Long-term deficits in health-related quality of life after recovery from thrombotic thrombocytopenic purpura

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BACKGROUND: After recovery from thrombotic thrombocytopenic purpura (TTP), patients commonly describe persistent problems with memory, concentration, and endurance.

STUDY DESIGN AND METHODS: The Oklahoma TTP-HUS Registry, an inception cohort of 364 patients, January 1, 1989, through June 30, 2007, has annually evaluated health-related quality-of-life since 1998 with the Short Form (SF)-36, a widely used questionnaire that assesses eight domains of physical and mental health.

RESULTS: A total of 128 patients were eligible for this study (age ≥ 18 years, alive in January 1998 without prior relapse, survival and no relapse ≥1 year after recovery, no overt disability or additional disorders); 118 (92%) completed the SF-36. At their initial assessment, these patients had significantly worse functioning and well-being than the US population for all domains ($p < 0.05$). Forty-nine patients who had their initial assessment more than 2 years after recovery had better scores for three domains than 69 patients who had their initial assessment 2 years or less after recovery ($p < 0.05$). Among these 69 patients, there was no difference between subgroups: 1) idiopathic versus other categories of TTP, 2) the presence or absence of severe ADAMTS13 deficiency, 3) the presence or absence of severe neurologic abnormalities during the episode of TTP, and 4) less than 10 or 10 or more plasma exchange treatments required to achieve remission ($p > 0.05$). Analysis of serial assessments in 72 (61%) of the 118 patients who had two or more assessments within 5 years of recovery and no intervening relapses demonstrated no significant improvement in any of the domains.

CONCLUSION: After recovery from TTP, patients may have persistent cognitive and physical difficulties.

Thrombotic thrombocytopenic purpura (TTP) is an acute disorder caused by systemic microvascular thrombosis with a mortality rate of about 15 percent in spite of current management.[1] Among survivors, recovery is assumed to be complete. There are no documented long-term health problems other than the uncommon occurrence of persistent overt neurologic or renal abnormalities and a potential risk for relapse.

Since 1996 the Oklahoma TTP-HUS (hemolytic-uremic syndrome) Registry has held three meetings every year for patients who have recovered from TTP, attended by a mean of 20 patients and 19 additional family members and friends.[2,3] Although conceived as a support group, these meetings have also become a valuable resource for qualitative research. Their format and function resemble a focus group: the group meets in a comfortable setting with dinner being served; one of the investigators (JNG) serves as a facilitator; and the patients and their families tell their stories, ask each other questions, and comment on each others' experiences.[4] A

ABBREVIATIONS: HRQoL = health-related quality-of-life; HUS = hemolytic-uremic syndrome; SF-36 = Short Form-36; TTP = thrombotic thrombocytopenic purpura.

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consistent topic of discussion at every meeting has been the perception that patients' recovery has been incomplete. Although they have returned to their usual activities and have been told by their physicians that their physical examinations and laboratory data are normal, many former patients do not feel that they are as capable, mentally or physically, as they were before their episode of TTP. Commonly described symptoms include difficulties with memory, concentration, and endurance. These impressions are corroborated by their families.

In response to these discussions, we expanded our follow-up protocol in January 1998 to explore these symptoms in adults via the collection of health-related quality-of-life (HRQoL) outcomes. Our objectives were 1) to determine if patients who have apparently recovered completely from TTP have deficiencies in HRQoL compared to the US population, 2) to determine if any features of the episode of TTP are associated with differences in HRQoL, and 3) to determine if there is a change in HRQoL over time since the episode of TTP.

