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POST-SURGERY OUTCOMES IN PATIENTS WITH POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA: A RETROSPECTIVE SURVEY

Short Title: Surgery in chronic myeloproliferative syndromes

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Abstract

A multicenter retrospective analysis was performed to estimate the frequency of thrombosis and haemorrhage after surgical procedures in patients with Polycythemia Vera (PV) and Essential Thrombocythemia (ET). Data from 105 PV and 150 ET patients were analyzed, for a total of 311 surgical interventions. An emergency procedure was performed in 25 (8.1%); 194 surgeries were done under general anaesthesia and 21/91 abdominal interventions (23%) under laparoscopy; 155 (50,1%) were major surgeries. Subcutaneous heparin was administered in 169/311 cases and antiplatelet therapy in 48/311 cases (54.3 and 15.4%, respectively) interventions. 188/255 (74%) were on cytoreductive therapy before surgery. No events were observed in 259/311 procedures (83.2%) during 3 months follow-up; there were 12 arterial and 12 venous thrombotic events, 23 major, 7 minor hemorrhages and 5 deaths. Arterial thrombosis were more frequent in ET (5.3 vs. 1.5%, P=0.08), venous events were more frequent in PV (7.7 vs. 1.1%, P=0.002). There was not a correlation between bleeding episodes and the type of diagnosis, use of antithrombotic prophylaxis or type of surgery. An high proportion of PV and ET surgeries was complicated by vascular occlusion (7.7%) or by a major hemorrhage (7.3%). Prospective investigations analyzing the optimal prophylaxis in these patients are suggested.

Introduction

Polycythemia Vera (PV) and Essential Thrombocythemia (ET) are two chronic myeloproliferative diseases (cMPD)[1] with clinical courses that are characterized by a low rate of transformation into acute myeloid leukemia and myelofibrosis [2-4], a long median survival and an increased risk of venous and arterial thrombosis and of hemorrhages [5, 6]. There is a common belief that surgery could present an important circumstantial risk factor for thrombosis and bleeding[7,8], although only limited data is available [9,11]. We carried out a retrospective evaluation of a cohort of PV and ET patients with the following aims: to estimate the incidence of thrombosis, hemorrhage and fatality after surgical procedures; to identify additional risk factors for adverse outcomes in these patients and to evaluate a possible effect of different peri-operative management strategies (control of the disease and prophylaxis for cardiovascular events and bleeding) on the frequency of an adverse outcome.

Patients, materials and methods

This study was approved by Institutional Review Boards and Ethics Committees in each participating institution. The ethics committees stated that written consents were not required by patients in order to report the encrypted anonymous data.

A retrospective chart review was performed for all PV and ET patients that were consecutively diagnosed from 1st January 1985 to 31 July 2005 at six major Italian hematology departments that had an electronic database for clinical records and belonged to the GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) network. Diagnoses of PV and ET were made locally according to the PVSG [12-14] and WHO criteria [15].

Patient selection

Patients were eligible for the study if they had undergone at least one surgical procedure from diagnosis to July 30, 2005, and if they had clinical and laboratory follow-ups from diagnosis to December 31, 2005. The following information was extracted from the chart for each eligible patient: personal data; individual risk factors for arterial thrombosis (treated diabetes mellitus; treated hypercholesterolemia; treated arterial hypertension; smoking; cardiovascular diseases, such as atrial fibrillation, and valvular or coronary disease; previous arterial thrombosis); previous history of venous or arterial thrombosis; date of diagnosis; laboratory characteristics at diagnosis; thrombosis and hemorrhagic complications during follow-up before surgery; specific therapy for the myeloproliferative disease; date and type of surgery and anti-thrombotic and anti-hemorrhagic peri-

operative prophylaxis procedures; thrombosis, hemorrhagic events and fatality occurring within 3 months after surgery.

