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Key Words:	THROMBOTIC HAEMOLYTIC ANAEMIAS, thrombotic thrombocytopenic purpura, recurrence, relapse, ADAMTS13

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DIFFERENT CLINICAL SEVERITY OF FIRST EPISODES AND RECURRENCES OF THROMBOTIC THROMBOCYTOPENIC PURPURA.

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SUMMARY

The clinical course of thrombotic thrombocytopenic purpura (TTP) is characterized by recurrent disease episodes in up to 50% of the cases. The clinical presentation and severity of different TTP episodes have not been systematically compared. Laboratory and clinical information from 51 patients with recurrent disease, stemming from 136 patients with TTP included in the Milan TTP registry (URL: http://www.ttpdatabase.org), were used to compare mortality, symptoms and disease-related laboratory measurements in different disease episodes. The prevalence of severe neurological symptoms (coma, seizures, and focal neurological defects) was significantly lower in recurrences than in the first episode. Platelet counts and haemoglobin levels at presentation were higher in recurrences than in the first disease episode, and lactate dehydrogenase levels were lower. Also mortality tended to be lower in the second and third disease episodes than in the first. Recurrences of TTP are generally milder than first episodes. These differences in severity should be taken into account in clinical research on TTP and in patient management.

KEY WORDS**:** thrombotic thrombocytopenic purpura, recurrence, relapse, ADAMTS13**.**

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INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening disease characterized by acute episodes of thrombocytopenia and microangiopathic hemolytic anemia due to disseminated microvascular thrombosis (Moake JL, 2002). The clinical presentation of TTP is variable in terms of type and severity of clinical symptoms (Peyvandi F et al, 2004; Scully M et al, 2008; = Vesely SK et al, 2003; Zheng XL et al, 2004). Before the introduction of plasma exchange (PEX) for the treatment of acute TTP episodes mortality reached 90% (Amorosi EL & Ultmann JE, 1966), but decreased to 8-30% following the adoption of PEX (Kremer Hovinga JA et al, 2010; Rock GA et al, 1991; Scully M et al, 2008;). Patients who survive the first acute episode of the disease may remain asymptomatic for the rest of their life or develop one or more recurrence. It is estimated that approximately one third of TTP patients recur, with a higher risk of recurrence in those with severe deficiency of the von Willebrand factor cleaving-protease ADAMTS13 during acute episodes (; Vesely SK et al, 2003; Veyradier A et al, 2001; Kremer Hovinga JA et al, 2010) and remission (Ferrari S et al, 2007; Jin et al, 2008; Peyvandi F et al, 2008). Few data are available on the clinical presentation and severity of recurrences. It is not uncommon in clinical practice to observe that TTP patients, aware of their condition and under close medical monitoring after the first episode, are diagnosed with recurrence before the development of such severe symptoms as coma or other signs of severe neurological involvement. Accordingly, Scully et al. observed that patients from the UK TTP registry needed less PEX procedures to reach remission during recurrences than during the first episode (Scully M et al, 2008). However, the different severity of recurrent TTP episodes has never been the object of a systematic investigation. In addition, it is possible that a number of patients who die during recurrences are not referred for recurrence to expert clinical centers which are the major source of studies on this disease, biasing the perception of the real severity of recurrent episodes. If confirmed, the knowledge that recurrences are clinically milder than first disease episodes would be useful for those who design and carry out observational studies or clinical trials in TTP, in order to avoid lumping together patients with first episodes and recurrences. It would

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also help in clinical practice to better balance the risk of recurrent disease with that of side effects from potentially harmful preventive therapies such as the use of immunosuppressive agents.

