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Original Article

Predictive preoperative factors of long-term survival rate after open surgery for abdominal aortic aneurysm

Wakaba Furuie[1)], Saya Nagai[1), 2)], Toshifumi Kudo[3)], Yoshinori Inoue[3), 4)], Miho Akaza[1)], Tetsuo Sasano[1)] and Yuki Sumi[1)]

1) Biofunctional Informatics, Biomedical Laboratory Sciences, Graduate School of Health Care Sciences, Tokyo Medical and Dental University
2) Department of Clinical Laboratory, Sanno Hospital
3) Division of Peripheral Vascular Surgery, Department of Surgery, Tokyo Medical and Dental University
4) Vascular Surgery, Ambulatory Vascular Surgical Clinic Tokyo

Abstract

Objective

We aimed to examine long-term survival rate and the risk factors of poor prognosis in patients who underwent open surgery (OS) for abdominal aortic aneurysm (AAA).

Materials and Methods

We performed a retrospective analysis of the patients who underwent elective OS for AAA between 2005 and 2011 at Tokyo Medical and Dental University Hospital. The relations between mortality rate and preoperative clinical factors were examined.

Results

For this study 195 patients were identified. The mortality was significantly related to size of aneurysm, type of aneurysm, massive bleeding during operation, age, anemia, uncontrolled hypertension, and comorbid chronic kidney disease. No specific leading causes of death were identified for these increases in the mortality rate. Cox proportional hazard model revealed that anemia, hypertension, and chronic kidney disease (CKD) were independent predictive factors of higher mortality in the patients who underwent OS for AAA.

Discussion

In our previous study, high preoperative CRP level was correlated to long-term death rate after endovascular aortic aneurysm repair (EVAR) for AAA. The difference might be attributed to the fact that OS relieves the aortic wall tension and reduces the aortic inflammation, whereas EVAR does not, because of endoleak or endotension.

Key Words: abdominal aortic aneurysm, open surgery, anemia, hypertension, mortality

Introduction

Abdominal aortic aneurysm (AAA) can be defined as an aortic diameter of 3.0 cm or more in the lower part of the aorta, most commonly in those over 50 years old.[1–3] The average growth rate of AAAs reported between 3.0 and 5.5 cm ranges from 0.2 to 0.3 cm per year.[1] Larger AAA diameters are associated with higher AAA growth rates.[1] Open or endovascular surgical repair is usually performed to prevent AAA rupture when an AAA's diameter grows to >5.5 cm in males and >5.0 cm in females.[1–3] We previously reported that the statistically significant risk factor for death rate in patients who underwent endovascular aortic aneurysm repair (EVAR) for AAA was high preoperative C-reactive protein (CRP) levels.[4] However, we could not find particular diseases leading to death in patients with elevated CRP compared to all the patients who underwent EVAR. Patients with chronic obstructive pulmonary disease (COPD) or anemia

Corresponding Author: Yuki Sumi, MD, PhD
Biofunctional Informatics, Biomedical Laboratory Sciences, Graduate School of Health Care Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan
Tel: +81-3-5803-5372 Fax: +81-3-5803-0165
E-mail: sumi-alg@umin.ac.jp
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had higher mortality, but the correlation did not reach the significant level. Age, concurrent hyperlipidemia, and high blood pressure were not related to death rate. The high CRP levels, COPD, and anemia are associated with inflammation. The pathogenesis of AAA is also thought to be the inflammation.

In this study, we sought predictive risk factors for the long-term mortality in patients who underwent open surgery (OS) for AAA.

Materials and Methods

Subjects

This study retrospectively investigated patients with AAA performed elective OS between January 2005 and December 2011 at the Tokyo Medical and Dental University (TMDU) Hospital. The patients who underwent surgery for other diseases such as cancer, thoracic aortic aneurysm, choledocholithiasis, ovarian cyst, or coronary artery bypass grafting in parallel with surgery for AAA were excluded. If we include patients who underwent simultaneous surgery for other diseases, the prognosis will also depend on the prognosis of the diseases. Because of diversity in the diagnoses of other diseases and the surgical procedures, we did not stratify them as the simultaneous surgery cases but excluded them.

Data Collection

Diagnosis, past medical history, age, gender, smoking history, operative procedure, complications, prognosis, and preoperative biomarkers were collected from the clinical records. Preoperative biomarkers included blood pressure, pulmonary function tests (PFTs), hematology, blood chemistry, hemoglobin A1c (HbA1c), and C-reactive protein (CRP). The patients who had not gone in for a checkup at TMDU hospital for over one year were asked about their physical conditions with letters.