End-point definitions

Major thrombotic events were defined according to Landolfi et al[16]. Diagnostic procedures for establishing thrombosis included cerebral computed tomography (CT) or magnetic resonance imaging for stroke, characteristic neurological symptoms for transitory ischemic attack, electrocardiography and/or increased cardiac enzymes for acute myocardial infarction (AMI), angiography for peripheral arterial thrombosis and ultrasonography of the arms or the legs, performed in patients with a clinical suspicion of thrombosis, or pulmonary ventilation–perfusion scan or CT scan for deep venous thrombosis (DVT) or pulmonary embolism .

Major hemorrhages were defined as intracranial (documented by imaging), ocular, articular, or retroperitoneal bleeding; episodes requiring surgery or angiographic intervention and any bleeding causing a hemoglobin reduction of 20 g/L or more and/or requiring transfusion of two or more blood units[17]. Minor hemorrhages included all cases of bleeding not classified as major, such as bruising, small ecchymoses or epistaxis, or microscopic hematuria.

Surgical bleeding was defined as minor if it was of severity grade 1 or 2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events [18] and major if it was of grade 3, 4 or 5.

In all Centers, charts review and data collection was performed by the physician(s) specifically caring PV and ET patients. Confirmation of the diagnosis of myeloproliferative disease and of every vascular events or bleeding episodes by an independent senior researcher was however required for each center, with a careful review of the original chart and the laboratory data.

Surgical definitions.

Surgeries involving the thorax, abdomen or pelvis lasting longer than 30 minutes in general surgery; hip or knee replacement or hip fracture in orthopedic surgery; valvular replacement and coronary by-pass in cardiovascular surgery; and intracranial intervention in neurosurgery were defined as major interventions; all other cases, including diagnostic procedures, were defined as minor interventions. Data regarding the type of anaesthesia (general or local) and type of operation (elective or emergency procedure; laparoscopy or laparotomy for abdominal surgery) were also collected.

Statistical analysis

Logistic regression was used to model the factors possibly influencing treatment options by the attending physicians at baseline or before surgery. In this model, use of cytoreduction, antiplatelet

therapy (aspirin or thyenopiridines) or oral anticoagulant therapy at baseline was used as a dependent variable of age, gender, presence of diabetes, hypercholesterolemia, arterial hypertension, smoking, previous cardiovascular disease, and previous history of venous or arterial thrombosis. Cox regression analysis was used to model the probability of developing an end-point during the follow-up period.

Results

Enrolled subjects

During the study interval, 716 PV and 1462 ET were diagnosed; 4.8% of patients in the whole cohort of patients were lost at follow-up; 255 patients (105 PV and 150 ET, Table 1) underwent at least one surgery, for a total of 311 interventions (212 patients: 1 intervention, 43 patients: 2 to 5 interventions).

At least one risk factor for arterial thrombosis was present in 128/255 (50.1%); risk factors were more prevalent in PV than in ET patients (58.5 vs. 46.8%, p=0.02). An excess of male and older age at surgery explained this latter finding in a multivariate analysis. Previous arterial thrombosis was present in 23/255 patients (9.0%: 9.5% in PV and 8.7 % in ET, p=0.81); previous DVT was present in 9/255 patients (3.5%), with a similar distribution between PV and ET patients. After diagnosis, antiplatelet drugs were given to 211/255 patients (82.7%); cytoreductive treatments to 188/255 (74%), and warfarin to 16/255 (6.2%); all PV patients were phlebotomized to reduce their hematocrit levels.

Surgical characteristics and antithrombotic prophylaxis

Table 2 reports the clinical features of patients at the time of surgery and by surgery type. Antithrombotic prophylaxis was significantly different between major and minor surgeries, with low-molecular weight heparin administered at dosages above 3000 anti-Xa units almost exclusively in patients undergoing major surgery. No prophylaxis was given to 41% of patients undergoing minor surgery. 26 patients started a short course of chemotherapy or phlebotomy just before intervention. Due to the retrospective nature of the study, the choice of antithrombotic prophylaxis, if any, and of chemotherapy or phlebotomy before intervention was based on each Center policy. Administration of low-molecular weight heparin (LMWH) once a day or of unfractioned heparin (UH) b.i.d. or t.i.d., starting before intervention and until day 7-15, was the usual antithrombotic prophylaxis. In a minority of cases, antiplatelet prophylaxis was chosen, initiating it 3 to 5 days before surgery until day 7-15 (see Table 2). To assess potential factors influencing the choice of antithrombotic prophylaxis and cytoreduction, we modelled with logistic regression the odds of being treated with heparin, antiplatelet drugs or both, and of phlebotomy or chemotherapy, considering significant