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PATIENTS AND METHODS

Patients and definition of clinical categories

Between 1999 and 2009 physicians from Italy and 10 additional countries (Hungary, Serbia, Canada, Germany, Iran, Lebanon, Romania, Russia, Slovenia and Turkey) referred patients who had a suspected diagnosis of TTP to the registry established at the Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre and provided detailed clinical information and, when available, plasma samples. Information was collected using a standardized clinical questionnaire (available upon request). When necessary to fill gaps of information, clinicians were asked to provide additional clinical documentation and samples. Physicians in Milan (L.A.L. or F.P.) reviewed the cases and confirmed or excluded the diagnosis of TTP. Criteria for TTP diagnosis were the documentation of at least one episode of: (a) thrombocytopenia, (b) microangiopathic haemolytic anemia (c) exclusion of alternative explanations for thrombocytopenia (such as the enterohemorrhagic form of hemolytic uremic syndrome, catastrophic anti-phospholipid antibodies syndrome, pre-eclampsia and related syndromes, sepsis, systemic inflammatory response syndrome, disseminated intravascular coagulation, disseminated malignancy and/or bone-marrow transplantation associated TTP-like syndrome). Remission was defined as persistence of normal platelet counts and hemoglobin levels for at least 30 days after the most recent acute episode and freedom from new disease symptoms. The study was approved by the Institutional Review Board of the Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico and all patients or their tutors gave informed consent. All cases were reviewed for a second time by a single physician (L.A.L.) in 2009 and patients judged to have insufficient information to establish the diagnosis were excluded. The first TTP episode was classified as secondary when associated to one or more of the following conditions: (1) pregnancy/post-partum, (2) use of drugs reported to be associated with TTP, (3) additional disease associated with TTP (autoimmune diseases and/or HIV infection). Patients who did not fit the aforementioned categories were classified as having idiopathic disease. Presence of symptoms in each TTP episode was defined as prevalence of symptoms at presentation and/or

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during the acute phase of the disease before remission or death. Symptoms related to thrombocytopenia included petechiae (purpura), ecchymoses and superficial hematomas. Renal involvement included the increase in the serum level of creatinine (serum levels above the normal reference value of each laboratory) and/or presence of alterations of urinalysis such as proteinuria or hematuria. Severe neurological symptoms were coma, seizure and focal neurological signs (motor/sensory deficit or aphasia). Less severe symptoms (headache, amaurosis fugax, mild gait alterations) were included in the category "other neurological symptoms". Cardiovascular involvement included acute myocardial infarction, other acute coronary syndromes, increase in cardiac troponin-T, T wave electrocardiographic alterations and severe hypertension. Gastrointestinal symptoms included abdominal pain, vomiting and diarrhoea, whereas jaundice was excluded from this category owing to the confounding effect of hemolysis. The category "other symptoms" included fatigue, dyspnoea and other symptoms not included in the aforementioned categories. PEX procedures for each episode were calculated as the number of 1 volume PEX sessions carried out since diagnosis until remission or death, double volume exchanges were considered equivalent to 2 single volume PEX sessions. According to Vesely et al. (Vesely SK et al, 2003), laboratory data recorded as 'at presentation' were the most abnormal findings recorded on the day of diagnosis ±7 days. To compare data from different laboratories, LDH values were normalized to an upper normal limit of 480 IU/L. The plasmatic activity of ADAMTS13 was measured centrally at the Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre using collagen binding assay on citrated plasma as previously described (Peyvandi F et al, 2008). Activity of ADAMTS13 below 10% was considered severely deficient. The normal range for ADAMTS13 activity was 46-160%. Data of all patients are included in a digital registry (URL: www.ttpdatabase.org).

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Study design

Fig 1 provides a flow-chart of the study design. To assess the severity of different episodes, mortality rates were compared. In addition, each disease episode was compared to the others in patients who had more than one episode. Indicators of disease severity used for comparison were the differences in the prevalence of symptoms, in laboratory values (platelet counts, hemoglobin, LDH, and creatinine), and in the number of PEX procedures carried out in the time span between diagnosis and remission/death. In this matched-pair analysis each individual served as a control for him/herself in different episodes. Patients referred for only one episode were followed-up for vital status to assess how many of them had died of recurrent disease without notification to the caregiver physician and to our registry, because these events might bias the selection of patients with recurrent disease towards non-fatal, less severe cases. This check was carried out only for patients referred from Italian centres. Information on their vital status and (when applicable) cause of death were searched for with different methods: (a) direct contact of the patient, (b) check against mortality registries, (c) postal follow-up through the vital statistic offices of the city of birth or last residence of the patient.