Stratification

The influences of the shape of aneurysms, operation procedures, and medical conditions of the patients on survival rate were analyzed. The aneurysms were classified by the locations (over or under the renal arteries, juxtarenal), the type of aneurysm (true aneurysms, pseudoaneurysms, and dissecting aneurysm), and the size. The operation procedures include the operation time, the amounts of bleeding, postoperative complications, or needs for reoperation. The following coexisting illness were selected as the medical conditions of the patients: the past medical histories of cardiovascular disease and chronic kidney disease. Presence of cardiovascular disease or chronic kidney disease (CKD) was diagnosed from medical record. Anemia (male: blood hemoglobin $<$ 13.7 g/dL, female: blood hemoglobin $<$ 11.6 g/dL) and elevated level of CRP (CRP $\geq$ 0.3 mg/dL) were defined according to the reference ranges at TMDU hospital. Elderly patients were defined as age $\geq$70 years. Uncontrolled hypertension was defined as systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg at admission according to the guideline published by The Japanese Society of Hypertension (Available at http://www.jpnsh.jp/data/jsh2014/jsh2014v1_1.pdf [in Japanese]). COPD was defined as forced expiratory volume in 1 second (FEV_1) / forced vital capacity (FVC) $<$ 70%.[5] Patients with COPD were classified by the severity of airflow limitation as Mild (GOLD 1: $FEV_1 \geq$ 80% predicted), Moderate (GOLD 2: 50% $\leq FEV_1 <$ 80% predicted), and Severe (GOLD 3: 30% $\leq FEV_1 <$ 50% predicted), and Very Severe (GOLD 4: $FEV_1 <$ 30% predicted) by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[5] Hyperlipidemia was defined as Low-density lipoprotein cholesterol (LDL-C) $\geq$140 mg/dL, High-density lipoprotein cholesterol (HDL-C) $<$40 mg/dL, or Triglycerides (TGs) $\geq$150 mg/dL according to the guideline published by Japan atherosclerosis Society.[6] Diabetes mellitus (DM) was defined as casual plasma glucose level $\geq$200 mg/dL or HbA1c $\geq$ 6.5% according to the guideline published by The Japan Diabetes Society (available at http://www.jds.or.jp/modules/en/index.php?content_id=1).

Statistical Analysis

Survival rates were calculated and compared with each other using the Kaplan–Meier method and the log-rank test. Cox proportional hazard model was used for multivariate analysis and estimation of hazard ratios (HR). Comparisons between the groups were made using the Mann-Whitney U test. All statistical data interpretations were conducted using EZR (version 1.37, Saitama Medical Center, Jichi Medical University, Tochigi, Japan),[7] which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.5.1, Vienna, Austria)[8]. A value of $p < 0.05$ was considered statistically significant.

The study protocol was approved by the Ethics Committees of the Tokyo Medical and Dental University (approval number 2050).

Results

Overall, 195 patients (172 males (88.2%) and 23 females (11.8%), with mean age of 71.8 ± 8.1 years) were eligible for analysis, including a patient who had been diagnosed as infected AAA. Nineteen patients had suffered from postoperative complications: six of them died as a result of surgical complications, such as disseminated intravascular coagulation, liver failure, respiratory insufficiency, and worsening general condition. Six patients required reoperation. Nine patients had aneurysms extending over the renal arteries, 27 patients were diagnosed with juxtarenal aneurysm, and 159 patients had an aneurysm under the renal arteries. For the type of aneurysm, 188 patients had true aneurysms, six patients had pseudoaneurysms, and one patient had focal dissecting aneurysm (Table1).

The mean follow-up for long-term survivors was 1890 ± 1056 days. Five-year survival rate was 0.799 (95% confidence level (CI): 0.730–0.853) (Figure 1A). The leading causes of deaths in the patients who underwent OS were cancer, respiratory insufficiency, cardiovascular disease, thoracic aortic aneurysm and surgical complication which accounted for 24%, 14%, 8%, 4% and 12% of total deaths respectively (Figure 1B).

The survival rates of the patients with larger AAA (AAA size ≥ 55 mm, n = 59) (Figure 2A) or pseudoaneurysm (n = 6) (Figure 2B) were significantly lower (p = 0.048, p = 0.007, respectively) during long-term follow-up, however, the location of AAA did not affect mortality (p = 0.236).

Table 1.

