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The Impact of Vascular Complications on Survival of Patients on Venoarterial Extracorporeal Membrane Oxygenation

Running Head: Vascular complication and ECMO survival

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Abstract

Background

There are various factors that can influence the survival of patients on Veno-arterial extracorporeal membrane oxygenation (VA ECMO). Vascular complications from femoral cannulation are common and are potentially serious. We analyzed the impact of vascular complications on survival of patients on VA ECMO.

Methods

Patients supported on VA ECMO via femoral cannulation from Oct 2010 to Nov 2014 were enrolled in this study. Data was gathered retrospectively by reviewing our institutional database. Patients were separated into two groups depending on the presence of major vascular complications, defined as patients that required surgical intervention. We evaluated predisposing factors for vascular complications and compared survival of patients in each group.

Results

There were 84 patients enrolled in the study. The rates of overall ECMO survival and survival to hospital discharge were 60% and 43% respectively. Major vascular complications requiring surgical intervention were seen in 17 (20%) patients. Ten patients (12%) had compartment syndrome requiring prophylactic fasciotomy and 10 patients (12%) had bleeding/hematoma requiring surgical exploration. The only significant predisposing factor for vascular complications was the absence of distal perfusion catheter (odds ratio 14.8, p=0.03). The rate of survival to discharge was 18% and 49% in patients with and without vascular complications (p=0.02). Vascular complications were an independent factor of significantly worse survival in patients on VA ECMO by multivariate analysis (hazard ratio 2.17; P=0.02).

Conclusions

Vascular complications negatively affect survival in patients on VA ECMO support via femoral cannulation. The utilization of distal perfusion catheter can decrease the incidence of complications.

Word count: 250

Introduction

Extracorporeal membrane oxygenation (ECMO) is increasingly used for treatment of patients with critical cardiopulmonary failure (1-4). Recovery from ECMO largely depends on the underlining disease process since ECMO is only a supportive measure (4). Major complications of ECMO can include neurologic, cardiac, pulmonary, hemorrhagic and vascular issues, which lead to serious consequences (6, 7). The most common cannulation technique for adults requiring Venoarterial (VA) ECMO is percutaneous, via the femoral vessels because of their size and accessibility (4, 5). However, vascular complications related to femoral cannulation are one of the most common and serious complications of ECMO (6-12). Leg ischemia is particularly worrisome and a distal perfusion catheter is often placed to prevent ischemia (13, 14). The relationship between major vascular complications and outcomes of patients on ECMO is still unclear (11, 12). We have evaluated the impact of vascular complications on survival in patients on VA ECMO via femoral percutaneous cannulation.

Patients and Methods

Patients

Adult patients (age > 16 years old) supported on VA ECMO via femoral percutaneous cannulation from October 2010 to November 2014 were enrolled in this study. Data was collected by retrospectively reviewing medical charts and our institutional database, which was approved by the institutional review board. All patients were included regardless of indication (cardiogenic shock, respiratory failure, or both). Major vascular complications related to cannulation were defined as those that required surgical intervention. Surgical indications include surgical bleeding that required more than 2 units of blood and/or symptomatic limb ischemia (change in appearance, decrease in oximetry and/or loss of pulse). Complications in which surgical intervention was withheld due to patient death or withdrawal of care were counted as major complications. Patients were separated into two groups depending on the presence of major vascular complications. Minor vascular complications managed conservatively were evaluated separately.

Procedure

All cannulation was performed percutaneously at the bedside without fluoroscopy by a modified Seldinger technique unless there was technical difficulty. The size of the cannula was chosen based on desired flow for the patient. A distal perfusion catheter (DPC) was placed routinely at the same time unless there was technical difficulty or the patient was too unstable. A single dose of heparin (5000-7500 IU) was administered upon cannulation. Continuous heparin was started no more than 24 hours after cannulation aiming for a PTT goal of 45 to 55 seconds (5).