Statistical analysis

Wilcoxon signed-rank test was used to compare continuous variables in the two disease episodes. Categorical variables were compared by McNemar test. P values <0.05 were considered significant. STATA 11 software was used for the analysis (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP)

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RESULTS

After exclusion of patients who did not match the diagnostic criteria and those with insufficient information to establish the diagnosis (n=167), 136 patients with TTP were included in the cohort (number updated at July 2009). The general features of the cohort and clinical information on the first disease episode are in Table I. Twelve patients died of the disease (9% of all patients), 10 during the first disease episode (7.3% of 136 patients with a first disease episode), 2 during the second episode (3.5% of 57 patients referred for more than one episode). None of the 33 patients who had 3 or more disease episodes died of the disease. Of the 12 patients who died, 9 had severe deficiency of ADAMTS13 (activity below 10%). Plasma samples for the centralized measurement of ADAMTS13 activity were available for 135 patients (99%): for 36 (27%) patients only acute disease samples were available, for 53 (39%) only remission samples and for 46 (34%) both acute and remission samples. The prevalence of severe ADAMTS13 deficiency was higher in the group of patients with availability of acute disease samples (67%, 55/82), whereas it was lower in patients with only remission samples available (36%, 19/53) (chi-square test, $p<0.001$). Among the symptom categories analyzed, cardiovascular symptoms had the lowest prevalence (Table I): an acute coronary syndrome was diagnosed in only 5 patients, 3 of whom had an acute myocardial infarction. Eight of the 136 patients had an acute renal failure according to the RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, End-stage renal disease) criteria for the definition of renal failure in critically ill patients (Bellomo et al, 2004). Two of these 8 patients had severe ADAMTS13 activity, three (one with severe ADAMTS13 deficiency) died of the disease at the first episode and only one, who had relapsing episodes, was included in the paired analysis of disease severity.

Of 57 patients who had two (or more) disease episodes, clinical information on the first two episodes of the disease was available for 51 (90%). Their general features and clinical information pertaining to the two episodes are summarized in Table II. The general characteristics and the clinical features at first episode in patients with recurrence were not different from those in patients

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without recurrence (not shown), but a severe deficiency of ADAMTS13 activity was more prevalent among patients who had recurrences (65%, 37/57) than those without (43%, 29/68) (chi-square test, p=0.02). In patients with multiple disease episodes, the prevalence of severe neurological symptoms and fever was significantly lower during the second episode (Table II). Among disease-related laboratory measurements, platelet counts and hemoglobin levels were higher in the second episode, whereas serum LDH was lower (Table II). Creatinine levels did not significantly differ between the two episodes. Finally, the number of PEX procedures carried out between diagnosis and hospital discharge was smaller for the second episode. Subgroup analyses were performed in groups of recurrent patients with (n=36) or without (n=15) severe deficiency of ADAMTS13. In the group of patients with severe deficiency of ADAMTS13 statistically significant differences were found for prevalence of severe neurological symptoms, fever, hemoglobin levels, platelet counts, LDH values and number of PEX until remission/death. In the group of patients in whom severe deficiency of ADAMTS13 was not found in the available samples (n=15) significant differences in the two episodes were found for platelet counts, hemoglobin and LDH levels. All statistically significant differences found in subgroup analyses were in the same direction of those observed in the primary analysis.

Thirty-three (65%) of the 51 patients included in the paired analysis of disease severity comparing the first and second episode in patients with recurrent disease had at least a third disease episode that developed at a median time of 1.3 years (range: 0.3-8 years) after the second episode. The third episode generally displayed milder clinical and laboratory features in comparison to the first and even to the second episode (Figs 2 and 3). The prevalence of purpura (p=0.004, McNemar's test, prevalence at first vs third episode), of severe (p=0.001) and other (p=0.007) neurological symptoms, and of fever (p=0.002) were lower in the third than in the first episode (Fig 2). Hemoglobin was largely influenced by episode number (p<0.001, Wilcoxon signed rank test, levels at first vs third episode) and smaller but statistically significant effects were also observed for platelets (p=0.004) and LDH (p=0.03), whereas creatinine levels were not influenced by recurrence

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(p=0.85) (Fig 3). Vital status information were requested for Italian patients reported to have survived the first TTP episode and not known to have had additional disease episodes (n=52, 75% of the 69 survivors of the first TTP episode not referred for recurrence) (Fig 1). Vital status information through October 2009 was collected for all 52 patients: by phone calls or e-mail contact with the patients (n=13, 25%), through mortality registries (n= 16, 31%), or from the vital statistic office of the birth or residence city (n=23, 44%). Only one of the 52 patients had died, from a cause that was deemed unrelated to TTP (rupture of mechanic aortic valve prosthesis).

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DISCUSSION

The results of this study show that TTP recurrences usually have a milder clinical course than first episodes of the disease. Neurological involvement, the degree of anemia and thrombocytopenia, which were previously shown to be predictors of 6-month mortality in TTP patients (Wyllie BF et al, 2006), were less severe in the second and third disease episodes than in the first. PEX sessions employed during second episodes were significantly less than those of the first, corroborating the other study findings. The third disease episode displayed even milder clinical course than the first two episodes.

