Department of Biomathematics

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Submitted in fulfilment of the requirements of the Master's degree in

'Research Methodology in Biomedicine, Biostatistics and Clinical Bioinformatics'

by

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January 2017

Acknowledgements

I have written this dissertation when being a postgraduate student at the Department of Biomathematics, in the University of Thessaly, from 2015 to 2017. I am wholeheartedly indebted to my principal supervisor, Professor Christos Karkos, Assistant Professor of Vascular Surgery at the Aristotle University of Thessaloniki, who is my guidance in my academic record. It is my great honour to have one publication and several conference presentations with him since I can truly feel that my ability of academic writing is growing dynamically within this process. With his help, I have gained valuable experiences in how to research, write scientific papers, reply the comments of reviewers and provide further convincing evidence. My sincere thanks to Professor Konstantinos Papazoglou, Professor of Vascular Surgery at the Aristotle University of Thessaloniki, Head of the Vascular Unit, 5th Department of Surgery, Hippocratio Hospital, where this research took place and the clinical data were collected. Professor Papazoglou is an international expert on the subject and his help and guidance was priceless. Also, I feel grateful to Professor Thomas Papathomas, Dean of the Busch Campus and Director of the Laboratory of Vision Research in Rutgers University for the full financial covering of the tuition fees of the programme. Lastly, I would like to sincerely thank my family for the psychological support and faith to my competences.

ASSOCIATION BETWEEN PREOPERATIVE FIBRINOGEN LEVELS AND OUTCOME FOLLOWING ENDOVASCULAR REPAIR OF RUPTURED ABDOMINAL AORTIC ANEURYSMS

Aim: To investigate the potential association between preoperative levels of fibrinogen and outcome following endovascular aortic repair (EVAR) of ruptured abdominal aortic aneurysms (RAAAs).

Methods: Consecutive patients undergoing EVAR for RAAA between March 2010 and May 2016 were recruited from a single vascular center. Patient details including fibrinogen levels on admission were extracted from case files and 30-day mortality was recorded. The association between fibrinogen and outcome, which included 30-day mortality, re-intervention, endoleaks, major adverse cardiovascular events (MACE) and survival at follow up, was tested using the independent samples t-test.

Results: Twenty-one patients (20 males, median 71 years) with a RAAA receiving EVAR and available preoperative fibrinogen levels were included in this study. There were 16 patients with a de novo RAAA and 5 with rupture after a previous EVAR. Of these, 3 patients died within 30 days (14.3%), one intra-operatively and two within 24 hours due to multiple organ failure. Fibrinogen levels on admission were significantly higher in the group of survivors when compared to those who died (mean ± standard deviation 456.36±183.72 mg/dl versus 192.57±52.26 mg/dl; p=0.026). None of the remaining examined variables had statistically significant association with the preoperative fibrinogen levels.

Conclusion: This study suggests a possible relationship between fibrinogen levels on admission and early mortality in patients undergoing EVAR for a RAAA. Higher fibrinogen levels, which may indicate a preoperative hypercoagulable profile, seemed to be associated with better chances of early survival in our small series. Further and larger studies are needed to clarify this issue and possible future therapeutic implications.

INTRODUCTION

RAAA is a lethal condition for which immediate surgical intervention is required [1][2][3][4][5]. Only half the patients reach the hospital alive and of those receiving an operation only 50% survive, for an overall population mortality of 80-90% [6][7]. For more than 50 years RAAAs have been treated with the traditional open surgical repair; a major surgical procedure that requires general anesthesia, midline laparotomy and cross-clamping of the aorta and iliac arteries.

In the early 1990s, Volodos in Ukraine and Parodi, Palmaz and Barone in Argentina [8][9] introduced a less invasive endovascular method for elective AAA repair. Over time, these pioneering devices were improved and commercial development of the technology has meant that the technique has spread worldwide.

Encouraged by the excellent results of elective EVAR, emergent EVAR has been also used for RAAAs [10]. Several observational studies suggested that EVAR is superior to open surgery for RAAAs. Additionally, three recent randomized controlled trials suggested that, although there were no statistically significant differences in 30-day mortality rates, there was a consistent but non-significant trend for lower mortality with EVAR at 1 year [11].

If the results of EVAR for RAAA are to be improved, identification of factors influencing survival is of paramount importance. One of these factors is the clotting profile of RAAA patients. Coagulation parameters are often found to be deranged in patients presenting with a RAAA and having a large retroperitoneal hematoma or a free intra-peritoneal rupture.

Building upon this literature, we hypothesized that serum fibrinogen on presentation is a potential biomarker of early or late outcome in RAAA patients undergoing EVAR [12]. Being an important component of the coagulation cascade, as well as a major determinant of blood viscosity, may, in part, explain its association with various vascular disorders and their prognosis [13]. An increase in plasma fibrinogen levels may reflect or promote a prothrombotic or hypercoagulable state which may prove to be partly protective in a RAAA case through hemorrhage cessation. The aim of this retrospective study was to examine the association between preoperative serum fibrinogen and outcome in patients undergoing EVAR for RAAA.

METHODS

A consecutive series of 21 patients undergoing EVAR for RAAA between March 2010 and May 2016 were enrolled in this retrospective study. Patient details were extracted from case files and only cases with available fibrinogen level on admission were included. The study was held in a single vascular center based at a university hospital which provides on-call vascular services for northern Greece every fourth day. The elective EVAR program started back in 1995, whereas the EVAR service for RAAAs was established in early 1998.

On suspicion of a RAAA, the patient was immediately brought to the computerized tomography (CT) scanner, with the whole process lasting no more than 15 to 20 minutes. As

a result, the admission to the scanning room and, subsequently, to the operating room in such patients usually required a total time of about 30 minutes. In case of a patient being transferred from a peripheral hospital with the diagnosis of a rupture already made on CT, the time from admission to the start of the endovascular procedure was even less, because the patient was taken directly into the operating room, bypassing the emergency room and the radiology department. In the latter patients, the delay from the onset of symptoms to aneurysm exclusion depended on several factors beyond our control, such as how quickly the patient sought medical advice, how quickly the diagnosis of a RAAA was made by the referring physician, and the distance the patient had to travel by ambulance from the peripheral hospital to our center.

Patient evaluation was done by means of contrast-enhanced spiral CT of the abdomen and pelvis [14]. There were no specific hemodynamic inclusion criteria for EVAR. In the presence of severe hemodynamic instability an aortic occlusion balloon was used. The vascular surgeon, along with the on-call radiologist, reviewed the CT images, confirmed the diagnosis of rupture, and assessed aneurysm morphology. All decisions about the type of treatment offered, including decisions on the type, configuration and size of the endograft, were made by the on-call vascular specialist.

The anatomic criteria for EVAR in RAAA patients were broadly similar to those used in the elective setting, the most important morphologic factor being the infrarenal neck. The general guidelines for suitability were an infrarenal neck length of 10 mm or more, a neck diameter of 32 mm or less, neck angulation of 60° or less, and a common iliac diameter of 22 mm or less; also, there could be no bilateral common iliac aneurysms or long iliac occlusions. With growing experience, however, our selection criteria for both elective and RAAAs had expanded to the extent that more and more technically challenging cases had been treated by endovascular means. Consequently, cases with difficult iliac anatomy, such as bilateral severe iliac occlusive disease, tortuosity, or aneurysmal involvement, had been considered as potential candidates. In addition, RAAAs with shorter (<10 mm), flared, or severely angulated proximal necks had also been accepted for EVAR.