When the patient had clinically improved, a weaning trial was performed at the bedside using the protocol previously described (15). If the patient tolerated the trial satisfactorily, the patient was taken to the operating room for decannulation. All decannulation was performed after exposing femoral vessels. The femoral artery was repaired primarily with interrupted sutures of 5-0 Prolene or using bovine pericardial patch. A purse-string suture of 4-0 or 5-0 Prolene was used to repair the femoral vein. A vacuum-assisted closure (VAC® KCI, San Antonio, Texas) dressing was routinely placed after closure of the fascia.

Study design

Patients were divided into 2 groups – group I with major vascular complications and group II without major vascular complications. Demographics between groups were compared using univariate and multivariate analysis including all variables to evaluate predisposing factors. The groups were also compared for outcomes. Mortality was the primary outcome and the secondary outcome was the occurrence of any major complications during ECMO support. Kaplan-Meier survival curves were drawn for each group and survival distributions were compared. Multivariate analysis was also performed to validate the result. Predisposing factors for mortality were evaluated by comparing 30-day survivors to non-survivors. After identifying significant predisposing factors for mortality, multivariate analysis was performed to determine the significance of vascular complications upon survival.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and compared with Student's t-test. Categorical variables were evaluated by chi-square test or Fisher's exact test as univariate analysis. Logistic regression analysis was utilized for multivariate analysis and odds ratios were calculated. Survival distributions were compared with log rank test as univariate analysis and Cox proportional hazards model as multivariate analysis. Hazard ratio was also calculated. P values of less than 0.05 were deemed statistically significant. Statistical analysis was performed using the R statistical software package version 3.1.2 (R foundation, Vienna, Austria).

Results

There were 84 patients who met enrollment criteria. The ECMO survival rate (patients successfully weaned from ECMO) and the rate of survival to hospital discharge were 60% and 43% respectively. Median length of survival was 32 days (95% confidence interval (CI) 17-200). Seventeen patients (20%) had at least one episode of major vascular complication, including 10 patients (12%) with leg ischemia who progressed to compartment syndrome requiring prophylactic fasciotomy and 10 patients (12%) with significant bleeding and/or hematoma at the cannulation site to require surgical exploration. Three patients had both ischemic and hemorrhagic complications. None of patients required limb amputation.

Predisposing factors for vascular complications

Table 1 shows demographics of patients with and without vascular complications. Age and absence of distal perfusion catheter were significantly different between the two groups by univariate analysis. However, by multivariate analysis, only absence of distal perfusion catheter was a significant predisposing factor (odds ratio 18.7; p=0.03) (Table 2). The other factors including history or risk factors of peripheral vascular disease and severity of baseline condition were not significantly associated with vascular complications.

Outcome

Table 3 shows outcome of patients with and without vascular complication. Patients with vascular complication required significantly more procedures (p=0.01) but there was no difference in the amount of transfusion required. Duration of ECMO support and hospital stay were not significantly different. Patients with a major vascular complication were more likely to experience disseminated intravascular coagulation (DIC).

Impact of Vascular Complications on Survival

Univariate analysis: The rates of survival to discharge were 18% and 49% in patients with and without a major vascular complication (p=0.02). Figure 1 shows Kaplan-Meier curves of patients with and without vascular complication. Survival length of patients without vascular complication was significantly better than that of patients with vascular complication by univariate analysis (p=0.002). Table 4 shows the hazard ratio for each vascular complication. Major ischemic complication (compartment syndrome) had highest hazard ratio (3.03; p=0.003) followed by major bleeding/hematoma that required surgical intervention (1.93; p=0.09). The hazard ratio of bleeding/hematoma was lower than that of ischemia. The hazard ratio of major complications (i.e. those that required surgical intervention) was higher than that of minor complications (i.e. those treated conservatively). The influence of a distal perfusion catheter on survival was also evaluated because its absence predisposed patients to a vascular complication. Length of survival tended to be worse in patients without a DPC initially although it was not significant (hazard ratio 0.79; p=0.48).