Subjects	
Number of subjects, n	195
Males, n (%)	172 (88.2 %)
Age, Mean ± SD (years)	71.8 ± 8.1
Postoperative complications, n (%)	19 (9.7 %)
In-hospital death, n (%)	6 (3.1 %)
Reoperation, n (%)	6 (3.1 %)
AAA	
location, above / juxtarenal / below, n	9 / 27 / 159
Size, Mean ± SD (mm)	50.8 ± 11.5
Type, true / pseudo- / focal dissecting aneurysm, n	188 / 6 / 1
Surgery	
Procedure time, Mean ± SD (min)	271 ± 82
Blood loss during the operation, Mean ± SD (mL)	1864 ± 1803
Preoperative biomarkers	
Hemoglobin, Mean ± SD (g/dL)	12.9 ± 1.8
CRP, Mean ± SD (mg/dL)	0.60 ± 1.62
Systolic blood pressure, Mean ± SD (mmHg)	127 ± 17
Diastolic blood pressure, Mean ± SD (mmHg)	74 ± 11
FEV1/FVC, Mean ± SD (%)	70.5 ± 10.2
LDL-C, Mean ± SD (mg/dL)	122 ± 31
HDL-C, Mean ± SD (mg/dL)	50 ± 11
TG, Mean ± SD (mg/dL)	145 ± 75
Glucose level, Mean ± SD (mg/dL)	106 ± 26
HbA1c, Mean ± SD (%)	5.9 ± 0.7

Demographic data of patients
Values are shown as a mean ± SD or numbers (%).

(A) (B)

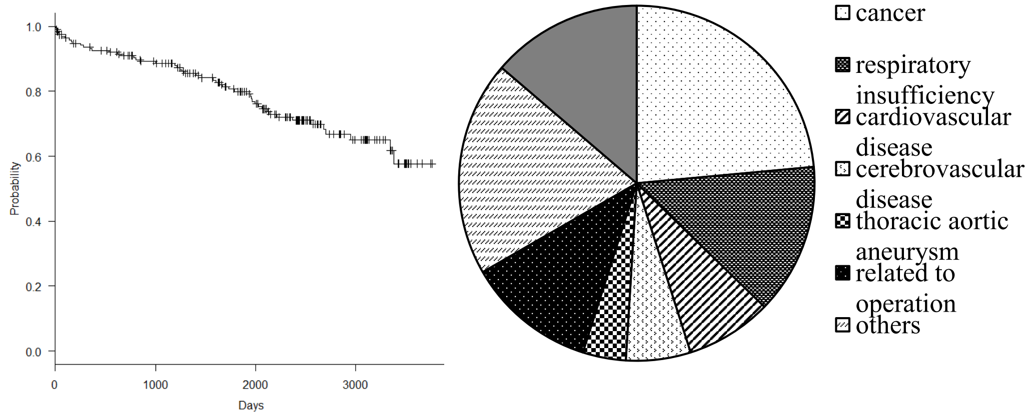

Figure 1.

A. Survival curve in all the patients who underwent OS for AAA.
Five-year overall survival was 0.799 (95% CI: 0.730–0.853).
B. The ratios of diseases responsible for death in the patients who underwent OS for AAA.

Table 2.

	Elderly	Younger
Number of data, n (%)	117 (60.0 %)	78 (40.0 %)
Age, Mean ± SD (years)	77.4 ± 4.5	63.5 ± 4.2
	Large AAA	Small AAA
Number of data, n (%)	59 (30.3 %)	136 (69.7 %)
Size, Mean ± SD (mm)	63.5 ± 8.6	45.3 ± 7.6
	Long procedure time	Short procedure time
Number of data, n (%)	117 (60.0 %)	78 (40.0 %)
Procedure time, Mean ± SD (min)	317 ± 71	200 ± 30
	Large amount of bleeding	Small amount of bleeding
Number of data, n (%)	61 (31.8 %)	131 (68.2 %)
Blood loss during the operation, Mean ± SD (mL)	3555 ± 2378	1076 ± 446
	Anemia (+)	Anemia (-)
Number of data, n (%)	106 (54.6%)	88 (45.4 %)
Hemoglobin, Mean ± SD (g/dL)	11.8 ± 1.4	14.3 ± 1.2
	Inflammation (+)	Inflammation (-)
Number of data, n (%)	72 (37.3 %)	121 (62.7 %)
CRP, Mean ± SD (mg/dL)	1.42 ± 2.46	0.12 ± 0.07
	Hypertension (+)	Hypertension (-)
Number of data, n (%)	50 (32.7 %)	103 (67.3 %)
Systolic blood pressure, Mean ± SD (mmHg)	146 ± 10	119 ± 12
Diastolic blood pressure, Mean ± SD (mmHg)	84 ± 10	70 ± 9
	COPD (+)	COPD (-)
Number of data, n (%)	70 (39.1 %)	109 (60.9 %)
FEV1/FVC, Mean ± SD (%)	60.4 ± 7.4	77.0 ± 5.4
	Hyperlipidemia (+)	Hyperlipidemia (-)
Number of data, n (%)	101 (64.3 %)	56 (35.7 %)
LDL-C, Mean ± SD (mg/dL)	136 ± 29	100 ± 21
HDL-C, Mean ± SD (mg/dL)	47 ± 11	55 ± 9
TG, Mean ± SD (mg/dL)	184 ± 77	97 ± 27
	Diabetes mellitus (+)	Diabetes mellitus (-)
Number of data, n (%)	25 (16.1 %)	130 (83.9 %)
Glucose level, Mean ± SD (mg/dL)	136 ± 36	100 ± 19
HbA1c, Mean ± SD (%)	7.1 ± 0.7	5.7 ± 0.5

