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ORIGINAL ARTICLE

Absolute lymphocyte count and risk of short-term infection in patients with immune thrombocytopenia

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Abstract Patients with immune thrombocytopenia (ITP) may be at increased risk of infection because of the steroids and other immunosuppressive agents used in its treatment. This study aimed to identify events that are associated with infection within 6 months of diagnosis and the impact that infection has on survival. We retrospectively evaluated 239 patients (107 men, 132 women; median age 61 years) diagnosed between January 1997 and August 2011. Every patient received steroid treatment according to the platelet count and the extent of bleeding. Logistic regression analysis was used to identify risk factors associated with the development of infection within 6 months of ITP being diagnosed. Sixty-two patients (25.9 %) developed an infection within 6 months of diagnosis. Multivariate analysis revealed that a lower absolute lymphocyte count (ALC) at diagnosis ($<1\times10^9$/l) was an independent risk factor for infection (P=0.039; 95 % confidence interval, 1.033–3.599; odds ratio, 1.928). The time to infection event is significant shorter in those of low ALC, compared with those of higher ALC (P=0.032). Furthermore, the 1-year mortality rate after ITP diagnosis was significantly higher in those patients who developed an infection (P=0.001). ITP patients with a low absolute lymphocyte count at diagnosis have an increased risk of infection, and those who develop infections have lower 1-year survival.

Keywords Immune thrombocytopenia (ITP) · Absolute lymphocyte count (ALC) · Lymphopenia · Infection

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Introduction

Adult patients with idiopathic or immune thrombocytopenia (ITP) are generally considered to have the same mortality risk as the general population [1]. However, considerable morbidity and mortality may still occur in these patients, particularly in those with severe thrombocytopenia that persists despite treatment [1]. It seems likely that patients with ITP will have an increased risk of infection as steroids and other immunosuppressive agents are the primary treatment for this condition. Indeed, in a study of high-dose steroid treatment for ITP patients younger than 60 years of age by the GIMEMA group, the infection risk was reported to be 2.7 % [2]. In a Danish population-based cohort study, the infection risk during the 1-year follow-up period was found to be 15.2 %, and an even higher infection rate was noted in patients who were older than 60 years [3]. In another single-institute cohort study of 47 consecutive elderly ITP patients (also aged over

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60 years), the incidence of bacterial infection after corticosteroid treatment was 17 % [4]. Moreover, in addition to life-threatening bleeding complications, infection has been considered a risk of morbidity and mortality in the long-term follow-up of patients with ITP [1, 2]. Most previous studies have addressed the success or failure of different therapies, or hematologic events and death after ITP, but far fewer have focused on the infection risk and related complications. Infection in patients with ITP may complicate therapy, increase the length of hospital stay or the need for admission, and influence their quality of life.

Interestingly, a low absolute lymphocyte count (ALC) has been suggested as a poor prognostic factor in lymphoma patients [5–7], but whether it is also a factor associated with the development of infection is unclear. However, a low ALC might imply an immune deficient status and could be a potential surrogate marker for infection risk. Indeed, our recent study showed that the combination of a low ALC and rituximab treatment was associated with a high risk of interstitial pneumonia in patients with diffuse large B cell lymphoma [5]. The aim of this study was to determine which factors are associated with the risk of short-term infection (within 6 months after diagnosis) in patients with ITP, particularly with respect to ALC, and to assess the 1-year mortality rate in these patients.