Multivariate analysis: For multivariate analysis, comparing 30-day survivors to non-survivors identified predisposing factors for mortality. Table 5 shows predisposing factors, which influenced 30-day mortality significantly by univariate analysis. It also shows the result of Cox proportional hazards model for each factor. A major vascular complication was an independent factor for significantly worse survival by multivariate analysis (hazard ratio 2.17; p=0.02). Neurologic complications also predicted mortality (hazard ratio 7.80; P<0.0001).

Comment

There are a number of factors that can influence survival of patients on ECMO (1-4). The preoperative factor that influences outcome the most is probably the underlining condition of the patient (4). Therefore, ECMO is indicated only if recovery is expected or as a bridge to further treatment . Once ECMO is initiated, it is often the complications of ECMO that determine the fate of the patient (6, 7). Neurologic complications are probably the most devastating because they are often irreversible and lead to the withdrawal of care from the patient (7).

Vascular complications are relatively frequent and serious in nature (6, 11). The majority of VA ECMO is performed by percutaneous femoral cannulation. Lower extremity ischemia and bleeding from the cannulation site can pose serious problems. In our study, vascular complications were an independent factor of significantly worse survival of patients on VA ECMO via femoral cannulation. Whereas there is usually a direct correlation between a major neurologic complication and mortality, the link between vascular complications and mortality is less clear (7). In our study, only 2 out of 17 patients with a major vascular complication seemed to have a direct link between the complication and mortality. Patients with vascular complications had a higher number of procedures per patient and an increased frequency of DIC. The ischemic process, multiple procedures and transfusions exacerbate the systemic inflammatory response related to ECMO, leading to increased risk for mortality (16).

Our data demonstrated that ischemic complications had a greater impact upon mortality than bleeding/hematoma, suggesting that the pathophysiology of the injury is more significant with ischemia. Ischemia can be caused by vascular occlusion from the cannula, thromboembolization or dissection of the artery. Bleeding and hematoma are usually caused by vascular injury (laceration, perforation, dissection). The inflammatory response and hemodynamic effects of ischemia are different from the response from blood loss and transfusions, potentially accounting for the differential effect on outcome.

Considering the impact of vascular complications on mortality, prevention is very important. Although the impact upon mortality of bleeding/hematoma is smaller than that of ischemia, prevention of this complication may be more difficult because it relies on cannulation technique and anatomy of the patient. While direct cut down may prevent some technical complications, we adopted a preference for percutaneous cannulation since we seemed to have a lower incidence of infection and bleeding after percutaneous cannulation compared to open cannulation. However, given the multiple variables involved and lack of a formal study protocol, we do not have adequate data to support this claim. Appropriate imaging with fluoroscopy helps for safer cannulation. However, fluoroscopic equipment is not readily available for emergency use in all areas of the hospital, necessitating a high reliance on cannulation without imaging. Concerning other predisposing factors for vascular complication, older age and elevated BMI tended to decrease the risk of vascular complication. The etiology of this apparent effect is unknown.

In our study, the only significant predisposing factor for vascular complication by multivariate analysis was absence of a distal perfusion catheter (DPC). The efficacy of the DPC has been reported in a few retrospective studies (1, 8, 13). There is a data that DPC can actually increase lower limb perfusion (17). In our institution, DPCs are placed routinely unless there is technical difficulty or patient instability. Placement of the DPC was associated with a lower risk of vascular complications in this study. Comparing survival of patients with and without DPC, there was a trend towards an increase in short-term survival in patients with DPC, although it was not statistically significant. The relatively small size of the study population may have limited our ability to discern a difference if it does exist. Utilizing an alternate cannulation site is another way to prevent ischemic complications (18-21). The risk of ischemic complication of axillary artery cannulation is reported to be lower than that of femoral cannulation (18). However, the risk of bleeding and limb hyper-perfusion is significantly higher in axillary cannulation (18). In addition, placement of ECMO cannulas via the femoral vessels requires less specialized training and equipment, and thus may have the advantage of quicker institution of ECMO support in many situations. Placement of DPC is the easiest and the most effective measure to prevent lower limb ischemia.