those factors with a p value below 0.05. Patients that were given heparin had a lower chance of being given antiplatelet prophylaxis at surgery (and conversely); heparin was preferentially given to those patients undergoing major surgery and those having a history of venous or arterial thrombosis. Antiplatelet treatment was preferred in patients with PV rather than in those with ET. Hematology intervention (i.e., phlebotomy or cytoreduction with either busulfan or hydroxyurea) was preferentially given in those patients with a platelet count at surgery higher than $1000x10^9$/L, with PV, with an age at surgery greater than 60, a thrombotic event during follow-up, undergoing major surgery and with a white blood cell count higher than $10x10^9$/L.

Vascular outcomes and risk factors

Clinical outcomes were recorded within a 3 month follow-up after surgery. No events were observed in 259/311 procedures (83.2%); there were 12 arterial and 12 venous thrombotic events, 23 major and 7 minor hemorrhages and 5 deaths (2 AMI, 2 ischemic stroke, one multiorgan failure). Figure 1 shows the incidence of major vascular outcomes and death during the follow-up. The incidence of all thromboembolic events was higher in the first two weeks, while it decreased throughout the remaining period of time (Table 3). Major surgery showed a slightly higher, but not statistically significant, risk of DVT (HR 2.0, 95% CI 0.6-6-6). Arterial thromboembolism (AT) was more frequent in ET patients (HR 3.3, 95% CI 0.7 – 15.3), while venous events were more frequent in PV patients (HR 7.3 95% 1.6 – 33.4). There was a strong risk gradient for arterial thrombosis associated with the presence of one or more arterial risk factors (HR for 3 or more risk factors: 49.7, 95% CI 9.0-273.2).

Treatment with heparin or antiplatelet drugs had no apparent effect on adverse outcomes, with a potential trend for heparin treatment in the prevention of venous thromboembolism (HR 0.55, 95% CI 0.1 – 2.1). The effect of heparin in the prevention of venous thromboembolism was unmodified by the inclusion of variables influencing the choice of a prophylaxis in the Cox regression model. White blood cells count, platelet count, hematocrit level and age at surgery, diagnosis (ET or PV), past history of DVT or AT and gender were not associated with an increased risk of death, arterial or venous thromboembolism in the multivariate Cox regression (data not shown).

Bleedings

The overall incidence of bleeding complications (major and minor) was 10.5% (30 episodes in 284 surgeries, 95% CI 7.6-14.3). There was a clear trend for an increased bleeding risk in those subjects receiving antithrombotic prophylaxis vs. no prophylaxis (heparin vs. no prophylaxis, HR 1.7, 95% CI 0.7 – 7.7; antiplatelet therapy vs. no prophylaxis (HR 2.4, 95% CI 0.8 – 7.7). Furthermore, the hemorrhagic risk was strongly related to the immediate post-surgical period with an incidence at periods 0-15 day, 15-30 days and 30-60 days of 3.1, 0.8 and 0.2 cases/1000 pt-

day in patients receiving no prophylaxis, 9.8, 0 and 0 in patients receiving antiplatelet therapy and 6.6, 0 and 0.2 in patients receiving heparin.

Discussion

Advanced age, a history of thrombosis and leucocytosis are the major risk factors for cardiovascular events [4,6,7,16,19-22] in patients with PV and ET, whereas the contribution of hereditary and acquired thrombophilic states or of the other well-recognized risk factors for cardiovascular disease, such as hypertension, diabetes mellitus, smoking and hypercholesterolemia, has not been firmly established.

