hemoglobin level and eGFR, operation duration, history of cardiovascular disease, and amount of bleeding and transfusion.17 However, unlike AKI, there was no significant difference in the incidence of postoperative CKD between OSAR and EVAR from one to five years after surgery.18–21 Age > 70 years, renal artery stenosis (RAS) \geq 70%, peri-procedural AKI, graft complications, larger neck diameter, and angio-CT followed by stent-graft implantation over a short time interval were independent risk factors for CKD.18,21–23 In this study, the HR of ESRD was significantly higher in the surgical group compared with the non-surgical group [HR: 1.82 (95% CI 1.38-2.4)]. However, the association between AAA and ESRD required more attention. In this regard, Barisione et al.24 provided clues for the increased CKD and cardiac damage risk profiles of AAA patients. The reason that this relationship is important is that the size of AAAs increases gradually. As shown by Olson et al., 25 26% of patients with a maximum transverse diameter of at least 4.25 cm exceeded sex-specific repair thresholds (5.5 cm for men and 5.0 cm for women) at two years. A significant number of patients under surveillance for AAA eventually required surgery. Therefore, an ESRD prevalence higher in AAA patients compared to a control group has significant clinical implications. First, the prognosis is better for those with an early CKD diagnosis who are provided appropriate treatment. This recognizes the potential for declining renal function in AAA patients, and active monitoring can help preserve kidney function in the long term. Second, since a significant number of patients under surveillance for AAA eventually undergoes surgery and ESRD has been reported as a major factor affecting outcomes in AAA surgery, focusing on preserving renal function in AAA patients can potentially improve the surgical and post-surgical outcomes.26

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The results of the subgroup analysis showed that the presence of CKD increases the likelihood of developing ESRD, and this was also true for the proteinuria group. AAA patients with proteinuria require particular attention. Proactive surveillance is necessary for these patients. Of course, one reason for these findings may be that surveillance in the AAA group often involves the use of contrast agents for CT scans or that renal function can be impaired due to surgical interventions. However, this is not always the case since Table 2 demonstrates that, even in the non-surgical subgroup, the prevalence of ESRD was higher in the AAA group compared to the control group.

DM, CKD, and proteinuria are significantly associated with and are risk factors for ESRD.27 Indeed, ESRD incidence increases when these conditions coexist with AAA. However, the reason these factors exhibit a negative interaction effect may be that the impact these variables have on ESRD shares common mechanisms with AAA influence on the onset of ESRD. This overlap might result in a lower relative contribution of AAA.

The study has some limitations. First, the observational design of our study restricts our ability to infer a causal relationship. To mitigate this limitation as much as possible, we only enrolled patients who had a one-year time lag; and we utilized a Cox proportional hazards regression model to approximate as closely as possible the direct associations with the variables.

Additionally, even if we strive to accurately estimate the associations between variables, our definitions for ESRD and the AAA patient group may lack precision since they were identified using disease codes. Second, the mean eGFR values of the AAA group and the control group were significantly different, although the eGFR values were in the same category (G2; 60-89 mL/min/1.73m2). The values were 75.39 for the AAA group and 79.51 for the control group. This could have been a natural result because there were many CKD patients in the AAA group, but this difference may have created a bias. Third, in this study, because the incidence of ESRD was low, careful interpretation of the results is necessary. The small number of events may have affected the statistical power and reliability of the results, which may limit the generalizability of our findings. Therefore, larger-scale studies with a greater number of events are needed in the future. Fourth, since the study was conducted only on Koreans, the effect of race could not be analyzed.

Nevertheless, our study possesses several strengths. First, we established a connection between AAA and ESRD, a relationship not explored in previous research. Second, our research utilized a substantial national dataset coupled with an extensive follow-up duration. Third, we examined the effect of the coexistence of CKD and proteinuria on the relationship between AAA and ESRD and analyzed interactions among several variables.

5.Conclusions

Through this research, we identified a high incidence of ESRD among AAA patients, highlighting the necessity of meticulous renal function monitoring during the treatment or surveillance of this patient group. Moreover, the particular attention required by patients with existing CKD or proteinuria has been highlighted as these conditions significantly increase the prevalence of ESRD. Ultimately, our suggestions will not only help preserve renal function in patients, but also positively influence the outcomes of AAA treatment, especially after surgery.

Author Disclosures

None of the authors have anything to disclose.

Declaration of conflicting interests

None declared.

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