Patients who were thought to be suitable for EVAR were immediately transferred to a dedicated vascular operating room with endovascular facilities. Endovascular repair was performed by the on-call team, which consisted of a vascular specialist and two vascular trainees. The procedure was performed with a mobile C-arm image intensifier with digital subtraction angiography facility (SIEMENS ARCADIS). Arterial access was obtained via bilateral surgical cutdowns of the common femoral arteries by using skin crease groin incisions. The procedure was usually performed under local anesthesia with 1% lidocaine. All patients were monitored noninvasively by the anesthesiologist. When needed intravenous sedation was administered in an attempt to minimize patient movement and discomfort. Intravenous fluid and blood resuscitation were kept to a minimum before aneurysm exclusion to allow hypotensive hemostasis (systolic blood pressure between 80 and 100 mm Hg). Endotracheal intubation and general anesthesia was reserved for patients who had lost consciousness and/or those in whom a patent airway could not be maintained. Then the procedure of EVAR was performed in the usual standard fashion by cannulation of both femoral arteries with suitably sized sheaths.

Intraoperative angiography was usually performed with manual injection of contrast via a 7F introducer sheath (Super Arrow Flex, 45 cm long; Arrow International, Reading, Pa) inserted from the femoral artery contralateral to the side chosen for deployment of the main body of

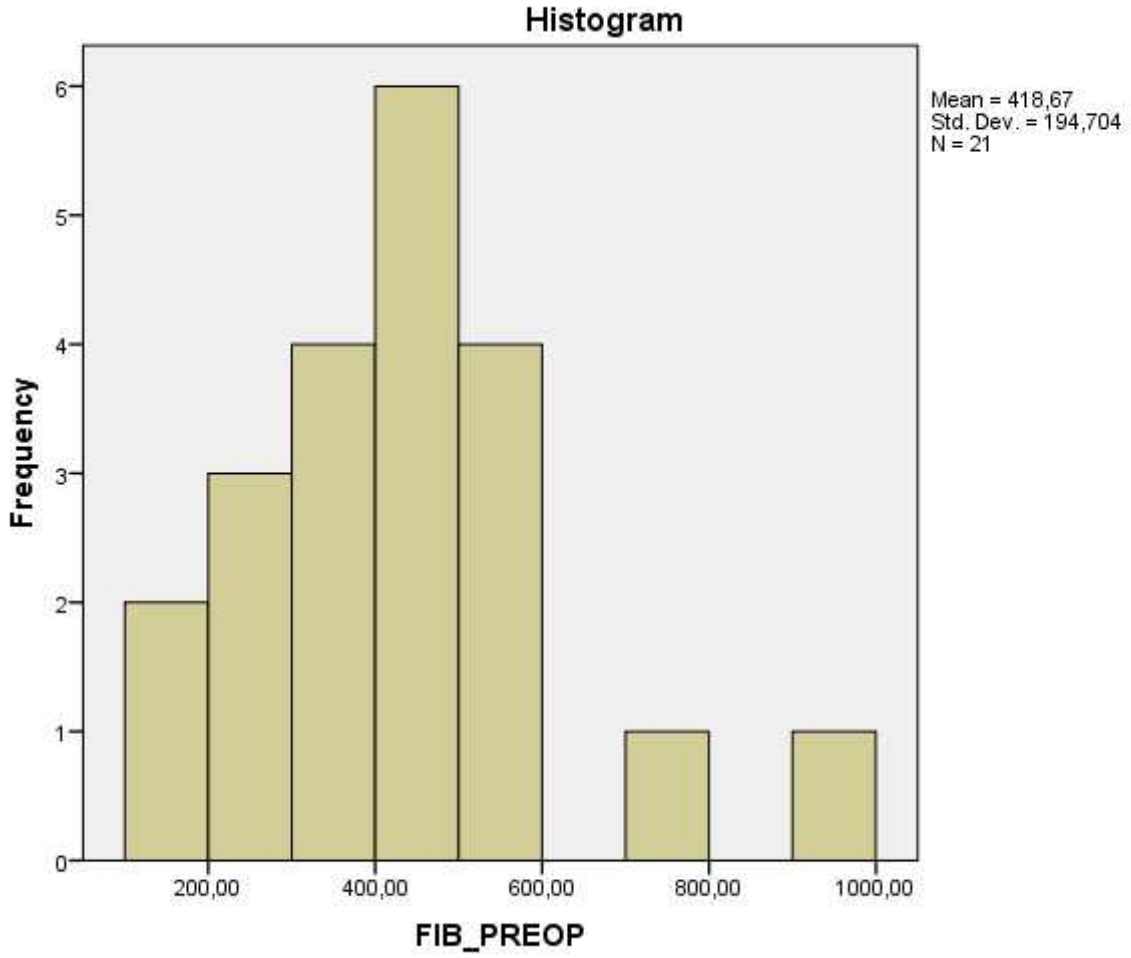
the stent graft. The contrast medium used was iodixanol (Visipaque; Amersham Health) or iopamidol (Iopamiro 300; Bracco, Italy). Intraoperative angiography determined the level of the lowest renal artery and, later in the procedure, the origins of the internal iliac arteries. The main body of the device was introduced over a stiff guidewire, such as the Amplatz Super Stiff (Boston Scientific, Watertown, Mass) or the Lunderquist guidewire (TSMG-35-260-5-LES2; William Cook Europe, Denmark) with the help of a 5F guiding catheter, such as the Headhunter (Boston Scientific, Meditech). The combination of a 5F cobra-shaped selective angiographic catheter (Boston Scientific, Meditech) and an angled Terumo guidewire (0.035 inches [180 cm]; Terumo Corporation, Tokyo, Japan) was used to catheterize the short limb of the main body of the bifurcated stent grafts in most cases. In all cases, stent grafts were additionally dilated with a suitable balloon to ensure adequate sealing. Postdilation was performed by using a compliant aortic balloon (Reliant; Medtronic, World Medical Manufacturing Corp, Sunrise, Fla) for proximal and distal landing zone fixation.

The type of stent graft was chosen depending on the surgeon's preference and expertise, the anatomic characteristics of the aneurysm, and, most importantly, the device availability [15]. As a result of local hospital policy, there is no inventory of an AAA stent graft available in our unit. Instead, emergency access to suitable endografts was through the locally based company representatives. As a result, whatever device was more readily available was used. Although this policy could potentially lead to inevitable logistic delays, frequent communication with the company representatives resulted in timely endograft availability. In cases in which the diagnosis of an RAAA was known or suspected through information from the referring hospital or the ambulance service, we alerted the company clinical specialists before patient arrival, and the stent graft was available to us as the patient was being brought to the operating room.