MATERIALS AND METHODS

The Oklahoma TTP-HUS Registry

The Registry includes all consecutive patients for whom the Oklahoma Blood Institute is requested to provide plasma exchange treatment for patients with a clinical diagnosis of TTP or HUS.[3,5] The Oklahoma Blood Institute is the sole provider of plasma exchange services for all hospitals in 58 of the 77 Oklahoma counties. Therefore, the Registry is an inception cohort of all consecutive patients within a defined geographic region in whom the diagnosis of TTP or HUS was established and a decision to initiate plasma exchange treatment was made. Because the Registry provides additional information and support for patients and their families and involves no change of management, all patients have consented to enroll. Since these syndromes in adults, with or without renal failure or neurologic abnormalities, are commonly known as TTP,[1] we describe patients in this report as having TTP. The Oklahoma TTP-HUS Registry is approved by the institutional review boards of the University of Oklahoma Health Sciences Center and each participating hospital.

Patients were assigned in a hierarchical, sequential order to one of six clinical categories related to associated conditions and potential etiologies at the time of their initial episode:[5] 1) after hematopoietic stem cell transplantation, 2) pregnant/postpartum, 3) drug association, 4) bloody diarrhea prodrome, 5) presence of an additional or alternative disorder that may have caused the presenting features, and 6) idiopathic, if none of the criteria for the previous five clinical categories were fulfilled. Demographic, clinical, and laboratory data were collected prospectively.[5] Serum for ADAMTS13 assays was collected immediately before the first plasma exchange procedure. ADAMTS13 activity measurements were performed by Drs Johanna A. Kremer Hovinga and Bernhard Lämmle (Department of Hematology, Inselspital, Berne, Switzerland) using two methods, the quantitative immunoblotting of proteolyzed von Willebrand factor multimers[6,7] and a fluorogenic assay using the FRETS-VWF73 substrate.[8,9] Severe ADAMTS13 deficiency was defined as less than 10 percent activity identified by either assay method.

HRQoL assessment

HRQoL was measured with a standardized questionnaire, the Short Form-36 (SF-36) Health Survey Version 1, which has been validated and is the most widely used health status questionnaire in the world.[10] The SF-36 can be completed in less than 15 minutes. The SF-36 was either interviewer-administered during telephone follow-up or self-administered during attendance at support group meetings or after arriving in the mail to patients' homes. Approximately one-half were administered by telephone and about half were self-administered.

The SF-36 contains 35 questions divided among eight different domains of physical and mental health that address the patient's health status within the past 4 weeks (Table 1).[10] One additional question of the SF-36 is distinct from the other questions as it asks about the person's health in general compared to 1 year ago (comparative

TABLE 1. Overview of the SF-36 health survey

Domains	Number of questions	Examples of health status assessed by each domain
Physical Functioning	10	Activities during a typical day, such as walking, climbing, lifting
Role Physical	4	Performance of work or other regular activities
Bodily Pain	2	Presence of pain that interferes with work
General Health	5	Overall perception of health
Vitality	4	Pep and energy or worn out and tired
Social Functioning	2	Limitations of activities with family and friends
Role Emotional	3	Limitations of regular activities by feeling anxious or depressed
Mental Health	5	Symptoms of depression
Summary Measures		
Physical Component Summary		A composite score for the physical components of the eight domains
Mental Component Summary		A composite score for the mental components of the eight domains

health). The results of this question were not analyzed since we used serial measurements of the other 35 questions to assess trends across time.

SF-36 score calculation

Raw scale scores were calculated by summing the responses to questions within each of the eight domains. Missing responses were replaced with a subject's average response for other questions within a domain, if the subject had answered 50 percent or more of the questions within that domain.[10] If the subject answered less than 50 percent of the questions for a domain, data for that domain were excluded from analysis. All raw scores were then converted to a 0 to 100 scale score. Then the 0 to 100 scale scores were transformed to norm-based scores using z-scores derived from the 1998 general US population.[10] The norm-based scores were created so that data derived from the 1998 general US population for all eight domains had a mean of 50 and a standard deviation (SD) of 10.[10] In addition to the results of the eight individual domains, physical and mental component summary scores were also calculated by first creating an aggregate score of the z standardized scores for the questions related to the mental and physical components of each domain and then performing the z-score transformation to make them norm-based, with mean scores of 50 and SDs of 10 for the US population. Age group- and gender-specific norm scores for the US population are lower, indicating worse HRQoL, as age increases and for women compared to men.[10] Since our patient group is older and has a higher proportion of women than the US population, an expected normal mean value for our patients based on their age and gender was calculated, using age group- and gender-specific norm scores.[10] Expected mean normal values for our patients ranged from 48.52 to 49.93 for the eight domains and the two summary scores, rather than 50, the mean normal value for the US population. Since these expected age/gender-adjusted mean normal values for our patients were very close to 50 and since they would not have changed the results of our analysis, for ease of interpretation we used the US population mean norm score of 50 $\pm$ a SD of 10 as the normal comparison value.