Materials and methods

Participants

The retrospective study enrolled adult patients (≥18 years) with ITP, who were diagnosed and treated in Taipei Veteran General Hospital during the period between January 1, 1997 and August 30, 2011. ITP was diagnosed in accordance with the guidelines of the American Society of Hematology, based principally on the clinical history, physical examination, complete blood count, and examination of the peripheral smear in order to exclude other causes of thrombocytopenia [8]. Moderate thrombocytopenia was defined as an initial platelet count of between 30.0×10^9/l and 100.0×10^9/l without a further reduction to below 30.0×10^9/l during the first 3 months of observation [1]. Severe thrombocytopenia was defined as a platelet count below 30.0×10^9/l at presentation or an initial count between 30.0×10^9/l and 100.0×10^9/l with a subsequent reduction to below 30.0×10^9/l during the following 3 months [1]. Bone marrow examination was performed when necessary, including cases of unexplained deterioration or severe thrombocytopenia, in patients older than 60 years for whom the possibility of myelodysplastic syndrome needed to be considered or in patients for whom etiologies other than ITP were suspected clinically.

Patients who were found to have malignancies, systemic autoimmune diseases, lymphoproliferative disorders, or other secondary thrombocytopenia within 3 months of ITP diagnosis were excluded, as were patients who did not receive steroid treatment after ITP diagnosis. Comorbidities including diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD), congestive heart failure (CHF), coronary artery disease (CAD), cerebral vascular accident (CVA), and chronic obstructive pulmonary disease (COPD) were also recorded.

Management

Patients with ITP in this study were treated in accordance with the American Society of Hematology and British Committee for Standards in Haematology guidelines, whereby patients with platelet counts less than 30.0×10^9/l or with bleeding should receive treatment [8, 9]. In this retrospective study, all patients received corticosteroid as a first-line treatment. In most cases, this consisted of a standard dose of methylprednisolone (1–2 mg/kg/day), although some with severe thrombocytopenia received high-dose steroids (dexamethasone 40 mg/day for 4 days or methylprednisolone 15 mg/kg/day for 4 days) [10, 11]. In addition to standard steroid therapy, intravenous immunoglobulin (1 g/kg for 2 days), azathioprine, and danazol were used as first-line treatments in combination with steroids or as second-line managements. Splenectomy was performed as a salvage therapy when severe thrombocytopenia or bleeding persisted after steroid treatment. Alternative managements including cyclosporine, cyclophosphamide, vincristine, and rituximab were used as salvage therapy on an individual basis at the discretion of the attending physician [12–14].

Definition of infection and the analysis of potential risk factors associated with infection

Infectious complications that occurred within 6 months of the initial diagnosis were documented. These included bloodstream infections, urinary tract infections (UTIs), pneumonia, soft tissue infections/abscesses, intra-abdominal abscesses, cholangitis, osteomyelitis, pseudomembranous colitis, and oral infections (including oral candidiasis, acute suppurative periodontitis, and acute suppurative tonsillitis). A series of infections affecting the same patient at different times were considered to be individual events. Infection was defined clinically (symptoms and physical signs compatible with the infectious process) and confirmed by a positive urine (leukocyturia with ≥10,000 cells/mm^3 and/or bacteriuria), blood culture, sputum smear/culture, or tissue culture test and/or a positive finding on radiography or another imaging modality. Herpes zoster infection was also screened for. The final diagnosis was based on the care physicians' and patients' documentation. In order to evaluate the potential risk factors for infection, patients were divided into two groups depending on whether or not they had had at least one episode of infection within 6 months of ITP being diagnosed.

To explore low ALC as a potential risk of infection, we predefined a cutoff value of ALC$<1\times10^9$/l. Previously, low ALC at the values of $<1\times10^9$/l has been suggested as a poor prognostic factor in patients with lymphoid malignancies [5, 6, 15–17]. In addition, in our previous study, ALC$<1\times10^9$/l was an important surrogate marker for predicting the occurrence of interstitial pneumonia [5]. ALC at time of ITP diagnosis and at time of infection were both documented, but only ALC at time of ITP diagnosis was considered in risk factor analysis. The cutoff point selected for ALC (1×10^9/l) was supported both by our data and those of previous studies [5, 6, 15–17]. Other risk factors tested included age (younger than 65 vs. 65 years or older), disease severity at diagnosis (moderate vs. severe), and whether or not the patient had any comorbidity including DM, HTN, CKD, CHF, CAD, CVA, and COPD; received a first-line treatment of high dose steroids; had Evan's syndrome; and had undergone a splenectomy.