Monitoring of lower extremity perfusion is also very important in the prevention and early recognition of ischemic complications. In addition to periodical physical examinations and laboratory tests, we use near-infrared spectroscopy to monitor lower extremity perfusion continuously. If spectroscopy suggests ischemia is present, patency of the DPC is checked to make sure there is no clot or kink, followed by angiography if necessary to check position and look for possible thrombosis or embolization. Prophylactic fasciotomy is performed if compartment syndrome is suspected. Utilizing those preventive measures, we have managed to avert any ischemia severe enough to require limb amputation.

There is limited data regarding the influence of vascular complications of ECMO on outcomes (11, 12). Bisdas and colleagues concluded that there was no significant difference in mortality between patients with and without vascular complications (11). A major difference from our study was that they compared mortality rates at certain periods rather than survival distributions of patients. Comparing survival distributions might have yielded more accurate data. Another difference is they included veno-venous (VV) ECMO via femoral cannulation in their analysis. VV ECMO is often used in a different patient population with a different expected survival than that seen in VA ECMO, largely due to differences in the underlying disease processes. In addition, the mechanism of vascular complication would be completely different from that seen in VA ECMO. Including such disparate groups of patients may obscure a difference in outcome if it did exist. We have focused our study on the complications of arterial cannulation to minimize the variables between the groups of patients studied. Finally, Bisdas and colleagues included minor and severe vascular complications together, and they did not seem to include bleeding from the cannulation site as a complication even though it is frequent and a potentially serious complication.

One limitation of the current study is its retrospective design using a database and medical charts. Therefore, analysis of predisposing factors for vascular complication might be biased, although we tried to minimize this using multivariate analysis. We had a very small number of patients with PAD in our study. Considering that the majority of patients with PAD are asymptomatic, we might have underreported the incidence of PAD in our patient population (22). We also looked at the presence or absence of a DPC, but did not identify why a DPC was not placed. It is difficult to tell whether absence of a DPC caused vascular complication or if the factor that prevented placement (like PAD) caused the vascular complication. We also have a relatively small sample cohort, especially in vascular complication group, which could make the data less accurate. Given the small cohort sizes, the lack of statistical significance does not necessarily imply the lack of clinical significance so there may be other factors that lead to vascular complication or affect survival that were not detected in this study.

In conclusion, vascular complications worsen survival of adult patients on VA ECMO via femoral cannulation. Ischemic complications influence outcome more than bleeding complications. Placement of distal perfusion catheter can decrease the risk of vascular complication.

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Table1: Demographics of patients with and without vascular complications

	With vascular complication	Without vascular complication	P value
Number	17	67	
Male	11 (65%)	48 (72%)	0.58
Age	40.9±13.5	50.3±14.3	0.02†
BSA	1.93±0.26	2.01±0.31	0.32
BMI	29.0±9.1	29.2±6.3	0.94
Smoking	3 (18%)	25 (37%)	0.16
CAD	6 (35%)	28 (42%)	0.78
PAD	1 (6%)	2 (3%)	0.50
Diabetes	5 (29%)	19 (28%)	0.99
COPD	2 (12%)	8 (12%)	0.99
Liver dysfunction	4 (24%)	8 (12%)	0.25
Steroid and/or Immunosuppression	4 (24%)	7 (10%)	0.22
Post cardiotomy	4 (24%)	9 (13%)	0.29
Cardiac failure	15 (88%)	55 (82%)	0.73
Respiratory failure	15 (88%)	60 (90%)	0.99
Sepsis	0	4 (6%)	0.58
Salvage or emergent	14 (82%)	53 (79%)	0.28
CKD class 4 or 5	5 (29%)	13 (19%)	0.32
APACHE II score	30.3±6.0	29.1±8.1	0.56
Arterial cannula (Fr)	19.8±2.3	19.7±1.7	0.72
Primary indication			0.44
Cardiac	16 (94%)	56 (74%)	
Respiratory	1 (6%)	11 (16%)	
No distal perfusion	7 (41%)	10 (15%)	0.02†

†: Statistically significant ($p<0.05$)

Continuous data are expressed as mean ± standard deviation.

