Research Article

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Prognostic factors in thrombotic thrombocytopenic purpura

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Abstract

Objectives: Thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathy with no standardized prognostic model to predict mortality. The aim of the study is to determine parameters associated with TTP-related mortality.

Methods: In this cross-sectional, retrospective study, 77 TTP patients, treated with therapeutic plasma exchange between 2001 and 2019 in Ankara University Faculty of Medicine were included.

Results: There was no significant relationship between ADAMTS13 inhibitor levels, activity and mortality. Median number of plasmapheresis was 10 (2–32), higher in patients with complete response. Anemia, kidney injury and LDH levels were associated with survival; there was no significant relationship between platelet counts at the time of diagnosis and mortality. Mortality was lower in patients with platelet counts above 100 × 10^9/L and normalized LDH after treatment. Hemoglobin, albumin, LDH and creatinine levels at the time platelet counts exceeded 50 × 10^9/L were associated with survival.

Conclusions: We determined several clinical and laboratory parameters associated with mortality. Fewer numbers of plasmapheresis was associated with mortality; thus other treatments as rituximab and caplacizumab should be considered early in non-responders. Including changes in laboratory parameters may be considered in prognostic scoring systems to be developed in the future.

Keywords: ADAMTS13; microangiopathic hemolytic anemia; plasma exchange; rose score; thrombotic thrombocytopenic purpura.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, and disseminated microvascular thrombus-related organ ischemia [1].

Therapeutic plasma exchange (TPE) is the basis of TTP treatment. In the first studies evaluating TPE, survival was reported as high as 70–79% [2]. Despite this proven efficacy, mortality is still high and information about prognostic factors is still not sufficient [3].

There are several studies, that have attempted to create new prognostic models and investigate factors affecting mortality [3–9].

In this study, we investigated the effects of the clinical features, laboratory values, treatment modalities and complications on not only mortality, but also on treatment responses and relapses.

Materials and methods

Patients and data collection

The records of Ankara University Faculty of Medicine, Ibn Sina Hospital Therapeutic Aphereses Center were scanned retrospectively, and all patients who were treated with the diagnosis of TTP between January 1, 2001 and November 1, 2019 were evaluated.

All patients older than 18 years of age who were diagnosed with TTP and received TPE were included in the study. Exclusion criteria: Patients under the age of 18 years, patients with suspected DIC, HUS or other thrombotic microangiopathies, pregnancy, stage 3 and above chronic kidney disease.

The study was designed restospectively and cross-sectionally, and the information of TTP patients was obtained from the Apheresis Center records, and through the database of the hospital’s electronic records (Avicenna). Anamnesis, clinical follow-up reports, apheresis center files and laboratory data were examined and patients’ age,
diagnoses, additional comorbidities, TTP etiology, clinical characteristics, laboratory parameters, treatment modalities, complications, ADAMTS13 activity and inhibitor levels, follow-up periods and treatment responses were recorded. Rose score was calculated for each patient.

Statistical analysis

The data were analyzed with the ”SPSS for Windows 23.0” version. Median ± SD was used in descriptive statistics of continuous variables; categorical variables were expressed in numbers and percentages. Whether continuous variables showed normal distribution or not was determined by Kolmogorov Smirnov test, Skewness and Kurtosis tests. Chi-square test was used for intergroup comparisons in categorical variables. A p<0.05 value was considered statistically significant. Independent effects of factors that may effect mortality, late relapse and early relapse were tested by multivariate regression analysis.

Results

Data of 77 patients were evaluated in the study. Thirty-seven of the patients were male (48.1%) and 40 of them were female (51.9%). The average age of the patients was 49.3 ± 17.5 years. The mean age of women was 45.5 ± 17.8 years and the mean age of men was 53.4 ± 16.4 years. There was no statistically significant difference between the mean ages of women and men (p=0.071).

TTP-related death was defined as death within the first 30 days after the start or end of treatment due to a TTP-related complication. The gender distribution of the patients was similar (p=0.418). The median age was 63 (19–84) in patients who died and 48.2 (18–85) in patients who did not (p=0.156).

The most frequent departments which patients were admitted to were hematology (n=31; 40.3%), emergency service (n=15; 19.5%), nephrology (n=8; 10.4%) and internal medicine intensive care unit (n=7; 9.1%).