Statistical analysis

Analysis was performed using computer software (SAS 9.1, SAS Institute, Cary, NC) and statistical significance was determined with an alpha of 0.05 for all hypothesis tests. To determine if our patients differed from the US population, we compared the norm-based means and 95 percent confidence intervals (CIs) for each of the domains of our patient groups to the US population norm of 50. An independent t test was used to determine if a significant difference in norm-based mean values exists between TTP patients whose first QOL was completed 6 to 24 months after treatment for their first episode of TTP (referred to as 6- to 24-month group) and those whose first QOL was completed greater than 24 months after treatment for their first episode of TTP (referred to as >24-month group). Independent t tests were also calculated to determine if there were differences in HRQoL between different clinical subgroups of patients. To determine if HRQoL improved over time, a trend test was performed using a mixed model that was built using a random intercept and elapsed time since the episode of TTP of less than or equal to 5 years. The 0 to 100 scale scores of the eight domains were used to allow interpretation as percent change per year. A trend for improvement of HRQoL would be indicated by a significant positive slope; the slope also provided information on the magnitude of change over time.

RESULTS

Patients

The Registry has enrolled and followed prospectively all 364 consecutive patients in our region of Oklahoma who had a clinical diagnosis of TTP from January 1, 1989, to June 30, 2007, and for whom plasma exchange treatment was requested. Since January 1998, SF-36 questionnaires have been an established part of the Registry follow-up protocol. The initial SF-36 assessment is to be completed approximately 1 year after recovery from the patient's initial episode of TTP, designated as the day of the last plasma exchange treatment, and is then administered annually. Therefore, patients enrolled in the Registry after June 30, 2007, were excluded from this analysis to allow all patients the opportunity for at least one initial SF-36 assessment. In practice the intervals before the initial SF-36 assessment and between subsequent assessments varied with the ability to contact former patients and for them to complete the evaluation.

One-hundred eighty-one (50%) patients were initially eligible for our analysis because they 1) were 18 years old or older at the time of the SF-36 assessment; 2) were alive on January 1, 1998, the date when SF-36 assessments were begun and had not relapsed before this date; and 3) survived for at least 1 year without a relapse after completion of plasma exchange treatment for their initial episode (Fig. 1). Patients who had a relapse of TTP before their initial SF-36 assessment were excluded to avoid the potential influence of multiple episodes. The goal of this study was to evaluate patients who had recovered from TTP without overt disabilities and who did not have major additional disorders that could affect HRQoL. Therefore, we excluded 53 (29%) of the 181 eligible patients who had 1) hematopoietic stem cell transplantation, 2; 2) received chemotherapy for cancer or immunosuppressive treatments for organ transplantation, 5; 3) had end-stage renal