Demographic data of patients after stratification
Values are shown as a mean ± SD or numbers (%).

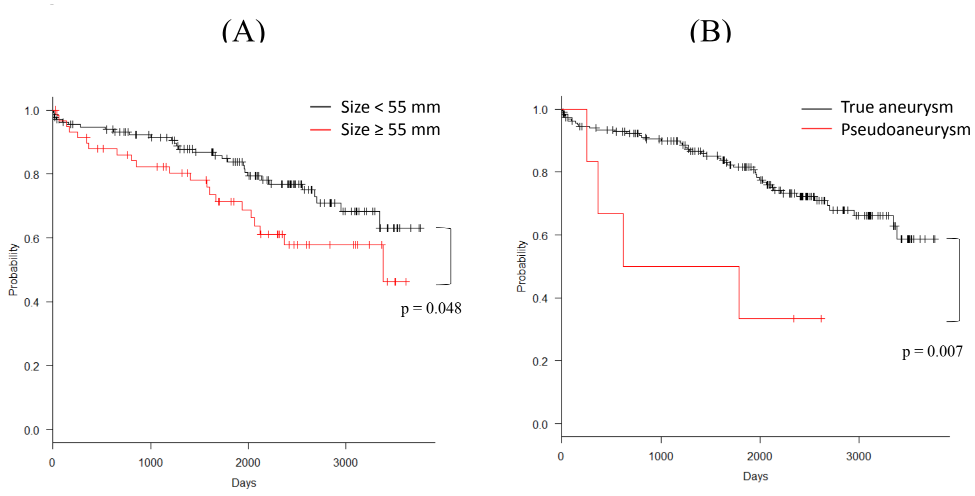

Figure 2.

A. Survival curve stratified by the size of aneurysm.
Patients with larger AAA (AAA size ≥ 55 mm, n = 59) had poorer prognosis (p = 0.0475). The 5-year survival rate of patients with larger AAA was 0.714 (95% CI: 0.568–0.818) while that of patients with smaller AAA was 0.838 (95% CI: 0.756–0.894).
B. Survival curve stratified by the type of aneurysm.
Patients with pseudoaneurysm (n = 6) had poorer prognosis (p = 0.00678). The 5-year survival rate of patients with pseudoaneurysm was 0.333 (95% CI: 0.046–0.676) while that of patients with true aneurysm was 0.815 (95% CI: 0.746–0.868).

The long-term survival rate of the patients with large amounts of bleeding (total blood loss ≥ 2000 mL, n = 61) during surgery was significantly lower (p = 0.031) (Figure 3).

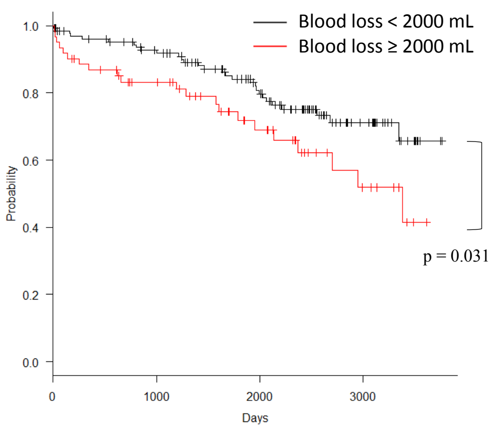

Figure 3.

Survival curve stratified by bleeding volume during surgery.
Patients with large amount of bleeding (≥ 2000 mL) had poorer prognosis (p = 0.0313). The 5-year survival rate of patients with large amount of bleeding was 0.718 (95% CI: 0.571–0.821) while that of patients without smaller amount of bleeding anemia was 0.841 (95% CI: 0.789–0.939).