Surgery is a strong circumstantial risk factor for venous thromboembolism, both in the general population and in cancer patients, increasing the DVT risk by at least two-fold [24]. Antithrombotic prophylaxis with heparin (either LMWH or UH) is effective at reducing the rate of DVT in cancer patients with a low incidence (3%) of bleeding complications [25, 26]. Unfortunately, there is no available data on the incidence of vascular complications, bleeding or fatalities after surgical interventions in PV and ET patients.

We performed a retrospective 20-year analysis of PV and ET patients who underwent surgical interventions to collect clinical data on vascular outcomes, bleeding and deaths. We tried to improve the quality of the data collection by enrolling consecutive patients only from Italian tertiary care hematology centers that had an electronic database for clinical records. Moreover, with the aim of reducing the unavoidable limitations of this study due to its retrospective nature, confirmation of the diagnosis of the myeloproliferative disease and of vascular events or bleeding episodes by a senior researcher was required for each center, with a careful review of the original chart and the laboratory data. Despite these efforts, the present study has some obvious limitations. First, the lack of a definite protocol for the assessment of thrombotic events and the ascertainment of only symptomatic thromboses may have led to an underestimation of thrombotic events. Thus, our reported incidence rates are not directly comparable with the results from randomized clinical trials that evaluated asymptomatic events. Second, the study could only analyze a small number of cMPD patients. In a post-hoc analysis, our study (enrolling 311 surgeries, with an incidence of arterial and venous thromboses of around 10%) had a power of only 0.36; thus, it is able to detect significant differences only if they are present in about one-third of the cases. Alternatively, given an observed incidence of thromboembolic complications of around 10%, about one thousand patients should be enrolled in a prospective study, with the expectation of a 50% relative reduction of risk. Even this latter figure is likely underestimated since it does not take the interaction between possible confounders (e.g., the different thrombotic risk of each surgery type) into account.

Despite these limitations, the study shows an increased risk of both thrombotic and bleeding episodes in cMPD. The majority of cases in this large cohort of patients (188/255, 74%) were treated with cytoreductive therapy and phlebotomy before surgery and, consequently, the platelet and white blood cell counts and the hematocrit level were above their respective normal ranges at the time of intervention in only a very small number of patients. Moreover, the large majority of patients were treated with antithrombotic prophylaxis (heparin or antiplatelet agents), even in the case of a minor surgery or a diagnostic procedure. Despite this active approach, a significant proportion of surgeries (8/155, 5.1% of major surgeries and 4/156, 2.5% of minor surgeries) were complicated by an episode of DVT. This incidence could be compared with the 6.3% rate of DVT in cancer patients receiving no prophylaxis and 1.8% in those receiving heparin, as detected by ultrasound evaluation [27,28]. The rate of symptomatic DVT in patients receiving heparin after major surgeries is, however, much lower, usually in the range of 0.5-2% [29]. Thus, we can estimate that the risk of DVT after major surgery in PV/ET patients is at least five-fold increased, confirming the predisposition to thrombosis in patients with cMPD. Unfortunately, other than the type of cMPD (DVT is more frequent in PV than in ET), no other personal characteristics, baseline clinical data or type of treatment found to be predictive of DVT occurrence. Given the retrospective design of this study, an evaluation of coagulation thrombophilic defects was not performed.

A similar rate of AT (12/311, 3.8%) was observed after intervention. Surgery is not a risk factor for AT, apart from patients that underwent cardiovascular interventions, and this seems to be a specific characteristic of cMPD patients. In contrast with DVT, two risk factors emerged for AT, namely ET diagnosis and the presence of more than one risk factor for cardiovascular thrombosis. Whether stratification of risk for these factors is required for optimal prophylaxis remains uncertain.

Interestingly, the risk of both DVT and AT dramatically decreases after one month following surgery, the incidence of arterial events becomes very similar to the incidence recently reported in the ECLAP study (0.2 vs. 0.15 of arterial events) [20]. This observation could suggest that there is no apparent need for prolonged prophylaxis in these patients.