A plausible explanation of the fact that TTP recurrences are less severe than first episodes is that recurrences are more rapidly diagnosed and treated. Indeed, many recurrences were diagnosed on the occasion of complete blood counts, in the presence of the laboratory features of TTP (microangiopathic hemolytic anemia and thrombocytopenia), but with mild or no clinical manifestations. A low prevalence of neurological symptoms, relatively high platelet counts and low number of PEX needed to achieve remission in TTP recurrences were previously reported by Bohm et al. in a study evaluating the course of ADAMTS13 activity during acute TTP, including 11 patients with relapsing TTP and 14 with a first disease episode (Böhm et al, 2005). However, only two of the relapsing patients of that study were also evaluated during the first episode, allowing a direct comparison. An advantage of this study is that 51 patients with 2 or more TTP episodes could be directly compared during their different episodes. This paired-comparison design allowed excluding confounding due to an influence of individual determinants of disease severity, which might arise when different individuals are compared in different episodes. The design of this study also allowed minimizing confounding due to heterogeneity in the ascertainment of clinical characteristics of different episodes in the same patient, because patients were usually referred to the same centre for first episode and recurrences. Limitations of this study were missing information on some patients and the small absolute number of patients studied. However, given the rarity of TTP and the difficulties of gathering detailed clinical information on clinical episodes we

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believe that the number and quality of data available for analysis were sufficient to enable the comparison of disease severity described in the study.

The overall prevalence of fatal TTP in the TTP cohort of this study was 9%, with lower mortality (even if not statistically significant) in relapsing episodes. This proportion of fatal disease is consistent with the rate of mortality reported for other cohorts. However, because ours is a tertiary care centre for TTP patients offering free ADAMTS13 testing and medical assistance and counseling, it is possible that recruitment of our patients is biased towards survivors of TTP episodes. Patients who died during the first episode without being referred to our registry do not affect the findings of this study, which is focused on survivors of the first episode who developed recurrences. Instead, we reasoned that deaths for TTP occurring during recurrences, not reported to our registry, might have biased this study towards the recruitment of survivors of TTP recurrence, i. e., a less severe subpopulation of recurrent patients. To exclude the presence of this potential distortion of the results, patients referred for a first TTP episode were followed-up to assess whether or not they had died of the disease without notice to the Hemophilia and Thrombosis Centre. The result of this evaluation showed no evidence of this bias, with the only death that occurred not being causally related to TTP.

Immunosuppressive drugs are used in some instances to prevent recurrent episodes in acquired TTP. In particular, Rituximab, a B-lymphocyte depleting drug, is increasingly used for this purpose. The use of immunosuppressive drugs and specifically Rituximab might in principle influence the results of our study, if the drugs reduced disease severity in patients that recur while under treatment. However, Rituximab was infrequently used in patients referred to our registry (n=23) and none of the treated patients recurred after treatment, so that the use of this potent immunosuppressive drug cannot have influenced our data on the severity of recurrences.

The knowledge that recurrences are generally milder than first disease episodes should be considered in the design and analysis of observational studies and clinical trials in TTP. An unbalance in the prevalence of patients with recurrent episodes in groups with a risk factor under

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evaluation or in two different treatment groups might indeed confound the ascertainment of the effect of an exposure or a treatment on acute disease clinical outcomes. The results of this study also have clinical relevance. Although recurrent episodes of TTP should always be regarded as a potentially fatal condition, the relatively less severe clinical course of recurrences should be taken into account when potentially harmful preventive therapies, like long-term immunosuppression, are being planned in patients considered at risk for TTP recurrence.

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Table I. General, clinical and laboratory features at first episode of the patients included in the study.