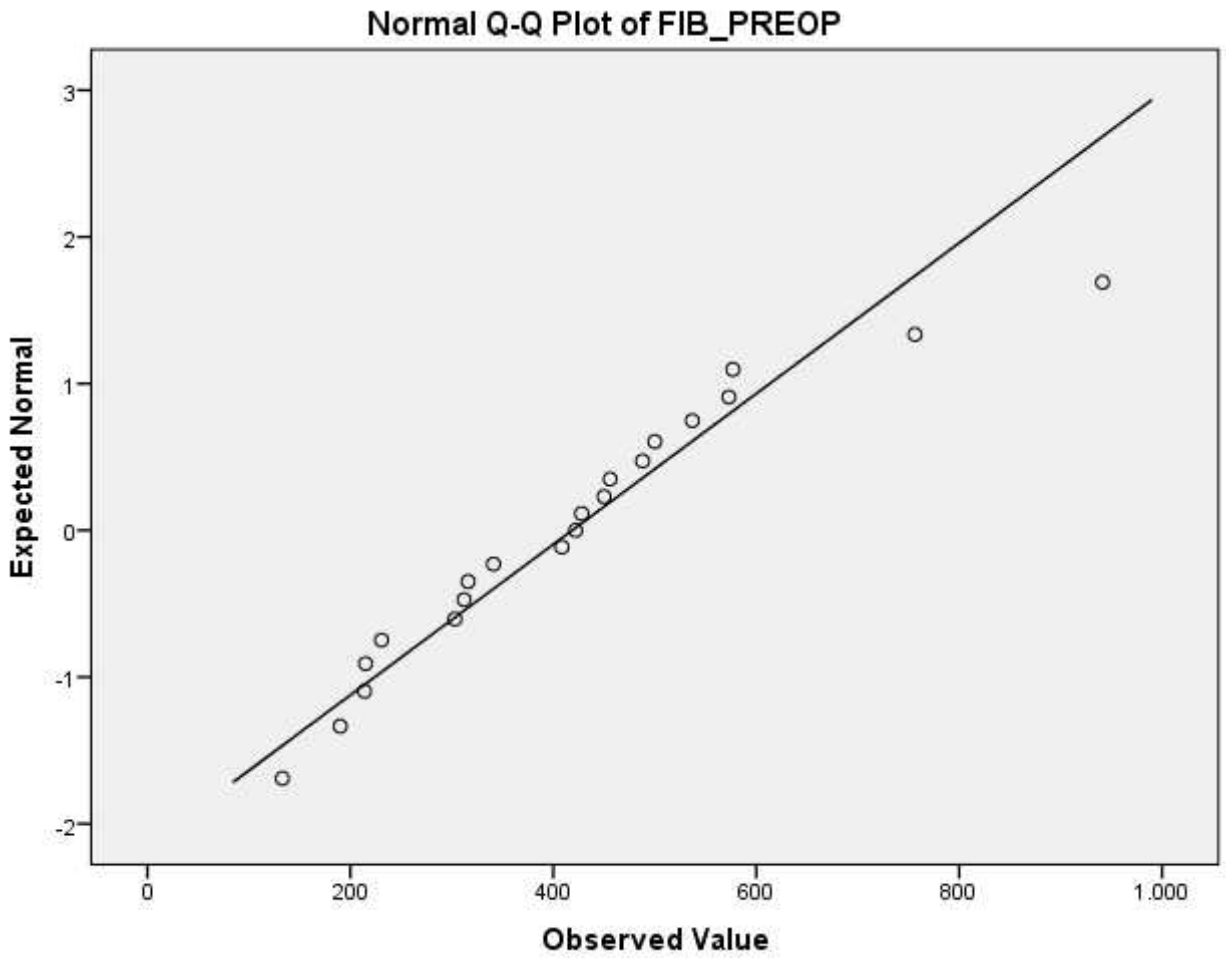
The primary outcome in this study included 1) 30-day mortality, 2) the survival at follow-up, 3) aortic related re-interventions, 4) endoleaks and 5) major adverse cardiovascular events (MACE). The latter was defined as all-cause mortality, major lower limb amputation, ischemic cardiac events, stroke and all-aortic stent-graft related events.

All statistical analyses were carried out using the statistical program SPSS® version 22 for Windows (IBM corp.) The level of statistical significance was set at $p < 0.05$. Preoperative fibrinogen data were tested for normality using the Shapiro-Wilk's test [16][17]. Both this test and a visual inspection of the histogram, normal Q-Q plot and box plot showed that the preoperative fibrinogen levels were approximately normally distributed across the study population with a skewness of 0.961 (SE= 0.501) and a kurtosis of 1.366 (SE= 0.972) [18][19][20].

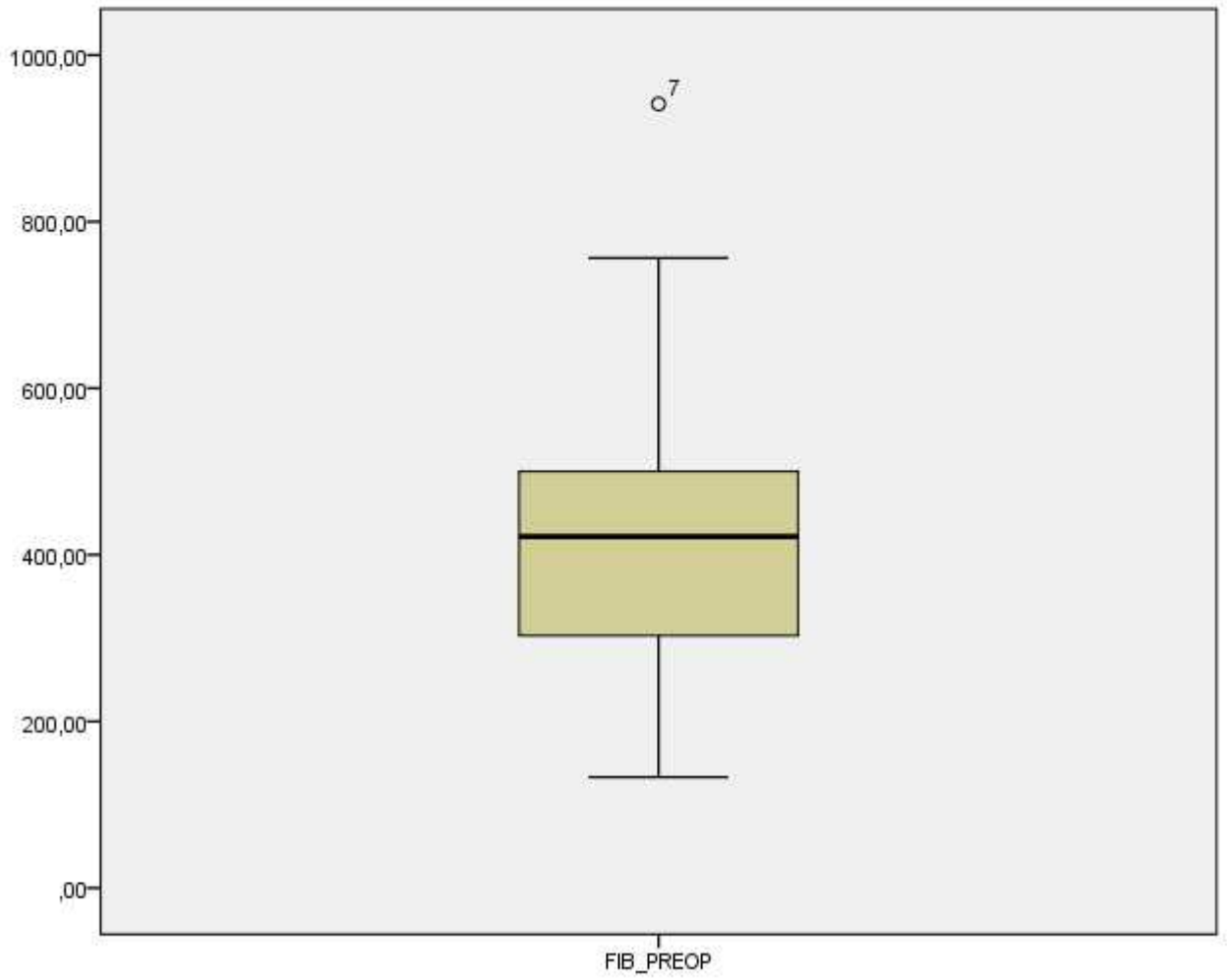
Consequently, the univariate association of the preoperative fibrinogen levels and the primary outcome (30-day mortality, survival at follow-up, re-intervention, endoleak and MACE) was assessed by Independent Samples t-test. The preoperative fibrinogen levels were presented as mean ± standard deviation (SD). The association of preoperative fibrinogen levels and the survival at follow-up was investigated by Cox regression survival analysis.