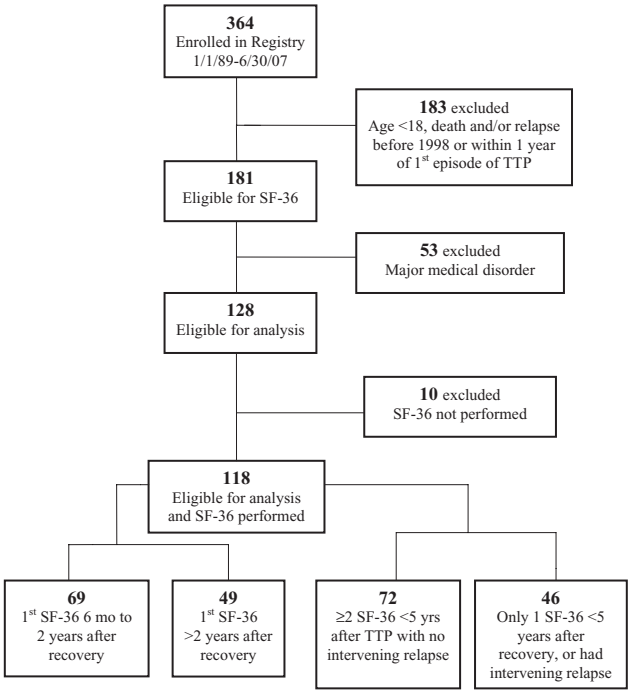

Fig. 1. Eligibility and selection of patients for analysis of HRQoL by the SF-36.

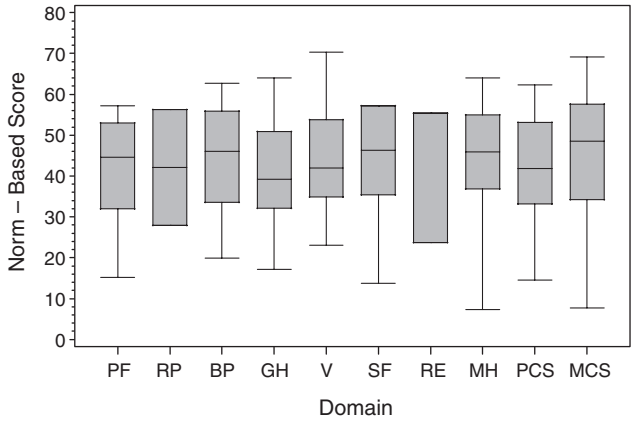

Fig. 2. Data are presented for the initial SF-36 assessment of the 118 patients selected for analysis. Data are the median values of the norm-based scores for each of the eight domains of the SF-36 and the two component summary scores. The solid line indicates the median score of the patient group (the median score of the role emotional domain is 55); the box indicates the 25th to 75th percentiles. The lines extended from the boxes indicate the minimum and maximum scores; for norm-based scores the possible minimum and maximum vary for each domain. Our patients' scores extended from the lowest possible score to the highest possible score for each domain. For the boxes without lines the minimum and 25th percentile as well as the 75th percentile and maximum scores were the same value. The domains of the SF-36 are designated by PF, Physical Functioning; RP, Role Physical; BP, Bodily Pain; GH, General Health; V, Vitality; SF, Social Functioning; RE, Role Emotional; MH, Mental Health; PCS, Physical Component Summary; and MCS, Mental Component Summary.

disease requiring maintenance dialysis or renal transplantation, 9; 4) had had a stroke with major residual disability, 4; 5) had human immunodeficiency virus infection, 4; 6) had a systemic autoimmune disorder (such as systemic lupus erythematosus, Sjögren's syndrome, or the antiphospholipid antibody syndrome), 21; or 7) were discovered after plasma exchange was begun to have an alternative disorder (sepsis, malignant hypertension, sickle cell disease with multiorgan failure) that was determined to be the etiology of their illness, 8. Therefore, 128 patients who appeared to have recovered completely from TTP and who did not have major additional illnesses or disabilities were ultimately eligible for analysis.

Of the 128 patients, 118 (92%) had at least one SF-36 assessment that was completed 6 months or more after recovery from their initial episode of TTP, the time we defined for allowing complete recovery to occur. The other 10 patients have not been assessed by the SF-36: 1 was lost to all follow-up efforts, 8 never responded to our requests to complete an SF-36 assessment, and 1 patient relapsed after 1 year but before her initial SF-36 assessment was distributed.