	PATIENTS
n=	136
GEOGRAPHIC ORIGIN	
Italy	107 (79%)
Other country[a]	29 (21%)
REFERRED DURING:	
Acute disease	56 (41%)
Remission	80 (59%)
MALE GENDER	29 (21%)
AGE AT FIRST EPISODE, years	37 (28-50)
DIED OF THE DISEASE	12 (9%)
IDIOPATHIC DISEASE	107 (79%)
SECONDARY DISEASE	29 (21%)
Pregnancy	13 (9%)
Autoimmune disease [b]	9 (7%)
Drug induced [c]	5 (4%)
More than one condition [d]	2 (1%)
SEVERE DEFICIENCY OF ADAMTS13 ACTIVITY [e]	74 (54%)
REFERRED FOR MORE THAN ONE EPISODE	57 (42%)
CLINICAL SYMPTOMS AT FIRST EPISODE (n=130)	
Severe neurological	64 (49%)
Other neurological	69 (53%)
Cutaneous manifestations of thrombocytopenia	71 (55%)
Bleeding	15 (12%)
Renal involvement	47 (36%)
Cardiovascular symptoms	15 (12%)
Gastrointestinal symptoms	49 (38%)
Fever	47 (36%)
Other symptoms	50 (38%)
LABORATORY MEASUREMENTS AT FIRST EPISODE (n=117)	
Platelet counts (x1000/mm3)(n=117)	14 (7-22)
Hemoglobin (g/dL) (n=117) [f]	8.0 (6.5-9.3)
Lactate dehydrogenase (IU/mL) (n=113)	1571 (953-2330)
Creatinine (mg/dL) (n=107)	0.9 (0.8-1.2)
TREATMENT AT FIRST EPISODE (n=129)	
Plasma exchange	118 (92%)
Number of plasma exchanges (n=105)	11 (7-19)
Other transfusional therapy	81 (63%)
Immunosuppressive treatment	118 (92%)

Continuous variables were expressed as median (interquartile range).
a Hungary (n=11), Serbia (n=10), Canada, Germany, Iran, Lebanon, Romania, Russia, Slovenia and Turkey (n=1 each)
b Autoimmune thyroid disease (n=5), systemic lupus eritematosus (n=3), myasthenia gravis (n=1).
c Ticlopidine (n=4), clopidogrel (n=1).
d Pregnancy and autoimmune thyroid disease (n=1), pregnancy and systemic lupus eritematosus (n=1).
e Measured during acute disease or during remission.

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Table II. General and clinical features at their first two episodes of the 51 recurrent patients included in paired analysis of disease severity.

	PATIENTS WITH TTP RECURRENCE		
n=	51		
GEOGRAPHIC ORIGIN			
Italy	41 (80%)		
Other country	10 (20%)		
FEMALE GENDER	11 (21%)		
AGE AT FIRST EPISODE, years	35 (26-44)		
AGE AT SECOND EPISODE, years	38 (30-48)		
TIME TO FIRST RELAPSE	1.7 (0.5-3.7)		
IDIOPATHIC DISEASE	37 (73%)		
SEVERE DEFICIENCY OF ADAMTS13 ACTIVITY[a]	36 (70%)		
REFERRED FOR MORE THAN TWO EPISODES	33 (64%)		
	FIRST EPISODE	*SECOND EPISODE*	p=
CLINICAL SYMPTOMS (n=51)			
Severe neurological	25 (49%)	9 (18%)	<0.001
Other neurological	35 (68%)	25 (49%)	0.06
Cutaneous manifestations of thrombocytopenia	33 (65%)	29 (56%)	0.48
Bleeding	9 (18%)	3 (6%)	0.09
Renal involvement	15 (41%)	18 (35%)	0.58
Cardiovascular symptoms	2 (4%)	2 (4%)	1.00
Gastrointestinal symptoms	18 (35%)	10 (20%)	0.13
Fever	21 (41%)	8 (16%)	0.003
Other symptoms	17 (33%)	11 (22%)	0.23
LABORATORY FEATURES (n=47)			
Platelet counts (x1000/mm3)	15 (8-20)	20 (10-34)	0.009
Hemoglobin (g/dL)	7.7 (6.2-9.7)	10 (8.1-11.7)	<0.001
Lactate dehydrogenase (IU/mL)	1691 (940-2379)	1110 (563-1900)	0.004
Creatinine (mg/dL)	0.8 (0.8-1.1)	0.9 (0.6-1.3)	0.24
NUMBER OF PLASMA EXCHANGES (n=37)[b]	12 (7-19)	7 (5-12)	0.01

Continuous variables were expressed as median (interquartile range). A dark gray shadow is used to highlight statistically significant p values (<0.05).
a Measured during acute disease or during remission.
b Information available on n=37 patients for both episodes; information was not available for the first episode in n=6 patients, for the second in n=2 patients, n=6 patients were not treated with PEX in one or both episodes.