The mortality rate did not differ significantly (p = 0.421) between the operation time less or more than five hours by log-rank test, but the operation time was significantly longer for the patients with postoperative complications or the patients who required reoperation (p = 0.031, p = 0.023, respectively).

Table 3.

	Postoperative complications (+)	Postoperative complications (-)
Number of data, n (%)	19 (9.7 %)	176 (90.3 %)
Procedure time (min)	304 (244 - 346)	250 (213 - 301)
	Reoperation (+)	Reoperation (-)
Number of data, n (%)	6 (3.1 %)	189 (96.9 %)
Procedure time (min)	346 (289 - 384)	250 (216 - 303)

Procedure time stratified by complications and reoperation
Values are shown as median (interquartile range) or numbers (%).

The survival rate of the patients with anemia (male: blood hemoglobin < 13.7 g/dL, female: blood hemoglobin < 11.6 g/dL, n = 106) was significantly lower (p = 0.012) (Figure 4A). The diseases responsible for death in patients with anemia were similar to those in the general population who underwent OS (Figure 4B).

Elderly patients (age ≥ 70 years, n = 117) had significantly poorer prognosis (p = 0.018) (Figure 5A). The ratios of diseases responsible for death did not differ from the general population (Figure 5B).

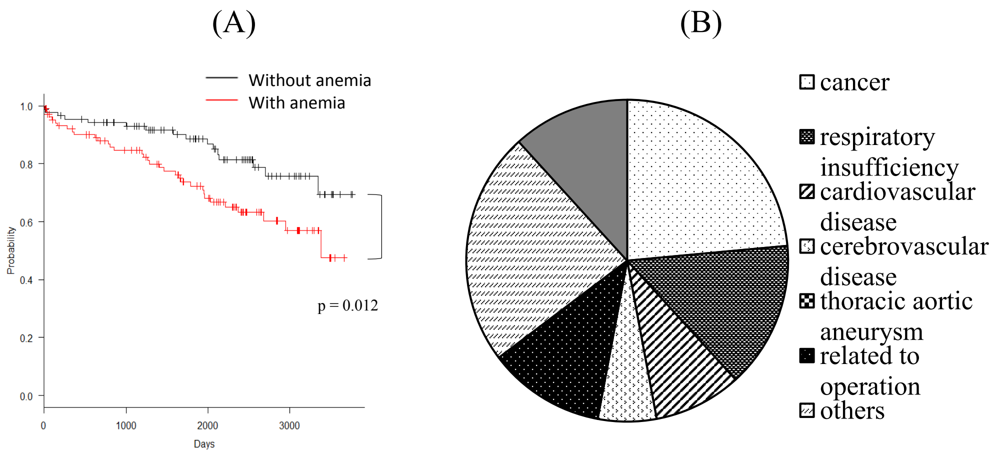

Figure 4.

A. Survival curve stratified by Hb level.
Patients with anemia (male: blood hemoglobin < 13.7 g/dL, female: blood hemoglobin < 11.6 g/dL) had poorer prognosis compared to without anemia (p = 0.012). The 5-year survival rate of patients with anemia was 0.723 (95% CI: 0.617–0.805) while that of patients without anemia was 0.885 (95% CI: 0.789–0.939).
B. The ratios of diseases responsible for death in patients with anemia.
The percentages corresponded to those in overall patients who underwent OS for AAA.

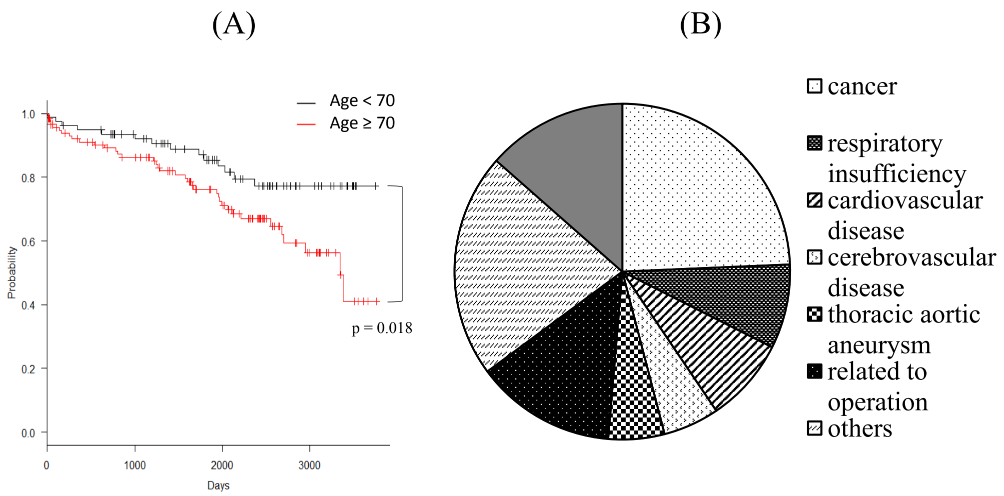

Figure 5.