Recently, a somatic G-T conversion at nucleotide position 1849 in exon 14 of the Janus Kinase 2 (JAK 2) gene was identified in Philadelphia chromosome-negative chronic myeloproliferative disorders [30-32]. This mutation results in the substitution of a valine to phenylalanine at position 617 (JAK2 V617F mutation), and it can be detected in the majority of patients with PV and approximately half of the patients with ET and idiopathic myelofibrosis. Whether this JAK2 mutation represents a risk factor for thrombosis in PV and ET remains questionable since the results from many studies are conflicting [33-36]. A JAK2 assay was not carried out in our cohort at surgery or at diagnosis, thus, a possible association with thrombotic complications could not be evaluated.

The evaluation of efficacy of prophylactic anticoagulation for patients with PV and ET before surgery must take the often unpredictable development of bleeding complications into account. In our cohort, 23/311 (7.3%) experienced major hemorrhage episodes that required transfusion treatment, prolonged hospital admission and, in some cases, new interventions. This rate is higher than those observed in clinical trials evaluating heparin prophylaxis and in surgical patients with cancer [25], which are around 1%. Given the retrospective, non-randomized study design, the actual rate of bleeding could not be accurately assessed, as it could be biased by the treating Center strategies, and should be considered with caution. However, it could confirm the apparent paradoxical predisposition to both bleeding and thrombosis in cMPD patients. There was not a correlation between bleeding episodes and type of diagnosis, use of antithrombotic prophylaxis or type of surgery. Five fatalities (1.6%) within 3 months following interventions were recorded, but it was not possible demonstrate a clear association with intervention, due to the paucity of clinical data in the medical chart. However, only one out of the five deaths occurred immediately after surgery (5 days), while all other deaths occurred two months after surgery.

In conclusion, this study shows that the rate of symptomatic DVT and AT after surgery remains very high in cMPD patients despite effective control of cell blood count with phlebotomy and cytoreduction and administration of standard antithrombotic prophylaxis. On the other hand, these patients exhibited an increased bleeding risk after surgery, with an unexpectedly high incidence of major bleeding. It seems appropriate to restrict the use of antithrombotic prophylaxis with LMWH in PV patients undergoing major surgery. Conversely, antiplatelet drugs may be the optimal choice in ET patients with several arterial risk factors. This approach should be weighed against the surgery-specific bleeding risk, e.g., for surgeries involving mucous tissues. Prospective studies are needed to define optimal antithrombotic management in these patients. The high heterogeneity of bleeding and thrombotic risk observed will probably require a stringent stratification of prophylaxis by surgery and cMPD subgroups. Until such results are available, a very careful clinical approach to patients with cMPD is still essential.

Authorship

MR, FR, AT and TB designed the research, analyzed the data and wrote the manuscript.

GC, FS, GF, FD, CM, AMV, EA, VDS, TZ, LG, AT, MGM, CS contributed the patients, discussed the data and gave the final approval to the manuscript.

Conflict of interest: none to declare

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Table 1. Clinical and laboratory characteristics of ET and PV surgical patients at diagnosis.

	PV (n =105)	ET (n=150)	P
Male/Female	66/39	62/88	**0.001**
Median age, years (range)	61 (28-85)	59 (20-84)	0.13
Presence of at least 1 cardiovascular risk factor* (%)	62 (59)	66 (44)	**0.02**
Previous arterial thrombosis (%)	14 (10.7)	22 (11.7)	0.79
Previous venous thromboembolism (%)	3 (2.8)	6 (4)	0.62
Symptoms at presentation (%)			
None	72 (68.5)	107 (71.3)	0.36
Microvascular disturbances	28 (26.6)	33 (22.0)	0.45
Arterial thrombosis	2 (1.9)	6 (4.0)	0.47
Venous thromboembolism	1 (0.9)	3 (2)	0.64
Hemorrhage	2 (1.9)	1 (0.7)	0.57
Hemoglobin (g/L) mean ± SD	180 ± 19.3	140 ± 14	**<0.0001**
Hematocrit (%) mean ± SD	55.1 ± 6.1	41.7 ± 3.6	**<0.001**
Leukocyte (x 10^9/L) mean ± SD	10.2 ± 4	10.2 ± 3.8	0.90
Platelet (x10^9/L) mean ± SD	516 ± 239	911 ± 376	**<0.001**

*: diabetes on treatment, hypercholesterolemia on treatment, arterial hypertension on treatment, previous AT, cardiovascular diseases (atrial fibrillation, valvular or coronary disease), smoke.