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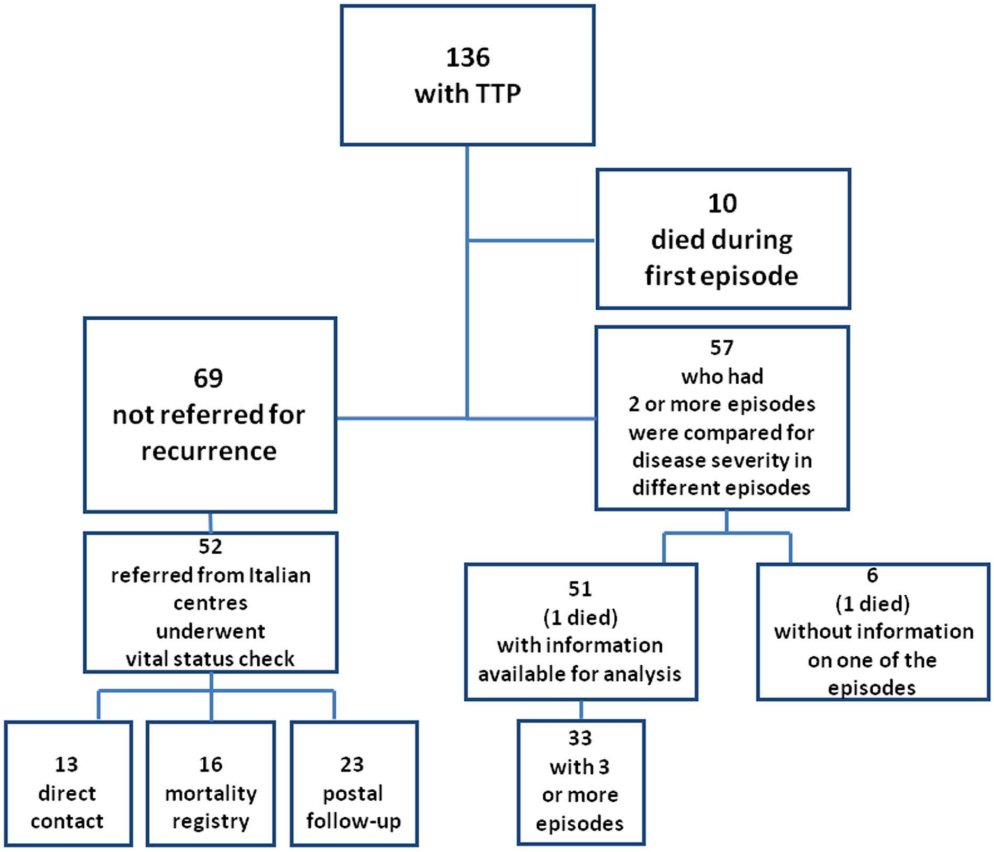
Figure 1



80x71mm (600 x 600 DPI)

Figure 2.