A. Survival curve stratified by age.
Elderly patients (age ≥ 70 years) had poorer prognosis compared to younger patients (log-rank test, p = 0.018). The 5-year survival rate of elderly patients was 0.762 (95% CI: 0.665–0.834) while that of younger patients was 0.854 (95% CI: 0.744–0.919).
B. The ratios of diseases responsible for death in elderly patients.
The percentages corresponded to those in overall patients who underwent OS for AAA.

Fifty patients had hypertension at admission to the hospital, 38 of whom were using antihypertensive agents and 12 were untreated. On the other hand, 72 patients had been diagnosed as hypertension in the past, but they had blood pressure controlled by antihypertensive agents. Thirty-one patients had no history of hypertension and did not use antihypertensive agents. The patients with uncontrolled hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg at admission, n = 50) had poorer prognosis (p = 0.049) (Figure 6A). The ratios of diseases responsible for death did not differ between groups. (Figure 6B).

One hundred and seventy-nine patients underwent pulmonary function tests before surgery, and 70 of them

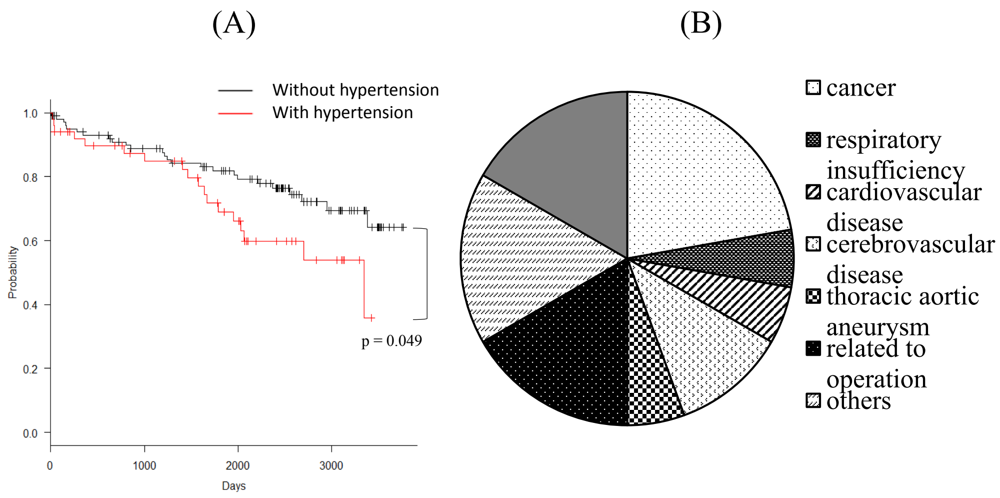

Figure 6.

A. Survival curve stratified by blood pressure at admission.
Patients with uncontrolled hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) had poorer prognosis compared to without uncontrolled hypertension ($p = 0.049$). The 5-year survival rate of patients with uncontrolled hypertension was 0.723 (95% CI: 0.617–0.805) while that of patients without uncontrolled hypertension was 0.885 (95% CI: 0.789–0.939).
B. The ratios of diseases responsible for death in patients with uncontrolled hypertension. The ratios of diseases responsible for death in patients with uncontrolled hypertension were similar to those in overall patients who underwent OS for AAA.