In total, 550 SF-36 assessments have been completed by these 118 patients. Follow-up is complete on all patients; the median follow-up to the current time is 7.3 years (range, 0.6-18.5 years). The clinical categories of these 118 patients were pregnant/postpartum, 17; drug association, 14 (quinine, 13; ticlopidine, 1); bloody diarrhea prodrome, 16; and idiopathic, 71. Ninety-five (81%) of the 118 patients were women; 92 (78%) were white and 20 (17%) were black; their median age was 50 years (range, 19-85 years).

HRQoL outcomes

Figure 2 displays the results of the initial SF-36 assessments of the 118 patients for each of the eight domains and the two component summary scores. The data are presented as norm-based scores. The results for each domain extended across the entire range of potential scores, which varied for each domain. Table 2 compares the results of the patient group to the US population using norm-based scores. For each of the eight domains and both summary scores, the patients were significantly worse than the US population, since the 95 percent CIs did not include 50, the mean value of the US population, indicating that patients with TTP had worse functioning and well-being.

For the entire group of 118 patients, the range of time between recovery from their initial episode of TTP and their initial SF-36 assessment was great (median interval,

TABLE 2. Mean norm-based scores for the initial SF-36 assessment (n = 118 patients)*

Domain/summary score	Number	Mean	95% CI
Physical Function	117	42.10	39.86-44.35
Role Physical	118	42.04	39.85-44.23
Bodily Pain	118	45.28	42.97-47.60
General Health	118	40.57	38.41-42.73
Vitality	118	43.97	41.74-46.19
Social Function	118	43.75	41.24-46.26
Role Emotional	118	44.00	41.43-46.58
Mental Health	116	45.12	42.57-47.66
Physical Component Summary	115	42.47	40.28-44.66
Mental Component Summary	115	45.27	42.57-47.96

* Data are the mean norm-based scores with the 95 percent CIs for each of the eight domains of the SF-36 and also for the two summary measures. Number is number of patients without missing data for that score. Scores for all eight domains and both summary scores are significantly less than the scores for the US population, which are norm-based to a mean score of 50 with a SD of 10.

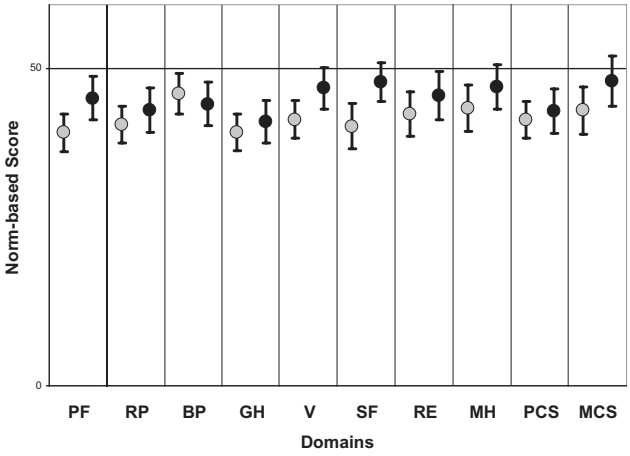

Fig. 3. Data are presented separately for the initial SF-36 assessments on 69 patients who were assessed between 6 and 24 months after recovery (○) and 49 patients whose initial assessment was more than 24 months after recovery (●). Data are the mean norm-based scores with the 95 percent CIs for each of the eight domains of the SF-36 and also for the two component summary measures. Data for each measurement are compared to the mean value for the US population that has been normalized to a mean score of 50 for each measure, designated by the line. The domains of the SF-36 are designated by PF, Physical Functioning; RP, Role Physical; BP, Bodily Pain; GH, General Health; V, Vitality; SF, Social Functioning; RE, Role Emotional; MH, Mental Health; PCS, Physical Component Summary; MCS, Mental Component Summary.