Histogram 1: the histogram of the preoperative fibrinogen levels' distribution has the approximate shape of a normal curve when visually inspected.



Normal Q-Q plot 1: the dots are approximately distributed along the line



Box plot 1: the box plot is approximately symmetrical

RESULTS

Overall, twenty-one patients, 20 men and 1 woman with a median age of 71 years (range, 55-87 years), underwent EVAR of a RAAA during the study period. **Table I** summarizes the preoperative details of the patients included, patient characteristics, pre-existing comorbidities and presenting features. The median duration of symptoms was 14 hours (range, 4-72 hours). Approximately half the patients (48%) presented with hemodynamic instability (i.e. a reduced level of consciousness and/or a systolic blood pressure (SBP) <80 mm Hg). A total of 5 patients presented with hypotension, defined as SBP < 90 mm Hg, and the median lowest recorded SBP was 85mm Hg (30 mmHg-120 mmHg). The initial hemoglobin was a median 11, 5 g/dL (range, 8, 05-13, 7 g/dL). Nineteen patients underwent operation with local anesthetic infiltration in the groins, whereas two patients underwent the procedure with general anesthesia.

De novo RAAAs were treated with fourteen bifurcated stent grafts and one aorto-uni-iliac endograft with femoro-femoral crossover bypass. One spontaneous rupture of the abdominal aorta was treated with tube endograft combined with the chimney-periscope technique. Those cases with previous EVAR were treated either with an aortic (n=2) or an iliac extension (n=3).

A total of 3 patients died during the first 30 postoperative days **(Table II)**. One died intra-operatively due to exsanguination leading to cardiac arrest, while two died within 24 hours after completion of the EVAR in the intensive care unit due to multiple organ failure triggered by severe hypovolemia. Both of them developed intractable intraoperative hypovolemic shock from which they never recovered, despite aggressive resuscitation and after having received transfusion of a large amount of blood, blood products, and inotropes. During a median follow-up of 10 months (range, 0-58 months) two further patients died. The first patient died from pancreatic cancer and the second from cardio-respiratory failure.

During the postoperative follow-up, aortic related re-interventions were necessary in 4 (19%) patients. The first encountered a type 1b endoleak within 3 months of the operation but refused initially treatment. He eventually underwent implantation of an iliac limb extension. Two patients developed a type 1a endoleak and subsequently underwent placement of an aortic cuff extension. Finally, a fourth patient was readmitted with symptoms of left leg ischemia due to endograft limb occlusion. A femoro-femoral crossover bypass was performed but the patient eventually required an above-knee amputation.

There were also 5 cases of endoleaks in this group of patients (1 type Ib, 3 type Ia and 1 type II). Finally, a total of 7 patients (33%) suffered a MACE during the existing follow-up. Details are presented in **Table III.**

On average, preoperative fibrinogen levels were higher in the survivors (mean ± SD; 456.36±183.72 mg/dl vs. 192.57±52.26 mg/dl) than in the patients who died within 30-days. This difference is statistically significant (p= 0.026). **(Figure 1)**

Beyond the 30-day follow-up, the preoperative fibrinogen levels were not significantly different between survivors (mean ± SD; 446.84 ± 192.66 mg/dl) and patients who died (mean ± SD; 328.54 ± 192.41 mg/dl, p= 0.245). **(Figure 2)**

Similarly, the preoperative fibrinogen levels were not significantly different in 1) patients that required an aortic related re-intervention (vs not requiring re-intervention) (mean ± SD; 521.85 ± 311.43 vs. 394.40± 160.98 mg/dl, p= 0.249). (**Figure 3)** 2) in patients with an endoleak (vs. no endoleak) (mean ±SD; 298.80 ± 167.00 vs 456.13 ± 191.90 mg/dl, p= 0.117) **(Figure 4)**, or 3) in patients suffering a MACE (vs not) (mean ± SD; 412.16 ± 270.20 vs 421.90 ± 156.80 mg/dl, p-value= 0.917) **(Figure 5)**.

Table I **Preoperative details**

VARIABLE	DATA: No. (%) or median (range)
Age (year), median (range)	71 (55-87)
Sex (male/female)	22/1
Comorbidities	
Coronary Artery Disease	13 (62%)
Hypertension	13 (62%)
Chronic pulmonary disease (COPD)	12 (57%)
Stroke	2 (9.5%)
Smoking	14 (67%)
Diabetes	7 (33%)
Chronic renal impairment	1 (5%)
Previous abdominal operation	9 (43%)
Previous EVAR/De novo rupture	5 (24%)/16 (76%)
Presentation	
Symptom duration (hours) median (range)	14 h (4-72 h)
Pain (abdominal/back)	21(100%)
Loss of consciousness	5 (24%)
Hemodynamically unstable	10 (48%)
Systolic Blood pressure (SBP) on admission	105 (30-170)
Hypotension on admission (<90mmHg)	5 (24%)
Lowest SBP	85(30-120)
Hb on admission g/dL, median (range)	11,5 (8,05-13,7)

Table II **Primary Outcome**

VARIABLE	n (%)	p-value
30-day mortality	3(14%)	0.026
Re-intervention (aortic related)	4(19%)	0.249
Endoleak	5(24%)	0.117
MACE	7(33%)	0.917
Survival at existing follow up	5(24%)	0.245

Table III **Details about MACE**

Patients	MACE
1	Myocardial infraction
2	Left endograft limb occlusion, -lower limb ischemia, femoro-femoral crossover bypass, -wound infection, above-knee amputation
3	Death in the ICU within 24 hours, multiple organ failure
4	Cardio respiratory failure, death 4 months later
5	Death in the ICU within 24 hours, multiple organ failure
6	Died intra-operatively, exsanguination leading to cardiac arrest
7	SFA occlusion causing claudication

Finally, we examined the estimates of % survival in our series for a unit increase in the preoperative fibrinogen level. A total of five patients died at follow-up and the value of Exp(B) for fibrinogen level means that the death hazard is reduced by 100%-(100%*0.996)= 0.4% for each unit of increase in the preoperative fibrinogen level. As a result, fibrinogen is supposed to be a protective factor for patients undergoing EVAR for RAAA giving better chances of survival. However, this observed difference is not statistically significant (p-value; p=0.218, 95% CI for Exp (B); (0,990-1,002)) in our small series. The cumulative survival probability is presented graphically in **Figure 6**.