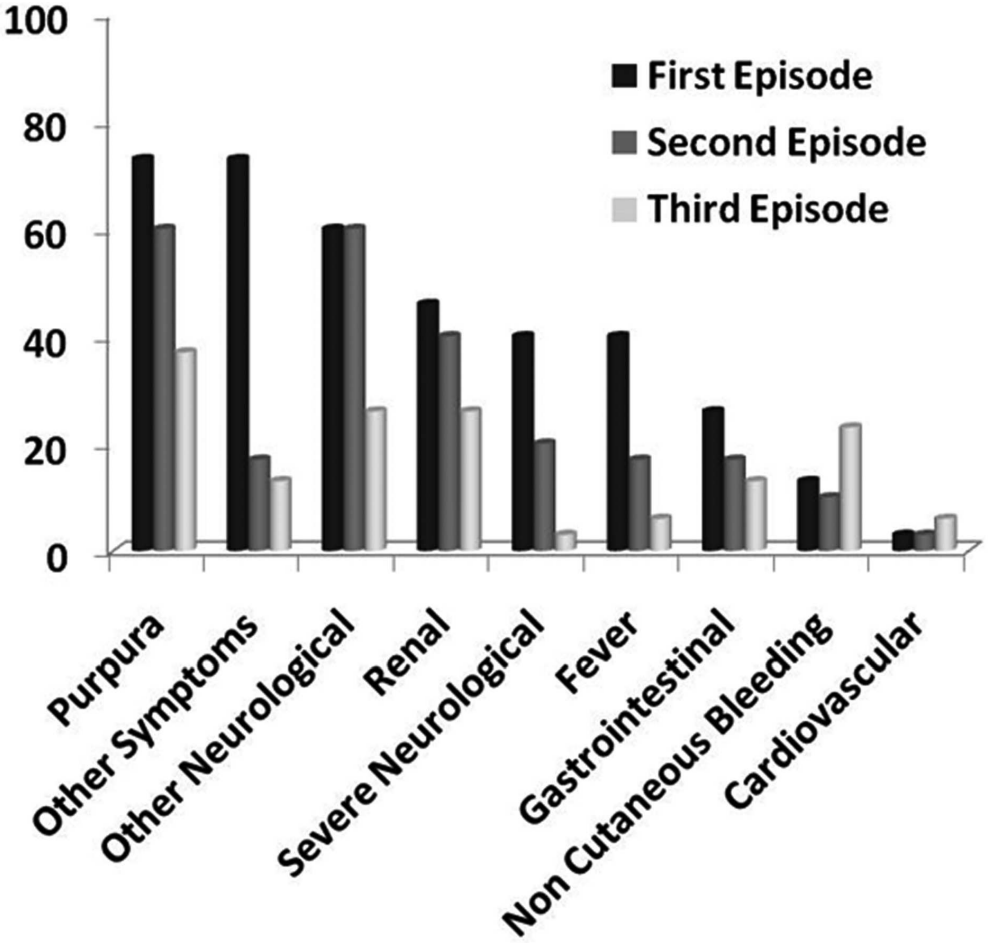


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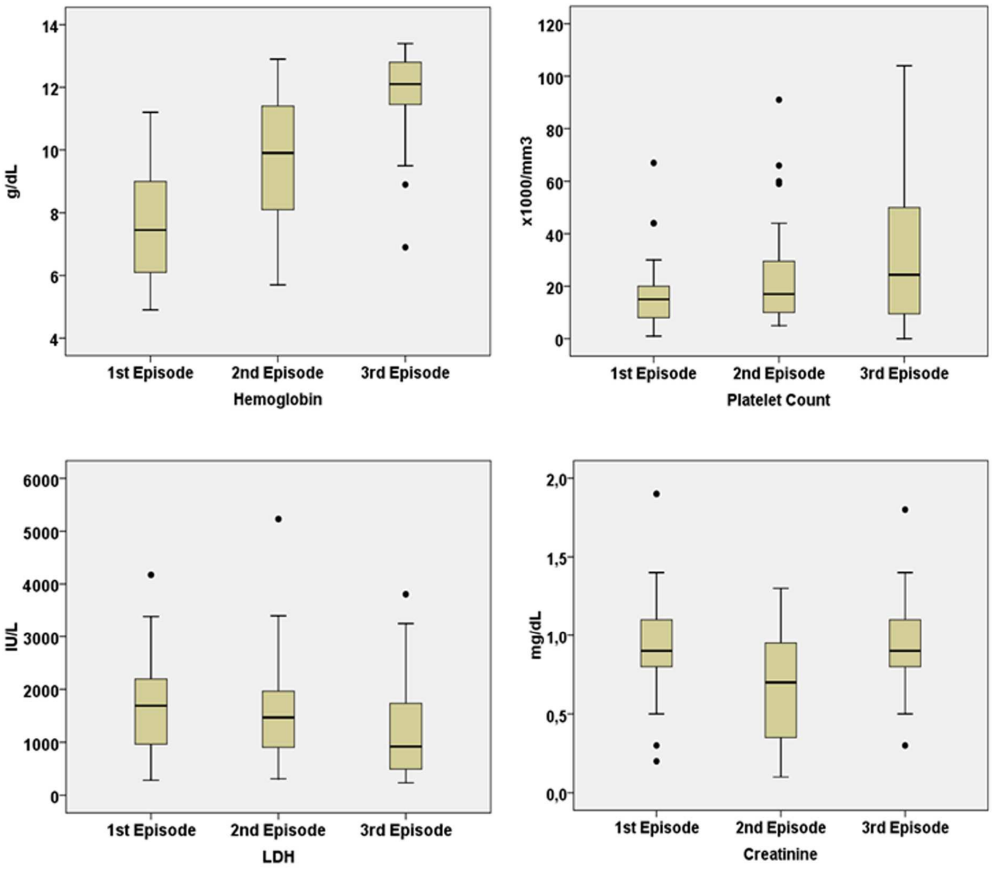
Figure 3.



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