Additional diseases and risk factors of the patients (diabetes mellitus, arterial hypertension, deep vein thrombosis, stroke, atherosclerotic cardiovascular disease, obesity, smoking history) were included in the study. In this study, obesity was defined as body mass index (BMI)>30 and smoking history as >10 pack-years. Mortality was higher in those with renal and neurological symptoms and signs (p=0.031, OR: 4.46, 95% CI, 1–18.9 and p=0.013, OR: 14.2, 95% CI, 0.8–253.5 respectively).

The classic pentad was found in 8 patients (10.4%) which was associated with increased mortality (p=0.001, OR: 10.5, 95% CI, 2.0–53).

The laboratory levels at the time of admission in patients with and without TTP-related death is shown in Table 2. Degree of the anemia and renal injury, LDH and INR levels were associated with mortality.

TPE was carried out in all patients and the median number of procedures was 10 (2–32). Nine patients (11.7%) were given rituximab and 36 patients (46.7%) steroids. One patient each were treated with (1.2%) vincristine and splenectomy.

Two patients who received rituximab and 1 patient who received vincristine were refractory to the initial treatment and died. There was no significant difference between the number of TPE and other treatment modalities and mortality.

Table 1: Distribution of fever, renal involvement and neurological findings.

|                | All patients | TTP-related death | p-Value |
|----------------|--------------|-------------------|---------|
|                | No           | Yes               |         |
| Fever          | n=67         | n=10              |         |
|                | (87%)        | (13%)             |         |
| No             | 36 (46.8%)   | 32 (88.9%)        | 4 (11.1%) |
| Yes            | 41 (53.2%)   | 35 (85.4%)        | 6 (14.6%) |
| Renal involvement | 0.031*    |                   |         |
| No             | 47 (61%)     | 44 (93.6%)        | 3 (6.4%) |
| Yes            | 30 (39%)     | 23 (76.7%)        | 7 (23.3%) |
| Neurological findings | 0.013* |                   |         |
| No             | 27 (35.1%)   | 27 (100%)         | 0       |
| Yes            | 50 (64.9%)   | 40 (80%)          | 10 (20%) |

*Chi-square test; *Mann Whitney-U test. The p-values below 0.05 are bold.
Table 2: Relationship between laboratory tests at admission and mortality.

|                      | All patients | TTP-related death | p-Value |
|----------------------|--------------|-------------------|---------|
|                      | n=67 (87%)   | n=10 (13%)        |         |
| n (%)/Mean ± SD/Median (min-max) |              |                   |         |
| Platelet <20×10⁹/L  |              |                   |         |
| No                   | 41 (53.2%)   | 38 (92.7%)        | 3 (7.3%)|
| Yes                  | 36 (46.8%)   | 29 (80.6%)        | 7 (19.4%)|
| Hgb <10.0 g/dL       |              |                   |         |
| No                   | 26 (33.8%)   | 25 (96.2%)        | 1 (3.8%)|
| Yes                  | 51 (66.2%)   | 42 (82.4%)        | 9 (17.6%)|
| Platelet (cells/mm³) | 36,532±31,863/26,000 | 38,269±33,243/28,000 | 24,900±17,227/16,000 | 0.467b |
| Hemoglobin, g/dL     | 9.1±1.7/8.7 (5.7–12.8) | 9.3±1.6/8.9 (5.7–12.8) | 8.1±1.9/7.6 (5.7–12) | 0.037b |
| Creatinine, mg/dL    | 1.84±1.83/0.97 (0.36–8.53) | 1.72±1.83/0.91 (0.36–8.53) | 2.66±1.68/2.44 (0.59–5.33) | 0.038b |
| Albumin, g/dL        | 3.24±0.74/3.1 (1.8–5.5) | 3.29±0.74/3.16 (1.8–5.5) | 2.93±0.66/2.95 (2.1–4.1) | 0.170b |
| LDH, U/L             | 1,038±930.7/676 (160–5,256) | 943.9±845.9/659 (160–5,260) | 1,652±1,245/1,193.5 | 0.033b |
| INR                  | 1.08±0.12/1.05 (0.83–1.5) | 1.07±0.13/1.04 (0.83–1.5) | 1.14±0.09/1.14 (0.99–1.29) | 0.038b |
| aPTT (s)             | 28.6±4.1/28.1 (21.1–39.6) | 28.2±3.9/27.8 (21.1–39.5) | 31.2±4.5/30.4 (25.6–39.6) | 0.069b |

aChi-square test; bMann Whitney-U test. The p-values below 0.05 are bold. s, second.