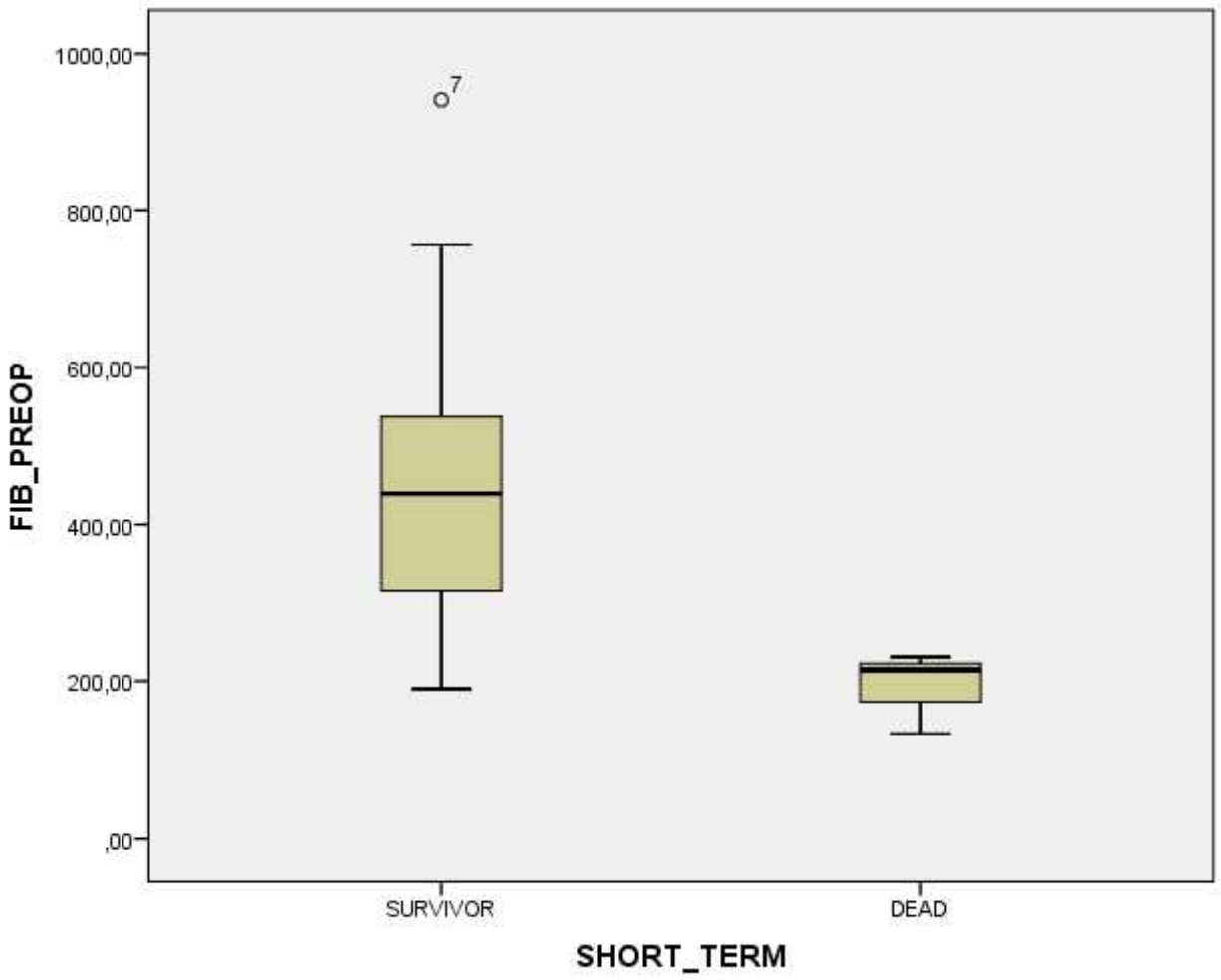


Figure 1: Box plot of the preoperative fibrinogen levels distribution across survivors and fatal cases in 30-day follow-up