Treatment responses and follow-up

Treatment responses were evaluated according to the consensus definition of the International Working Group [18]. "Complete response" (CR) was defined as a platelet count equal to or greater than 100.0×10^9/l. "Response" (R) was defined as a platelet count of more than 30.0×10^9/l and at least a doubling of the baseline count, and "no response" (NR) was defined as a platelet count lower than 30.0×10^9/l or less than a doubling of the baseline count. The definition of response also required the concurrent resolution of bleeding symptoms [18].

For each patient, the observation period started on the day of the initial diagnosis. Patients were followed until the observation period ended on August 30, 2011 or until death (due to any cause) if it occurred before this date. One-year survival after diagnosis was used for statistical analysis.

Statistical analysis

Categorical variables were compared using the χ^2 test or the Fisher exact test between patients with or without infection after treatment, and the log-rank test was used to compare the survival curves. Logistic regression was applied for univariate and multivariate analyses to determine the potential risk factors associated with infection. Variables with P values<0.1 in univariate analyses were entered into multivariate analyses. A P value of <0.05 was regarded as statistically significant in two-sided tests. Kaplan–Meier methods were used to evaluate time to infection event and 1-year survival after ITP diagnosis. Log-rank tests were used for comparisons. A Cox proportional hazards model was used to analyze the contribution of ALC on the time to infection event. All statistical analyses were performed using SPSS statistical software version 18 (SPSS, Chicago, IL, USA).

Results

Demographic and clinical characteristics of ITP patients

The medical records of 294 patients with ITP were reviewed. Of these, 55 patients were excluded because of secondary disease, including autoimmune disease, malignancy, or lymphoproliferative disorder. Table 1 summarizes the general characteristics of the 239 enrolled patients. Among these, 107 (44.8 %) were men and 132 (55.2 %) were women. The median age at diagnosis was 61 years (range, 18–97 years), and the median follow-up time was 19.36 months (range 0.1–155.3 months). The majority of patients had severe thrombocytopenia (197 patients, 82.4 %). A total of 98 (41.0 %) patients had at least one comorbidity, including 72 (30.1 %) patients with HTN, 35 (14.6 %) with DM, 11 (4.6 %) with CKD, 9 (3.8 %) with CHF, 12 (5.0 %) with a history of CVA, and 8 (3.3 %) with COPD (Table 1). Among the 35 patients with DM, most of them were under oral hypoglycemic agent control (94.3 %). Only two patients (5.7 %) received insulin treatment.

All patients received steroids as a first-line treatment. A total of 18 patients (7.5 %) received splenectomy as a salvage therapy for severe and refractory disease during their course of treatment (median time to splenectomy after diagnosis was 2.4 months, range 0.23–18.6 months).

Response to steroid treatment

Of the 236 patients included in this study, 155 (65.7 %) displayed CR, 44 (18.6 %) displayed R, and 37 (15.7 %) displayed NR to treatment. Among the 37 NR patients, eight patients received more than two different medications as a second-line treatment. Two of these patients remained refractory after splenectomy and second-line management, and the remaining six patients subsequently developed treatment-dependent chronic ITP.

Clinical characteristics of infection

Sixty-two patients (25.9 %) had a total of 73 infections within 6 months of ITP diagnosis and treatment, including ten patients who had two separate episodes of infection and one patient who had three separate episodes of infection. Among these infections, 32 (43.9 %) were pneumonia, 13 (17.8 %) were UTIs, 9 (12.3 %) were caused by herpes zoster, 11 (15.1 %) were soft tissue infection, and 8 (10.9 %) were other infections, including oral candidiasis, cholangitis, fungemia, bacteremia, intra-abdominal abscess, osteomyelitis, and pseudomembranous colitis (Table 2).