After the initial treatment, the platelet count of 65 patients (84.4%) increased above 100,000 after a median number of 5 (1–19) TPEs. Fifty-seven patients’ (74%) platelet counts increased above 150,000 on median day 7 (3–25) and after a median 6 TPEs (2–23). Fifty-one (98%) patients’ LDH levels were normalized on median day 6 (0–29). Mortality was significantly lower in patients with platelet counts above 100×10⁹/L and a normalized LDH after treatment (p<0.001). There was no significant relationship between the number of plasmapheresis applied to reach the target values and the time passed until the target values were reached, and mortality (Table 3).

Laboratory parameters during follow-up, platelet transfusion counts, Rose score and mortality relationship is summarized in Table 4.

Acute kidney injury developed in 21 (27%) patients during the treatment course, 10 of these patients (47.6%) died. One patient who had an ischemic stroke and 4 (80%) of 5 patients who had a myocardial infarction died. Intracranial hemorrhage was not observed in any of the patients, and there was no significant relationship between deep vein thrombosis and mortality. Mortality was significantly higher in patients who had acute kidney injury and myocardial infarction (p<0.001, OR: 10.5, 95% CI, 2.0–5.3 and p<0.001, OR: 44, 95% CI, 4.2–459.2).

After treatment, a complete response was defined as platelet counts above 150×10⁹/L at least 2 consecutive days, near-normal LDH levels and absence of clinical features [1, 10]. Partial response was defined as platelet counts exceeding 50×10⁹/L or doubling of initial platelet count and absence of new clinical events [11]. Early relapse was defined as clinical worsening within the first 30 days after treatment or a decrease in the platelet count below 100×10⁹/L, or >1/3 decrease from the highest platelet count with no other cause. Refractory disease was defined as no response within 30 days or no sustainable response within 60 days. Relapse after 30 days was defined as late relapse [1, 10]. The number of patients responded to treatment was found to be 67 (87%). Except for one patient who had a partial response, none of these patients died. It was noted that the only patient who had a partial response and died had advanced age and many additional comorbidities, mostly cardiovascular diseases. A significant correlation was found between treatment refractoriness and mortality (p<0.001). All of the early-relapsed patients responded to second-line treatments and none of these patients died Although the treatment modalities and responses of patients with late relapse were not included in this study, none of these patients died during the follow-up period (Table 5).

When factors that may affect TTP-related mortality were evaluated with multiple regression analysis, only smoking was found to be an independent factor (p=0.012).
Table 3: Post-treatment platelet and LDH values, recovery times and mortality.

|                                   | All patients | TTP-related death | p-Value     |
|-----------------------------------|--------------|-------------------|-------------|
|                                   |              | No n=67 (87%)     | Yes n=10 (13%) |
|                                   |              | n (%)/Mean ± SD/Median (min-max) |              |
| Post-treatment platelet count > 100 x 10^9/L |              |                   |              |
| No                                |              |                   | <0.001^a     |
| Yes                               |              |                   |              |
|                                   |              |                   |              |
| Number of TPE applied to reach the target value | |                   |              |
| No                                |              |                   |              |
| Yes                               |              |                   |              |
|                                   |              |                   |              |
| Post-treatment platelet count > 150 x 10^9/L |              |                   | <0.001^a     |
| No                                |              |                   |              |
| Yes                               |              |                   |              |
|                                   |              |                   |              |
| Number of TPE applied until LDH normalized | |                   |              |
| No                                |              |                   |              |
| Yes                               |              |                   |              |
|                                   |              |                   |              |
| Days until target value is reached |              |                   |              |
| No                                |              |                   |              |
| Yes                               |              |                   |              |
|                                   |              |                   |              |
| Post-treatment LDH level          |              |                   | <0.001^a     |
| Above normal                      |              |                   |              |
| Normal                            |              |                   |              |
| Number of TPE applied until LDH normalized | |                   |              |
| No                                |              |                   |              |
| Yes                               |              |                   |              |
|                                   |              |                   |              |
| Days until LDH normalized         |              |                   |              |
| No                                |              |                   |              |
| Yes                               |              |                   |              |
|                                   |              |                   |              |

^aChi-square test; ^bMann Whitney-U test. The p-values below 0.05 are bold.