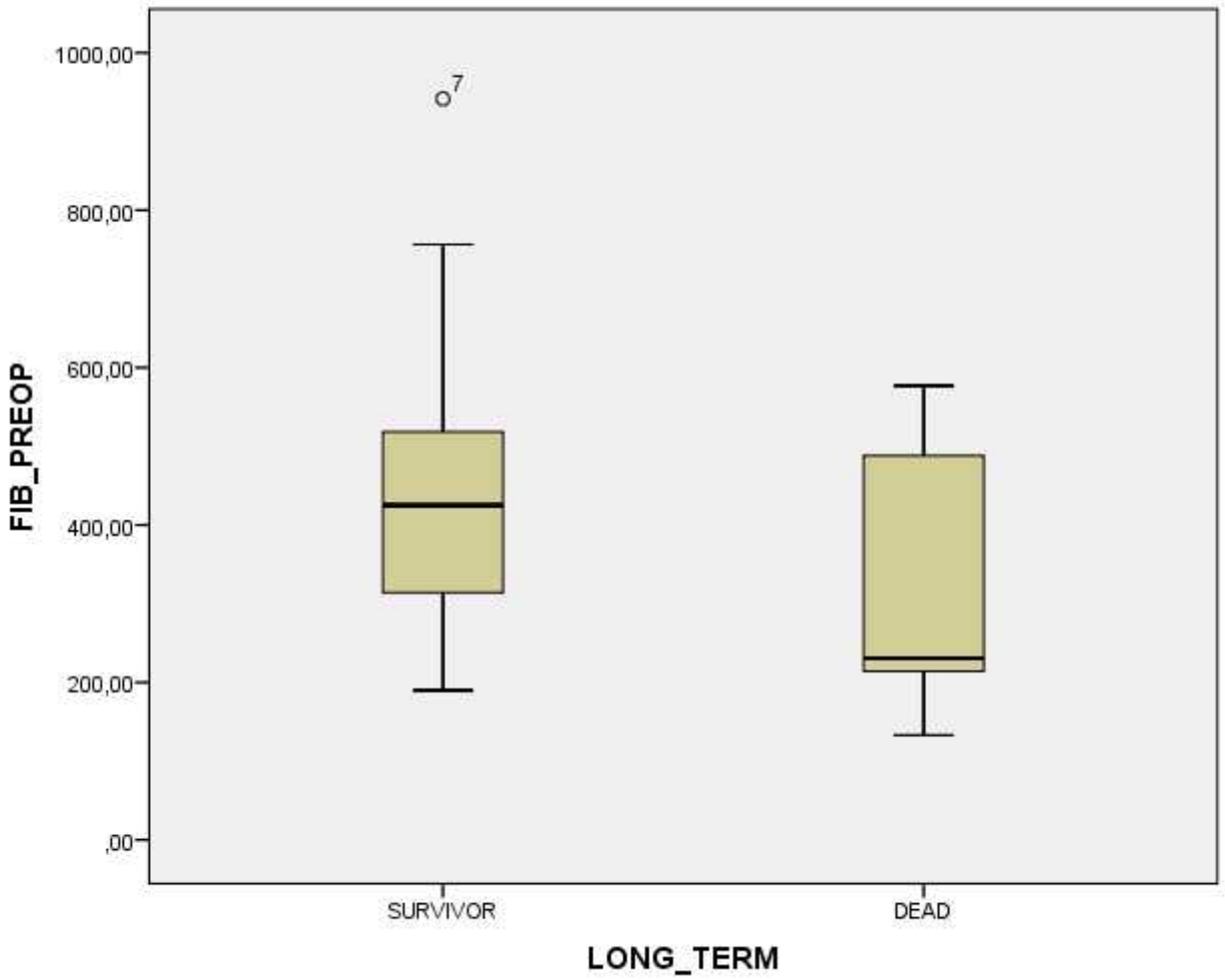


Figure 2: Box plot of the preoperative fibrinogen levels distribution across survivors and fatal cases during existing follow-up.

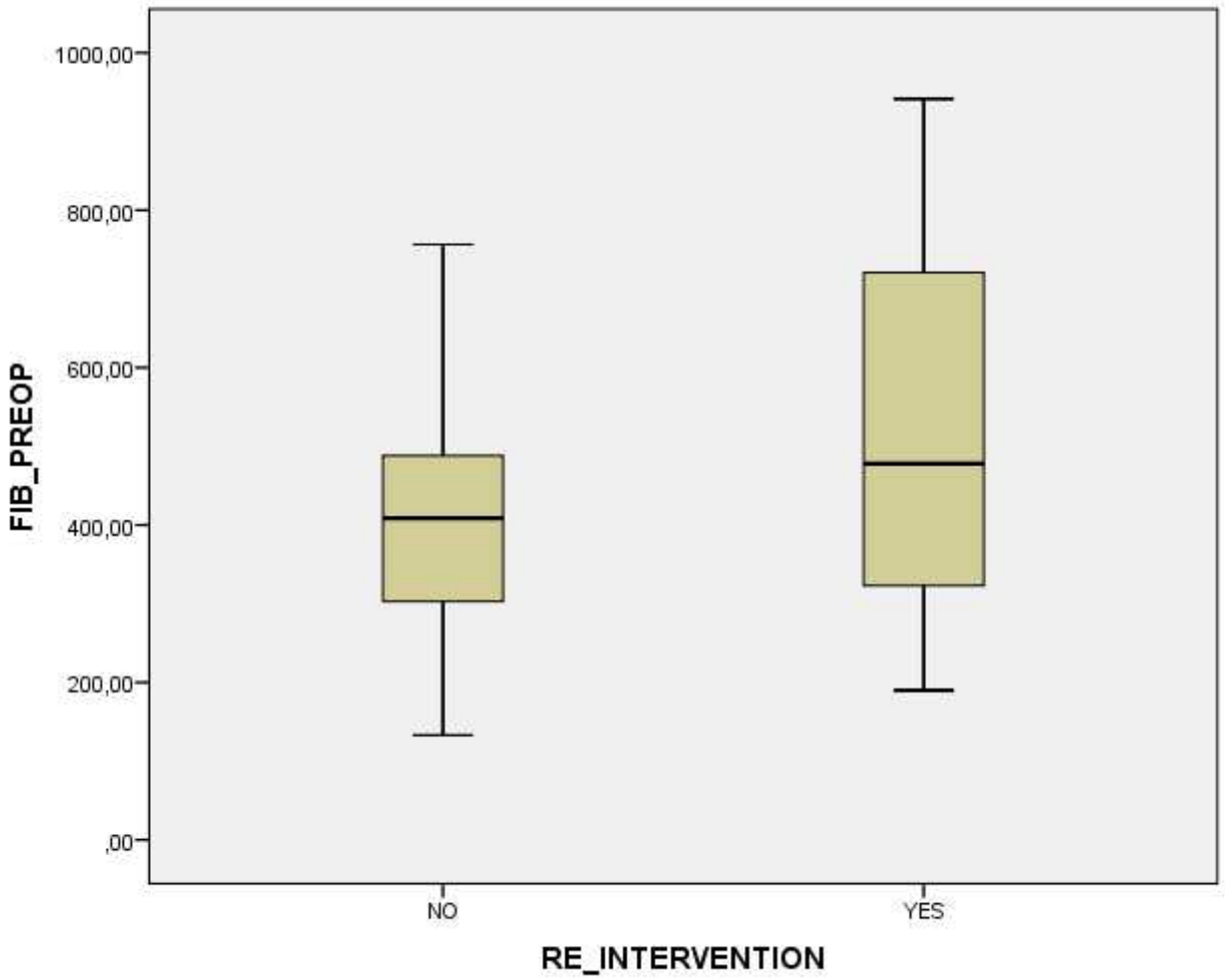


Figure 3: Box plot of the preoperative fibrinogen levels distribution across patients requiring re-intervention and patients with no need for re-intervention.