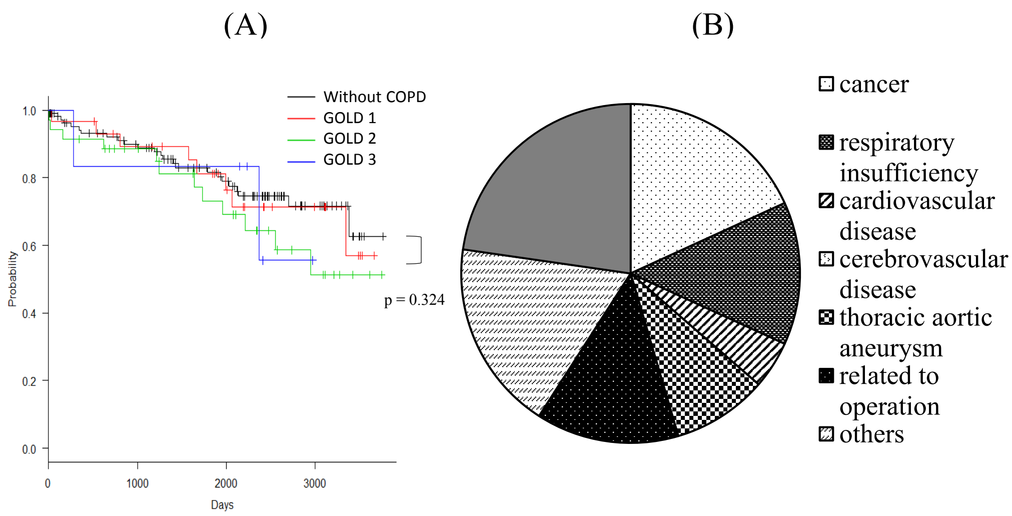

Figure 7.

A. Survival curve stratified by airflow limitation severity.
The severity of COPD did not affect prognosis ($p = 0.635$).
COPD: Chronic Obstructive Pulmonary Disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease
B. The causes of death in patients with COPD (forced expiratory volume in 1 second (FEV_1) / forced vital capacity (FVC) < 70%). The ratios of diseases responsible for death in patients with COPD were similar to those in overall patients who underwent OS for AAA.

(39.1 %) had COPD. The patients with COPD had poorer prognosis but the differences were not significant level ($p = 0.324$) (Figure 7A). They were classified as Mild (GOLD 1) in 29 patients (41.4%), Moderate (GOLD 2) in 35 patients (50.0%), and Severe (GOLD 3) in 6 patients (8.6%) by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[5] There was no significant difference by the severity of patients with COPD in the mortality rate ($p = 0.635$) (Figure 7A). The ratios of diseases responsible for death in patients with

COPD resembled those in the general population who underwent OS (Figure 7B).

Among the patients who underwent OS, 37 patients had cardiovascular disease and 25 patients had chronic kidney disease. The survival rate of patients with chronic kidney disease was significantly lower ($p < 0.001$) (Figure 8), but comorbid cardiovascular disease was not related to the survival rate ($p = 0.574$).

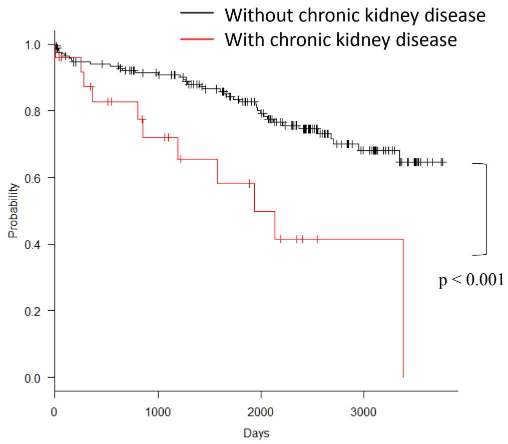

Figure 8.

Survival curve stratified by the presence of chronic kidney disease (CKD).
Patients with CKD (n = 25) had poorer prognosis ($p = 0.0004$).

Hyperlipidemia ($p = 0.547$), elevated level of CRP level ($p = 0.677$), and DM ($p = 0.704$) at hospitalization did not affect survival rate in the patients with AAA who underwent OS. (data not shown).

Multivariate analysis using Cox proportional hazard model was performed on seven factors that were found to be significant prognostic factors by log rank test. Cox proportional hazard models indicated that anemia (HR = 2.572, 95% CI 1.305-5.070), hypertension (HR = 2.015, 95% CI 1.064-3.819), and chronic kidney disease (HR = 3.873, 95%CI 1.753-8.558) were independent poor prognostic factors.

Discussion

The leading causes of deaths in patients who underwent OS were cancer, respiratory insufficiency, cardiovascular disease, thoracic aortic aneurysm and surgical complication (Figure 1B). According to the Ministry of Health, Labour and Welfare,[9] Japanese mortality probabilities at age 65 by malignant neoplasms were 28.89 % in male and 18.41 % in female, by heart diseases were 14.32 % for male and 17.91 % for female, by cerebrovascular disease were 8.17 % for male and 9.63 % for female, and by aortic aneurysm and dissection were 1.20 % for male and 1.23 % for female. Accordingly, the proportions of death by aortic aneurysm and surgical complication were higher in the patients who underwent OS.