Table 4: Laboratory values at the time platelet count exceeded 50 x 10^9/L, number of platelet transfusions, rose score and mortality.

| Laboratory values at the time platelet count exceeded 50 x 10^9/L, number of platelet transfusions and rose score | All patients | TTP-related death | p-Value |
|-------------------------------------------------------------------------------------------------------------|--------------|-------------------|---------|
|                                                                                                            |              | No n=67 (87%)     | Yes n=10 (13%) |
|                                                                                                            |              | n (%)/Mean ± SD/Median (min-max) |              |
| Hemoglobin, g/dL                                                                                           | 9.7 ± 1.4/9.6 (6.1–13.1) | 9.8 ± 1.3/9.7 (7.4–13.1) | 8.5 ± 1.8/8.1 (6.1–12.4) | 0.009^a |
| Albumin, g/dL                                                                                               | 3.4 ± 0.6/3.5 (2.1–5)  | 3.5 ± 0.6/3.5 (2.1–5)  | 2.9 ± 0.4/2.9 (2.4–3.6)  | 0.005^b |
| LDH, U/L                                                                                                     | 473.7 ± 523.7/329 | 366.6 ± 225.1/301 | 1,317.3 ± 1,173.4/1,003.5 | <0.001^b |
| (109–3,777)                                                                                                  | (109–1,394)  | (366–3,777)       |                     |         |
| Creatinine, mg/dL                                                                                            | 1.5 ± 1.5/0.8 (0.3–8.5) | 1.4 ± 1.5/0.8 (0.3–8.5) | 2.2 ± 1.4/2 (1–5.5) | 0.002^b |
| Number of platelet transfusions                                                                            | 2.4 ± 4.4/0 (0–20)  | 1.3 ± 2.8/0 (0–10)  | 9.2 ± 6.5/10 (0–20)  | <0.001^b |
| Rose score                                                                                                   | 4.2 ± 1.5/4 (1–8)  | 3.8 ± 1.2/4 (1–7)  | 6.7 ± 0.8/7 (5–8)  | <0.001^b |

^aChi-square test; ^bMann Whitney-U test. The p-values below 0.05 are bold.

Ten patients (13%) died due to TTP. Causes of these deaths were recorded to be infection in 6 (7.8%), cardiac causes in 2 (2.6%) patients and neurological complications in 1 (1.3%) and bleeding in 1 (1.3%) patient.

No statistically significant correlation was found between age, gender and early relapse. There was also no significant correlation between comorbidities, clinical and laboratory features and relapse. When the effects of the same parameters on late relapse were also examined, no significant relationship was found.

Discussion

The limitations of our study are that our sample size is limited and it is difficult to access all of the data due to retrospective evaluation. On the other hand, the incidence of acquired TTP varies in different series, and is approximately 3 in a million, being a rare disease, and there are few studies aiming to determine prognostic factors [12].

The demographic characteristics of the patients in terms of age are compatible with the other series in the
Table 5: Treatment responses and mortality.

|                               | All patients       | TTP-related death | p-Value |
|--------------------------------|--------------------|-------------------|---------|
|                                | n=67 (87%)         | n=10 (13%)        |         |
| **Complete response**          |                    |                   | <0.001a |
| No                             | 23 (29.9%)         | 13 (56.5%)        |         |
| Yes                            | 54 (70.1%)         | 54 (100%)         |         |
| **Partial response**           |                    |                   | 0.533a  |
| No                             | 64 (83.1%)         | 55 (85.9%)        |         |
| Yes                            | 13 (16.9%)         | 12 (92.3%)        |         |
| **Refractory disease**         |                    |                   | <0.001a |
| No                             | 67 (87.1%)         | 66 (98.5%)        |         |
| Yes                            | 10 (12.9%)         | 1 (10%)           |         |
| **Refractory disease treatment**|                   |                   | <0.001a |
| TPE                            | 5 (50%)            | 1 (25%)           |         |
| TPE and steroids               | 3 (30%)            | 0                 |         |
| TPE, vincristine, rituximab, steroids | 1 (10%) | 0 |         |
| TPE and rituximab              | 1 (10%)            | 1 (100%)          |         |
| **Early relapse**              |                    |                   | 0.427a  |
| No                             | 73 (94.8%)         | 63 (86.3%)        |         |
| Yes                            | 4 (5.2%)           | 4 (100%)          |         |
| **Early relapse treatment**    |                    |                   | 0.960a  |
| TPE                            | 1 (25%)            | 1 (100%)          |         |
| TPE and steroids               | 1 (25%)            | 1 (100%)          |         |
| TPE and rituximab              | 1 (25%)            | 1 (100%)          |         |
| TPE, steroids and rituximab    | 1 (25%)            | 1 (100%)          |         |
| **Late relapse**               |                    |                   | 0.166a  |
| No                             | 66 (85.7%)         | 56 (84.8%)        |         |
| Yes                            | 11 (14.3%)         | 11 (100%)         |         |