Table 2. Clinical features at the time of surgery, according to the type

	Type of surgery		P
	Minor (n=156)	**Major (n=155)**	
PV/ET	63/93	64/91	0.87
Male/Female	95/61	69/86	**0.004**
Median age at surgery, years (range)	66 (21-87)	56 (25-90)	0.57
Presence of at least 1 cardiovascular risk factor* (%)	77 (49.3)	70 (45.2)	0.45
History of vascular disease ** (%)	50 (32.1)	50 (32.3)	0.96
Emergency procedure (%)	6 (3.8)	19 (12.3)	**0.006**
General anesthesia	49 (31.4)	145 (92.9)	**<0.001**
Hemoglobin (g/L) mean ± SD	141 ± 16	133 ± 18	**0.001**
Hematocrit (%) mean ± SD	42.7 ± 5.0	41.1 ± 5.2	**0.004**
Leukocyte (x 10^9/L) mean ± SD	8.1 ± 4.0	9.5 ± 5.1	**0.007**
Platelet (x10^9/L) mean ± SD	494 ± 221	506 ± 231	0.64
Type of prophylaxis at surgery (%)			
None	64 (41.0)	30 (19.3)	
Antiplatelet	32 (20.5)	16 (10.3)	**<0.0001**
Heparin lower dosage ***	59 (37.8)	30 (19.3)	
Heparin higher dosage ****	1 (0.6)	79 (50.9)	
Chemotherapy or phlebotomy	9 (5.7)	17 (10.9)	0.09

*: diabetes on treatment, hypercholesterolemia on treatment, arterial hypertension on treatment, previous AT, cardiovascular diseases (atrial fibrillation, valvular or coronary disease), smoke.

** defined as history of cardiovascular disease or venous thromboembolism before or after diagnosis

*** < 3000 U anti-Xa/die for low molecular weight heparin or 5000 U b.i.d or t.i.d for unfractionated heparin (38 surgeries)

**** > 3000 U anti-Xa/die for low molecular weight heparin

Table 3. Incidence of thromboembolic events (Cases/1000 pt-day and Cumulative % at end of period) by post-operative period, and hazard ratios by specific risk factors in the observed cohort. 90% confidence intervals are reported within brackets.

	Event					
	Venous Thromboembolism		Arterial Thrombosis		Death	
	Cases/1000 pt-day	Cumulative %	Cases/1000 pt-day	Cumulative %	Cases/1000 pt-day	Cumulative %
Incidence at days						
0-15	1.4 (0.7-2.8)	2.3 (0.8-5.0)	1.4 (0.7-2.8)	2.3 (0.8-5.0)	0.2 (0.0-1.2)	0.3 (0.02-1.8)
15-30	1.0 (0.4-2.2)	3.9 (2.1-6.5)	0.7 (0.3-1.9)	3.5 (1.8-6.0)	0	0.3 (0.02-1.8)
30+	0.1 (0-0.4)	4.7 (2.7-7.5)	0.2 (0.1-0.5)	4.7 (2.7-7.5)	0.3 (0.1- 0.6)	1.9 (0.7-4.0)
Overall	0.5 (0.3-0.8)	-	0.5 (0.3-0.8)	-	0.2 (0.1 - 0.4)	
Event-specific hazard ratios						
Major vs. minor surgery	2.0 (0.6-6.6)	-	1.0 (0.3-3.1)	-	1.5 (0.2-9.2)	
PV vs. ET	7.3 (1.6-33.4)	-	0.3 (0.1-1.3)	-	0.4 (0.04-3.4)	
Antiplatelet vs. no active treatment	0.5 (0.1-4.0)	-	0.5 (0.1-4.0)	-	1.4 (0.2-12.8)	
Heparin vs. no active treatment	0.8 (0.3-2.6)		1.7 (0.5-5.6)		0.6 (0.1-3.4)	

Figure legend

Figure 1. Probability of death, venous or arterial thromboembolism after surgery in the studied cohort