In risk stratification, we found that patients with anemia, age, uncontrolled hypertension, large or pseudo-aneurysm, bleeding, or chronic kidney disease had significantly increased mortality. Meanwhile, in our previous similar study to find the risk factors for death rate after EVAR for AAA,[4] high preoperative CRP levels were significantly related to a poorer prognosis. The patients with obstructive lung disease or anemia also had high mortality without significant difference. Despite long energetic research, we have limited knowledge about mechanisms for AAA. Inflammation due to a variety of causes is observed in AAA.[10] Recently, micro-RNA and epigenetic alterations have been implicated in the pathogenesis of vascular diseases.[11-13]

The main difference in consequence between OS and EVAR might be that OS relieves the inflammation (high level of CRP), whereas EVAR does not. In the OS procedure, the aneurysm sac is opened with interposition of a synthetic graft; hence, aortic wall tension is relieved, and inflammation is thought to be reduced. On the other hand, after an EVAR procedure, wall tension and inflammation are assumed to remain because of endoleak or endotension. This may explain why the preoperative CRP value is related to an increase in the rate of death in patients who underwent EVAR, but not in patients who underwent OS. We further need to test the hypothesis that OS relieves the high level of CRP after the operation, which EVAR does not.

It was reported that endovascular repair of an abdominal aortic aneurysm, as compared to open repair, was associated with a substantial early survival advantage that gradually decreased over time.[14] In our result, prognosis after EVAR was worse than that of OS. The overall 5-year survival rate after EVAR was 0.592 (95% confidence level (CI): 0.440–0.715),[4] while that after OS was 0.799 (95% confidence level (CI): 0.730–0.853). This was attributed to the selection of the operative procedure. For patients with poor general condition, EVAR has been adapted in our institution.

Elderly patients who underwent OS have significantly poorer prognosis. The proportion of respiratory insufficiency as causes of death tended to be lower in patients with uncontrolled hypertension and elderly patients. In the general Japanese population, causes of death were: cancer, 28.4%; cardiovascular, 15.2%; pneumonia, 9.5%; cerebrovascular, 8.7%.[15] Respiratory deaths tended to be more frequent in patients with AAA who underwent OS, especially in patients without hypertension and younger patients.

Patients with uncontrolled hypertension also have significantly poorer prognosis. A meta-analysis of 13 cohort studies including 176389 Japanese participants for 10 years showed for all-cause mortality ratio aged 70 to 79 years for each 10-mm Hg blood pressure increase were 1.14 (men, systolic blood pressure), 1.21 (men, diastolic blood pressure) 1.12 (women, systolic blood pressure) 1.25 (women, systolic blood pressure).[16] In this study, the Cox proportional hazard model showed that the hazard ratio of mortality was 2.015 when divided into two groups with or without preoperative hypertension. Generally, the mortality rate of patients with hypertension is higher than those without hypertension, but high blood pressure is one risk factor in patients undergoing AAA surgery. Therefore, patients with AAA and hypertension are advised to control their blood pressure strictly.

According to a systematic review and meta-analysis study predicting long-term survival following AAA repair (OS and EVAR), patients with end stage renal disease and COPD requiring supplementary oxygen had the worst long-term survival.[17] In our study, patients with end stage renal disease or COPD requiring supplementary oxygen were not included. Our study revealed that the prognosis was poor in patients with CKD even without end stage renal disease. In the global study, causes of death in patients with COPD were: respiratory, 35%; cancer, 25%; cardiovascular, 11%; sudden cardiac death, 4.4%; sudden death, 3.4%; other, 8.8%; unknown, 12.4%.[18] The “respiratory” is the most common cause of death in general COPD population, however, “cancer” was the leading cause of death in our patients with COPD.

As Cox proportional hazard model did not show age as an independent prognostic factor significantly, age was thought to be confounding factor of anemia, hypertension, and chronic kidney disease. Nevertheless, age could be a simple indicator for determining the prognosis.

In conclusion, size of aneurysm, type of aneurysm, large amount of blood loss during operation, age, anemia, uncontrolled hypertension, and CKD affected the mortality rate of patients who underwent OS for AAA. Anemia, hypertension, and CKD were independent predictive factors of higher mortality in patients who underwent OS for AAA.

Ethics approval

This investigation obtained ethics approval from Tokyo Medical and Dental University ethical committee (approval number 2050).

Disclosure Statement

The authors declare no conflict of interest associated with this manuscript.

Author Contributions

Study conception: YS
Data collection: WF, SN, TK, YI, YS
Analysis: WF, YS
Investigation: WF, SN, TK, YI, YS
Writing: WF, YS
Critical review and revision: All authors
Final approval of the article: All authors
Accountability for all aspects of the work: All authors

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