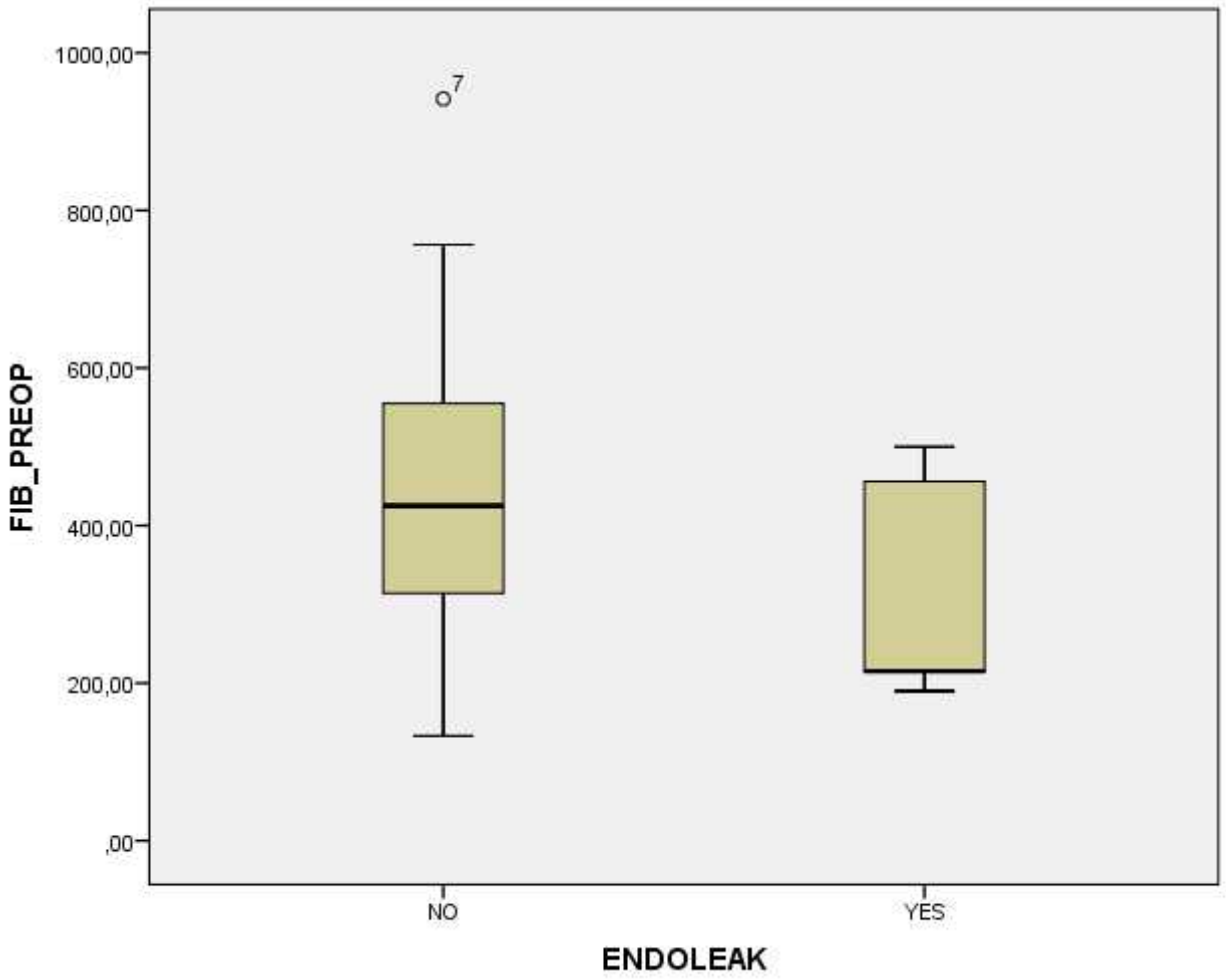


Figure 4: Box plot of the preoperative fibrinogen levels distribution across patients with an endoleak and patients without endoleak

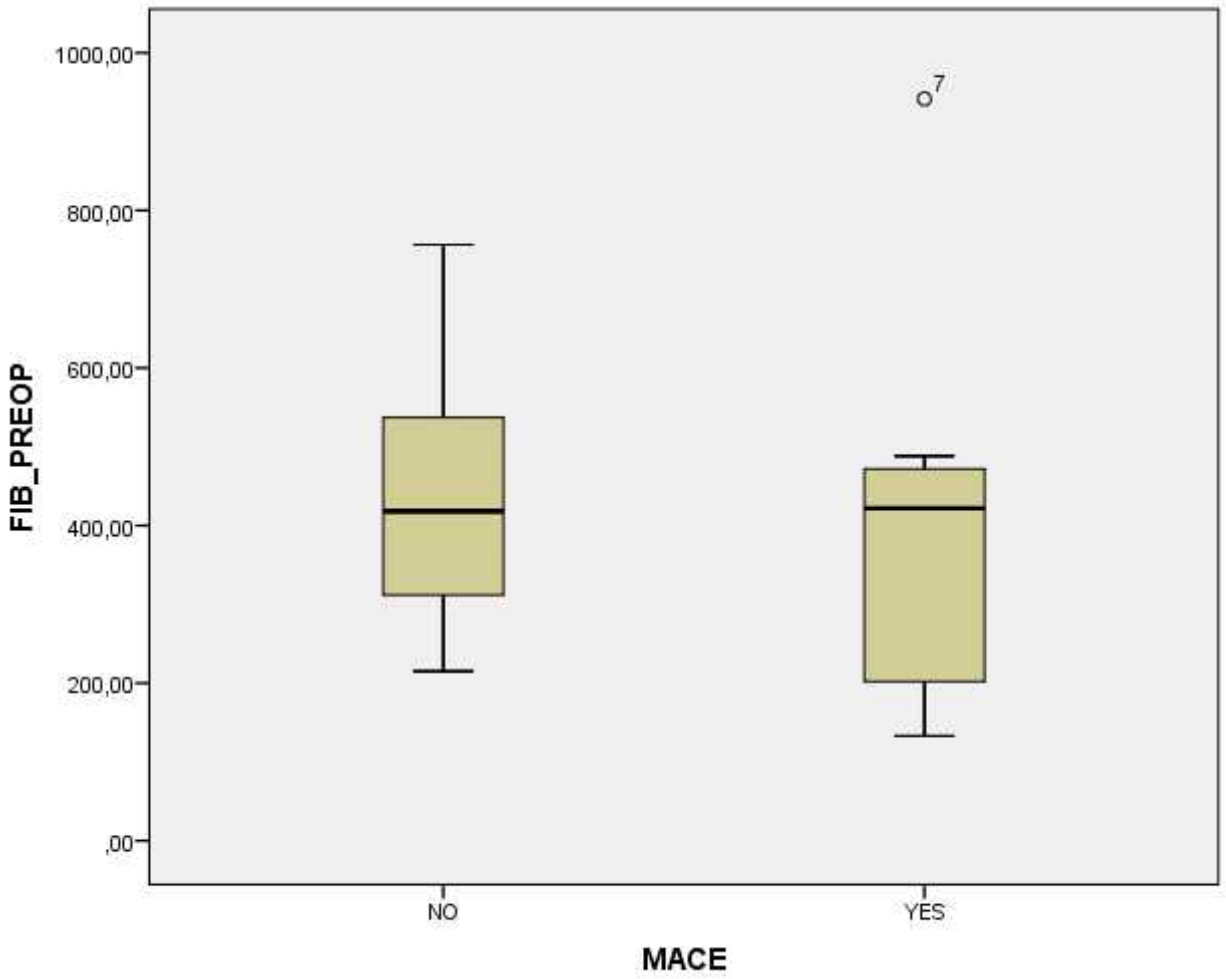


Figure 5: Box plot of the preoperative fibrinogen levels distribution across patients who suffered MACE and those who did not