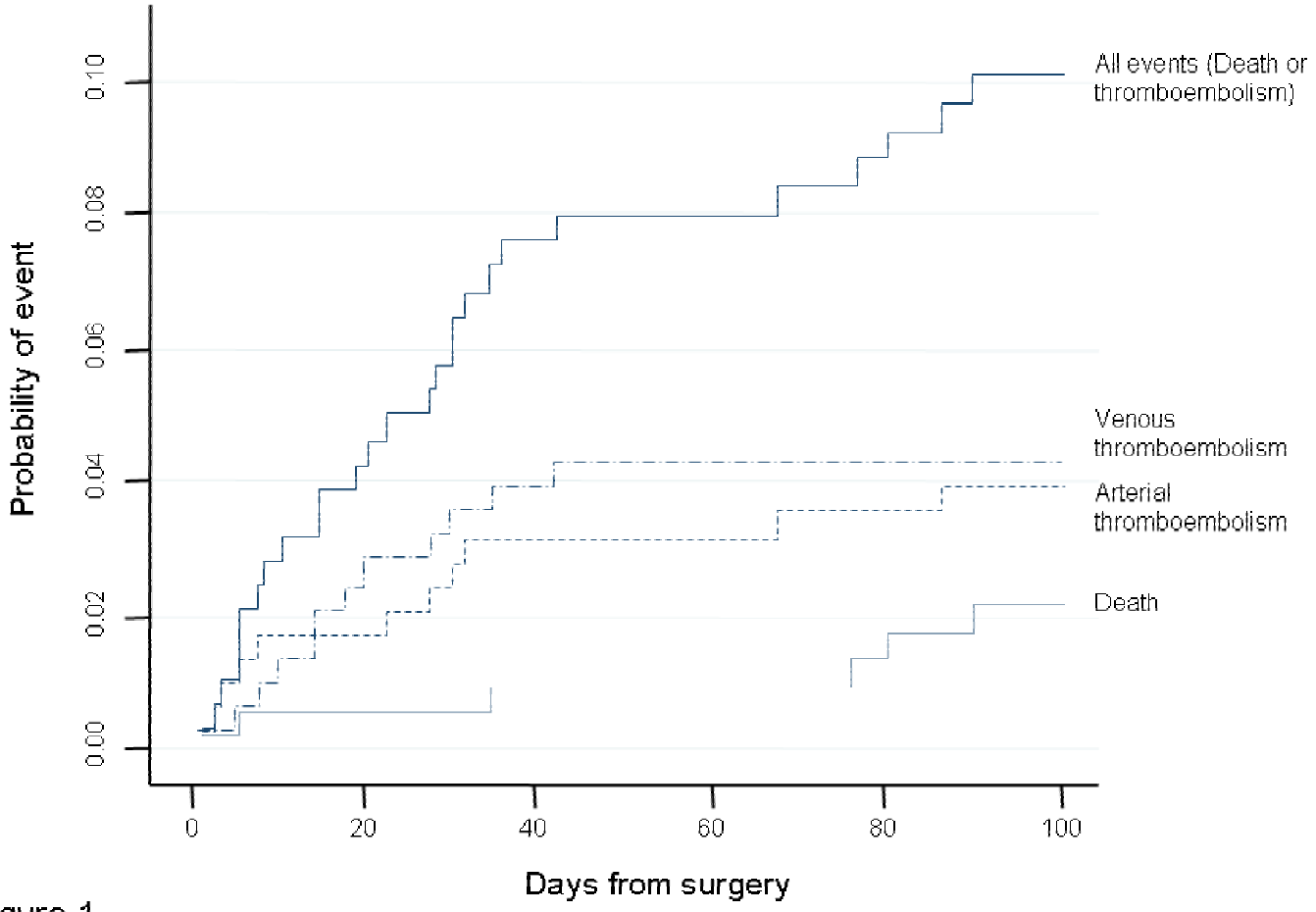

Figure 1

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Post-surgery outcomes in patients with polycythemia vera and essential thrombocythemia: a retrospective survey

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