*aChi-square test; *aMann Whitney-U test. The p-values below 0.05 are bold.

consistent with other series, the mean age of the patients who died was higher. In the study of Benhamou et al. prior diagnosis of arterial hypertension was found to be significant in patients who died, but there was no significant association for other comorbidities [6]. Goel et al. showed that there was no significant relationship between obesity, diabetes and hypertension and in-hospital mortality [3]. In our study, although mortality rates were higher in patients with prior comorbidities, the relationship was not statistically significant. Higher mortality may be associated with the higher incidence of these diseases in the elderly. Mortality was significantly higher in patients with obesity and smoking history. Although it is difficult to obtain detailed information due to the retrospective design, these are known to be two important cardiovascular risk factors. There are reports showing that cardiac involvement and stroke during the course is poor prognostic [3, 15]. In the light of this information, it may be appropriate to evaluate TTP patients in detail in terms of additional comorbidities and cardiovascular risk factors, and prospective studies are needed on this subject.

The distribution of TTP etiology of the patients in our study is compatible with other series. In different reports, idiopathic TTP rates vary between 50 and 90% [2, 13, 14]. In the study of Korkmaz et al. primary disease rate was reported as 85.9%, and malignancy was found to be the most common secondary cause. The response rates of primary and secondary TTPs were found to be similar [11]. Although the results of our study are consistent with these findings, there are studies reporting that the survival of TTP patients secondary to systemic infections, malignancy and allogeneic transplantation is significantly lower [2]. It is also known that chronic diseases, acute inflammatory and prothrombotic processes can cause a decrease in ADAMTS13 levels [16–18]. Secondary TTP patients appear to be a heterogeneous group and differential diagnosis with other secondary TMAs may be difficult.

The finding that neurological involvement is a poor prognostic factor is consistent with other series in the
literature [5, 6]. Also, there are other studies showing that renal involvement is associated with prognosis [3, 6]. In our study, the incidence of pentad was low, consistent with other series. The rare occurrence of classic pentad and the heterogeneous clinical features suggest that the importance of TTP pentad in the diagnostic process is limited. The disease triad appears to be more important between studies [5, 6]. These findings suggest that clinical features, especially renal and neurological involvement, included in the pentad have prognostic importance.

TTP patients’ hemoglobin, platelet and creatinine values are included in the previous prognostic scales [3, 5, 6]. However, laboratory changes during the treatment period were not included in these systems. One study has shown that the rate of platelet count recovery is associated with survival [9]. Our findings suggest that it may be appropriate to add changes in laboratory values during the treatment period to prognostic scales that may be developed in the future.

The duration of treatment and the number of TPEs required for remission vary in different series [19]. Similar with our findings, Korkmaz et al. found the number of plasmapheresis to be higher in patients with complete response [11].

In accordance with the study of Goel et al. [3], mortality was significantly higher in patients with higher platelet transfusion counts. Also, mortality was significantly associated with higher Rose scores.

It is remarkable that none of the relapsed patients died. There are studies reporting that mortality and symptoms are less severe during relapses [20, 21]. Favourable prognosis may be related to earlier initiation of treatment, and the fact that these patients’ already responded to treatment in the first episode.

Currently, the only specific biomarker that can be used to predict TTP relapses is known to be ADAMTS13 [1]. Previous studies also could not demonstrate a significant and consistent relationship between initial laboratory values and clinical features of the patients and the risk of relapse, and the prognostic scales developed mostly focus on TTP-related mortality.

In our study, TTP-related mortality was associated with clinical and laboratory features, comorbidities, cardiovascular risk factors and changes in laboratory parameters and complications. Although being the cornerstone of the treatment, fewer TPE procedures were associated with increased mortality. This finding supports that other treatment modalities such as rituximab and caplacizumab should be considered early in patients who do not respond to initial treatment. Including changes in the laboratory parameters and complications may be considered in the prognostic scoring systems to be developed in the future.

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Ethical approval: The local Institutional Review Board deemed the study exempt from review.

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