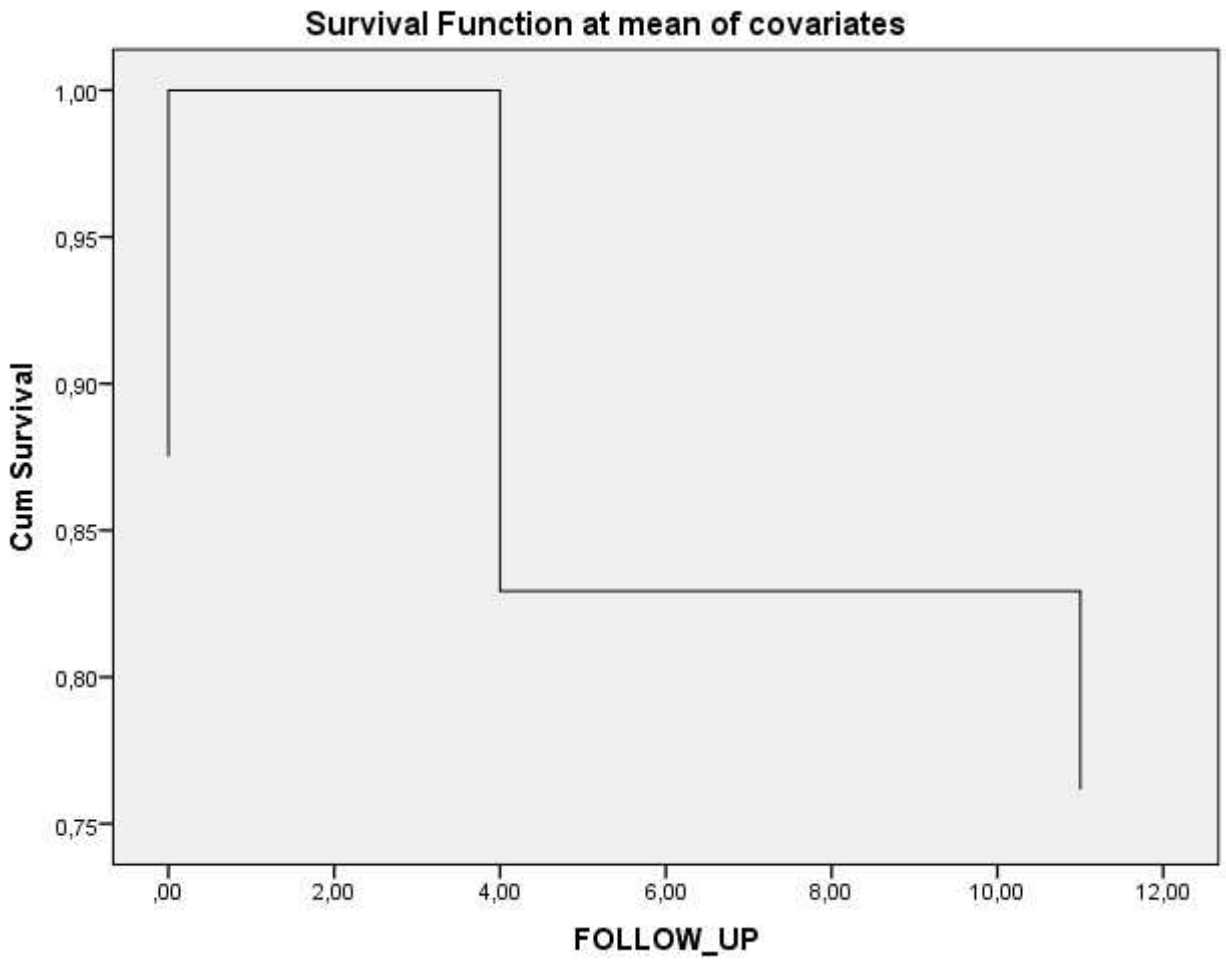


Figure 6: Cox regression for survival analysis. The basic survival curve is a visual display of the model predicted time to death for the "average" patient. The horizontal axis shows the time to event in months. The vertical axis shows the probability of survival

DISCUSSION

Despite the advances made in the surgical and the anesthetic techniques, RAAA remains one of the most feared and difficult vascular emergencies with perioperative mortality figures ranging in the 50 % range [21][22]. Major hemorrhage and hypotension after RAAA are associated with worse outcome. In a study by Davies et al.[23] the major cause of immediate intra-operative death in patients with a RAAA was related to hemorrhage. In RAAA-related hemorrhage, survival is dependent upon immediate surgery and the application of an aortic cross-clamp above the rupture site. Even if patients survive the hemorrhage, post-operative mortality is still high due multiple organ failure, myocardial infarction, and thromboembolism. A possible contributing mechanism for these complications is an imbalance between the activation of the coagulation system and the fibrinolytic system.

Hemodynamic presentation can differ remarkably depending on the preoperative bleeding which is related to the site and containment of the aortic rupture. If the outcome is to be improved immediate efforts must be made to minimize perioperative blood loss. The coagulation system is activated in patients with RAAA and shock, and the development of coagulopathy predicts poor outcome [24].

In RAAA patients, shock on admission is a well-known prognostic risk factor for mortality. Apart from bleeding, a significant proportion of the deaths and complications in RAAA patients are related to thrombosis. Activation of the coagulations system is regarded as an important part of the thrombosis development.

The management of the patient with hemorrhage due to RAAA included rapid administration of red blood cells, along with sufficient fresh frozen plasma and platelets to treat or prevent coagulopathy. Furthermore, Adam et al. [25] concluded that the procoagulant state in patients with RAAA may contribute to microvascular and macrovascular thrombosis that, in turn, lead to the common causes of perioperative morbidity and mortality, namely myocardial infarction, multiple organ failure and thromboembolism.

The normal hemostatic system limits blood loss by a precisely regulated interaction between components of the vessel wall, circulating blood platelets and coagulation factors. Thrombin induces local hemostasis by activating platelets and by converting fibrinogen to fibrin. The platelet aggregate with polymerized fibrin form a thrombus at the site of vascular injury. Excessive thrombus formation is prevented by fibrinolysis. tPA and PAI have a central role in the hemostatic balance. However, when these activities are not properly regulated the organism is subjected to either excessive bleeding or thrombosis.

The hemostatic response during elective operation for AAA and in patients with multiple trauma is well documented [26][27]. However, little is known about the hemostatic changes during hemorrhage and shock in the patient with a RAAA. The use of the anti-fibrinolytic drug, aprotinin, in cardiac surgery has reduced blood transfusion requirements [28]. It was thought that a similar effect might occur in surgery for a RAAA. However, a clinical trial by Robinson et al. [29] failed to demonstrate any benefit of the use of high-dose aprotinin during the repair of a RAAA.

With regard to EVAR for RAAA, limited data exist examining correlations between preoperative coagulopathy and outcome. Preoperative detection of coagulation abnormalities may play a vital role to early correct deficiencies in the emergency surgical situation. Fibrinogen, acts as one of the key-factors in the coagulation cascade, and has previously been suggested as a biomarker for increased perioperative bleeding in other areas such as cardiac, orthopedic, obstetric, and trauma surgery [30][31][32][33].

The present study attempted to investigate the impact of fibrinogen levels in the outcome of RAAA patients undergoing EVAR. Statistical analysis revealed a significant association between preoperative fibrinogen levels and 30-day mortality. It seems that the higher the levels of fibrinogen are on presentation, the better chances of early survival the patients have. However, no association was found between fibrinogen level and the possibility of the patient presenting back to the hospital for an aortic related re-intervention or the possibility of encountering an endoleak or a MACE. Equally, the findings showed no statistically significant association between fibrinogen level and survival during the existing follow up.

The present study has certain limitations. First, the study suffers from small numbers, and as such, may lead to a type II error. Second, this being a retrospective study, important variables may not have been captured. Another limitation is lack of complete clinical information for patients who were transferred from one hospital to another where treatment was received. There could be unknown variables that affect patient outcome. Nevertheless, this is an important pilot study and the results should be taken into account for future and larger studies.

In conclusion, higher fibrinogen levels on admission, which may indicate a preoperative hypercoagulable profile, may be associated with better chances of early survival in RAAA patients undergoing EVAR. Whether the outcome of these patients can be improved by technically increasing fibrinogen levels through proactive administration of plasma or other blood products, as soon the diagnosis of RAAA is made, remains to be seen.

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