In 30 (41.1 %) of the 73 infections, a specific pathogen could be identified by culture, including 16 cases where two pathogens were identified. Regarding the time at which the

Table 1 Demographic and clinical characteristics of patients with immune thrombocytopenia

Patient characteristic	All patients (n=239)
Sex, no. of patients (%)	
Male	107 (44.8 %)
Female	132 (55.2 %)
Medium age, years (range)	61.0 (18~97)
Medium follow-up period, months (range)	19.36 (0.1~155.3)
Thrombocytopenia[a] no. of patients (%)	
Severe	197 (82.4 %)
Moderate	42 (17.6 %)
Evan's syndrome, no. of patients (%)	21 (8.8 %)
Splenectomy, no. of patients (%)	18 (7.5 %)
Comorbidity, no. of patients (%)	
DM	35 (14.6 %)
HTN	72 (30.1 %)
CKD	11 (4.6 %)
CHF	9 (3.8 %)
CVA	12 (5.0 %)
COPD	8 (3.3 %)
Any	98 (41.0 %)
First-line treatment	
Standard dose methylprednisolone	149 (62.3 %)
High-dose methylprednisolone	90 (37.7 %)
Other treatment	
Immunoglobulin	
First line	17 (7.1 %)
Salvage	9 (3.8 %)
Azathioprine	
First line	20 (8.4 %)
Salvage	38 (15.9 %)
Danazol	
First line	3 (1.3 %)
Salvage	6 (2.5 %)
Cyclosporine	
First line	0 (0.0 %)
Salvage	7 (2.9 %)
Cyclophosphamide	
First line	0 (0.0 %)
Salvage	17 (7.1 %)
Vincristine	
First line	0 (0.0 %)
Salvage	6 (2.5 %)
Rituximab	
First line	0 (0.0 %)
Salvage	7 (2.9 %)

DM diabetes mellitus, *HTN* hypertension, *CKD* chronic kidney disease, *CHF* congestive heart failure, *CVA* cerebral vascular accident, *COPD* chronic obstructive pulmonary disease

[a] Moderate thrombocytopenia=platelet counts between 30.0×10^9 /l and 100.0×10^9 /l; severe thrombocytopenia counts below 30.0×10^9 /l

Table 2 Characteristics of infections

Patient characteristic	No. of events (%)
Type of infection	
Total infections	73
Pneumonia	32 (43.8 %)
UTI	13 (17.8 %)
Herpes zoster	9 (12.3 %)
Soft tissue infection[a]	11 (15.1 %)
Others[b]	8 (11.0 %)
Pathogens	
Event with definite cultured pathogen	30 (41.1 %)
Polymicrobial	16 (21.9 %)
Staphylococcus aureus	9 (12.5 %)
E. coli	4 (5.6 %)
Pseudomonas aeruginosa	5 (7.0 %)
Klebsiella pneumonia	6 (8.3 %)
Stenotrophomonas maltophilia	4 (5.6 %)
Yeast[c]	6 (8.3 %)
Others[d]	12 (16.7 %)
Infection event date	
1st month	23 (31.5 %)
2nd month	19 (26.0 %)
3rd month	7 (9.6 %)
4th month	8 (11.0 %)
5th month	7 (9.6 %)
6th month	9 (12.3 %)

[a] Soft tissue infection include cellulitis (eight), facial abscess (one), acute suppurative periodontitis (one), and acute suppurative tonsillitis (one)

[b] Other infection includes oral candidiasis (two), cholangitis (one), fungemia (one), bacteremia (one), intra-abdominal abscess (one), osteomyelitis (one), and pseudomembranous colitis (one)

[c] Including *Candida albicans* and *Aspergillus*

[d] Other pathogen including *Acinetobacter baumannii* (four cases), *Enterobacter* spp. (three cases), *Streptococcus agalactiae* (one case), *Serratia* spp. (one case) *Clostridium dificile* (one case), *Chryseobacterium meningosepticum* (one case), and gram-positive cocci (one case)

infection was first noted, 23 (32.9 %) occurred in the first month after diagnosis, and the remaining 19 (26.0 %), 7 (9.6 %), 8 (11.0 %), 7 (9.6 %), and 9 (12.3 %) infections occurred in the second, third, fourth, fifth, and sixth month after diagnosis, respectively (Table 2).