APACHE: acute physiologic and chronic health evaluation; BMI: body mass index; BSA: body surface area; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive lung disease; PAD: peripheral artery disease

Table 2: Predisposing factors for vascular complications (multivariate logistic regression)

	Odds ratio	95% Confidence interval	P value
Age ≥ 60	0.16	0.002 to 9.28	0.38
Obesity (BMI ≥ 30)	0.17	0.01 to 3.87	0.26
CAD	0.11	0.01 to 1.76	0.12
Post cardiotomy	10.2	0.34 to 404	0.17
CKD class 4 or 5	4.02	0.29 to 56.4	0.30
APACHE II score ≥ 30	3.82	0.50 to 29.2	0.20
Arterial cannula ≥ 20 Fr	1.46	0.16 to 13.6	0.20
No distal perfusion	18.7	1.34 to 261	0.03†

Only factors with p values less than 0.5 are shown.

†: Statistically significant ($p<0.05$)

APACHE: acute physiologic and chronic health evaluation; BMI: body mass index; CAD; coronary artery disease; CKD: chronic kidney disease

Table 3: Outcomes

	With vascular complication	Without vascular complication	P value
Medical resources			
Number of procedures	2.8 ± 2.1	1.3 ± 1.5	0.002†
PRBC (units)	20.0 ± 20.7	14.4 ± 17.0	0.25
Days on ECMO if survived	14.6 ± 6.7	10.6 ± 7.5	0.16
Length of stay if survived	33.0 ± 2.4	53.3 ± 63.0	0.10
Complications			
Cardiac complications	0	11 (16%)	0.11
Respiratory complications	5 (29%)	15 (22%)	0.54
Neurologic complications	7 (41%)	17 (25%)	0.23
Acute kidney injury	6 (35%)	15 (22%)	0.35
Disseminated intravascular coagulation	5 (29%)	2 (3%)	0.003†
Survival			
ECMO survival	8 (47%)	49 (73%)	0.08
Survived to discharge	3 (18%)	32 (48%)	0.02†
Median survival (days)	11 (4-30)	48 (21-NA)	0.002†

†: statistically significant ($p<0.05$)

PRBC: packed red blood cells

Table 4: Impact of each vascular complication (Cox proportional hazards model)

	Severity	Hazard ratio	95% confidence interval	P value
All vascular complication	Major	2.52	1.37 to 4.63	0.003†
	Minor	1.22	0.54 to 2.77	0.63
Cannulation site bleeding/hematoma	Major	1.93	0.90 to 4.13	0.09
	Minor	1.12	0.44 to 2.86	0.81
Lower extremity ischemia	Major	3.03	1.50 to 6.10	0.002†
	Minor	1.37	0.42 to 4.46	0.60

†: Statistically significant ($p<0.05$)

Major complications are those that required surgical intervention. Minor complications are those managed conservatively.

Table 5: Impact of each complication on survival of patients on VA ECMO by multivariate analysis (Cox proportional hazards model)