1.53 years; range, 0.52-10.29 years). Because we considered that HRQoL may improve with time after recovery from TTP, the 118 patients were divided into two groups according to the interval between recovery from their episode of TTP and their initial SF-36 assessment. Sixty-nine patients were in the 6- to 24-month group (median interval, 1.10 years; range, 0.52-1.96 years). Forty-nine patients were in the more than 24-month group (median interval, 4.18 years; range, 2.03-10.29 years); these were principally patients who had their episode of TTP before 1997. Figure 3 demonstrates that the 6- to 24-month group had significantly lower scores than the US population across all of the eight domains and both summary measures. The more than 24-month group had significantly lower scores than the US population for five of the eight domains and for the Physical Component Summary; their scores did not differ from the US population for the Vitality, Social Function, and Mental Health domains and for the Mental Component Summary. Further, the mean scores of the more than 24-month group were higher (better HRQoL) than the 6- to 24-month group for both of the summary measures and for all of the domains except Bodily Pain. These differences between mean values assessed by an independent t test demonstrated a significance for three of the eight domains: Physical Function ($p = 0.018$), Vitality ($p = 0.028$), and Social Function ($p = 0.004$).

Because it appeared that the patients' HRQoL assessed by the SF-36 may improve with time after recovery from TTP, analyses of clinical features of the TTP episode were limited to the 69 patients in the 6- to 24-month group. These patients were considered to be more uniform and therefore this group was used for analyses to investigate whether clinical features of the TTP episode resulted in differences in HRQoL. Among these 69 patients, there was no difference in results for any of the eight domains or either of the two summary measures when the patients with different clinical features were compared: 1) 41 patients with idiopathic TTP compared to 28 patients who were pregnant or postpartum, had a drug-associated etiology, or who had a bloody diarrhea prodrome; 2) 25 patients with severe ADAMTS13 deficiency (<10% activity) compared to 42 patients with 10 percent or greater activity (ADAMTS13 activity was not measured in two patients); 3) 25 patients who had severe neurologic abnormalities (coma, stroke, seizure, or focal neurologic signs) at the time of their episode of TTP compared to 44 patients who did not have severe neurologic abnormalities; and 4) 23 patients who required less than 10 plasma exchange treatments to achieve a remission compared to 36 patients who required 10 or more plasma exchange treatments ($p > 0.05$ for all comparisons).

To assess whether HRQoL changed over time, we analyzed serial measurements of 72 (61%) of the 118 individual patients who had at least two assessments during

TABLE 3. Trend analysis of 233 serial assessments of 72 patients with two or more assessments within 5 years of recovery from TTP without an intervening relapse*

Domain	Slope	p Value
Physical Function	1.02	0.247
Role Physical	1.23	0.454
Bodily Pain	–0.09	0.941
General Health	–0.03	0.973
Vitality	0.37	0.681
Social Function	0.54	0.687
Role Emotional	1.60	0.419
Mental Health	–0.29	0.723

* The slope is presented as the change per year of the SF-36 score converted to a 0 to 100 scale score. Positive values represent a trend toward higher (better) values; negative values represent a trend toward lower (worse) values. p Values describe the difference between the observed slope and a slope of 0.

their first 5 years after recovery from TTP with no intervening relapses. The analysis was based on 233 total SF-36 assessments, 2 to 5 per patient (median, 3 assessments per patient). Table 3 demonstrates that the point estimates of the slopes ranged from –0.29 percent per year, indicating slight worsening, to +1.60 percent per year, indicating slight improvement; however, none of the slopes of the eight domains were different from zero.