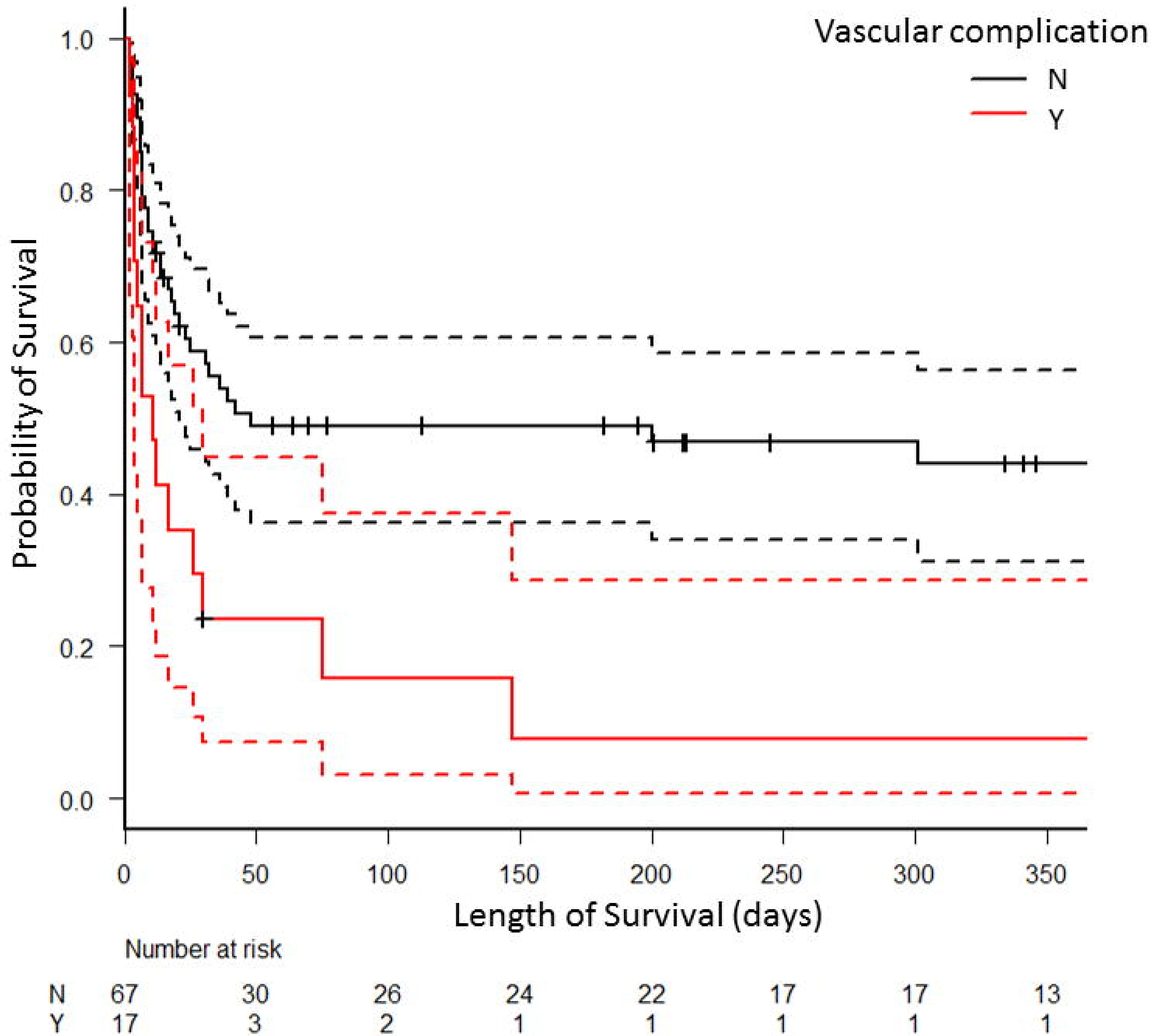
	Hazard ratio	95% confidence interval	P value
Vascular complication	2.17	1.12 to 4.20	0.02†
Neurologic complication	7.80	3.44 to 17.72	<0.001†
Acute kidney injury	0.99	0.51 to 1.88	0.96
Disseminated intravascular coagulation	1.57	0.57 to 4.30	0.38
Clinically significant thrombosis/embolization	0.84	0.36 to 2.00	0.70

†: Statistically significant ($p<0.05$)

Figure Legends

Figure 1: Kaplan-Meier survival curve of patients with and without vascular complication

Dashed lines show 95% confidence intervals.



Vascular complication
N
Y
1.0
0.8
0.6
0.4
0.2
0.0
Probability of Survival
0
50
100
150
200
250
300
350
Length of Survival (days)
Number at risk
N 67 30 26 24 22 17 17 13
Y 17 3 2 1 1 1 1 1