DISCUSSION

Using a standard instrument to measure HRQoL for the past 10 years as part of our annual follow-up of patients in the Oklahoma TTP-HUS Registry, we have confirmed the consistent impressions of our patients that their recovery may indeed be incomplete. Even though our patients were selected for apparent complete recovery, without significant disabilities or additional health problems, the results of all domains that measure different aspects of physical and mental health were significantly worse than the US population. Although some improvement was suggested by the improved HRQoL scores among patients who had their initial assessment later after recovery, no significant improvement was present for any of the eight domains when serial assessments on individual patients over 5 years after recovery were analyzed. Serial assessment of individual patients may be a more valid measure of changes of HRQoL over time than the comparison of two different groups of patients. These observations support the validity of our patients' persistent concerns about their memory, concentration, and endurance in spite of their apparent complete recovery, suggested by normal physical examinations and laboratory data.[2,3]

We could not identify any patient characteristics that predicted the deficits in HRQoL. Patients described as idiopathic were not different from patients in other clinical categories; patients who had deficient ADAMTS13 activity were not different from patients without ADAMTS13 deficiency; patients who had severe neurologic abnormalities with their acute episode were not different from patients without severe neurologic abnormalities; and patients who required less than 10 plasma exchange treatments to achieve a remission were not different from patients who required 10 or more plasma exchange treatments. These data suggest that deficits of HRQoL may occur in all patients who have the clinical syndrome of TTP, regardless of etiology and severity. The observation that only 37 percent of our patients had ADAMTS13 activity of less than 10 percent is consistent with our previous data[5] but less than the frequency of ADAMTS13 deficiency reported in other case series.[11] This is related to our inclusion of all patients who were initially diagnosed as TTP or HUS in the Registry region and for whom plasma exchange treatment was requested,[5] methodology that is less selective than other case series.[11]

Deficits in HRQoL may be caused by minor cognitive abnormalities resulting in limitations that are subtle, mild, and vague yet nonetheless the source of significant problems of daily life. In a preliminary study, we have demonstrated persistent neurocognitive abnormalities causing deficits of attention, processing speed, and memory in patients who had recovered from TTP.[12] These abnormalities can make daily tasks more difficult and require more effort, causing people to feel more tired, both emotionally and physically. These cognitive abnormalities may be the result of the diffuse microvascular thrombosis that is characteristic of TTP.[1]

Another potential source of the deficiencies in HRQoL may be limitations of cardiac function. Although data on clinical cardiac abnormalities during acute episodes of TTP are extremely limited,[13] one retrospective study has reported that 41 percent of patients with TTP had evidence for myocardial infarction.[14] It is possible that persistent abnormalities of cardiac function may limit patients' ability to comfortably perform physical activities and therefore contribute to decreased HRQoL.

This study has important limitations. Patients' HRQoL before their episode of TTP was not known. Although the SF-36 is widely used and validated for many diverse health conditions,[10] the opportunities for interviewer bias, patient recall bias, and survey nonresponse bias are all important considerations. The items from within the SF-36 have been carefully selected and tested to minimize recall bias and standardized procedures were used to administer the survey. However, HRQoL is subjective. Nonresponse bias may limit interpretation of this data, although only 10 (8%) of 128 patients were either lost to follow-up or did not complete their surveys. To minimize nonresponse bias we used multiple methods of administering the SF-36 questionnaire. However, we acknowledge that responses may be different related the method of questionnaire administration.

To complete the circle of this study, which was initiated in response to patients' discussions at support group meetings, we presented the results of our HRQoL analyses to our patient support group. We were apprehensive about presenting data that did not provide a basis for optimism about improvement with time. However, the patients were neither surprised nor disappointed. In fact, they were relieved that there had not been a significant improvement of the group data, because they recognized that they as individuals had not improved. They felt some comfort that, as a group, the results were what they as individuals would have predicted.

TTP may not be an acute, episodic disorder with complete recovery. The thrombotic microangiopathy causing ischemic damage to multiple organs may result in persistent abnormalities. These abnormalities may go unrecognized by physicians, based on routine clinical evaluations, but can be a source of important limitations and frustration for patients. Definition of the cognitive abnormalities and investigation for persistent cardiac abnormalities may allow targeted rehabilitation techniques that could provide better adaptation and functional ability. Recognition of these persistent abnormalities will allow more effective emotional support for patients who currently feel that their health problems are not being acknowledged or addressed.

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