Among these 62 patients with infection, mean ALC count at diagnosis and at infection was 1.469×10^9/l and 1.329×10^9/l, respectively (P=0.286). There was no significant difference with regards to the proportion of patients with lymphopenia (ALC<1×10^9/l) at time of ITP diagnosis and at time of infection among these 62 patients (41.9 % at ITP diagnosis vs. 51.6 % at time of infection, P=0.123). Compared with ITP patients without infections, patients who had infections within 6 months after ITP diagnosis had older age, more comorbidities, and lower ALC count (Table 3).

Table 3 Baseline characteristics of patients

Character	No infection (n=177)	Infection (n=62)	P value
Sex			0.006*
M	71 (39.5 %)	37 (59.7 %)	
F	107 (60.5 %)	25 (40.3 %)	
Age (years)			0.007*
Median	57	65	
Range	14~90	10~97	
Q25~Q75	34~75	53~79	
Thrombocytopenia			0.462
Moderate	33 (18.6 %)	9 (14.5 %)	
Severe	144 (81.4 %)	53 (85.5 %)	
Evan's syndrome	15 (8.4 %)	6 (9.7 %)	0.764
Splenectomy	12 (6.8 %)	6 (9.7 %)	0.457
Cormobidity			
DM	21 (11.8 %)	14 (22.6 %)	0.040*
HTN	51 (28.8 %)	21 (33.9 %)	0.455
CKD	6 (3.4 %)	5 (8.1 %)	0.131
CHF	6 (3.4 %)	3 (4.8 %)	0.606
CVA	8 (4.5 %)	4 (6.5 %)	0.549
COPD	5 (2.8 %)	3 (4.8 %)	0.448
Any	66 (37.2 %)	32 (51.6 %)	0.048*
Median ALC ($\times 10^9$/l)	1.420(0.993~1.922)	1.182(0.873~1.705)	0.027*
ALC$<1\times10^9$/l	45 (25.3 %)	27 (43.5 %)	0.007*
Response[1]			0.220
CR	111 (63.8 %)	44 (71.0 %)	
R	37 (21.3 %)	7 (11.3 %)	
NR	26 (14.9 %)	11 (17.7 %)	

M male, *F* female, *DM* diabetes mellitus, *HTN* hypertension, *CKD* chronic kidney disease, *CHF* congestive heart failure, *CVA* cerebral vascular accident, *COPD* chronic obstructive pulmonary disease, *ALC* absolute lymphocyte count, *CR* complete response, *R* response, *NR* no response

*Statistical significance (p<0.05)

Factors associated with infection in ITP patients

Univariate analysis revealed that an ALC of less than 1×10^9/l at diagnosis (P=0.008; odds ratio, 2.263), being older than 65 years (P=0.004; odds ratio (OR), 2.416), and having at least one comorbidity (P=0.050; OR, 1.794) were risk factors for infection within 6 months of ITP diagnosis. Multivariate analysis revealed that a low ALC was the most significant risk factor (P=0.039; 95 % confidence interval, 1.033–3.599; OR, 1.928) associated with short-term infection in patients with ITP.

Analysis of 1-year survival after ITP treatment

A total of 11 patients died during the follow-up period after ITP diagnosis, of whom ten died of infectious disease and the remaining patient died of a complication resulting from bleeding. Nine of these patients died within 1 year of diagnosis. The Kaplan–Meier analysis revealed that patients who developed an infection within the first 6 months after treatment for ITP had a poorer 1-year survival compared to those who did not (P=0.001) (Fig. 1).

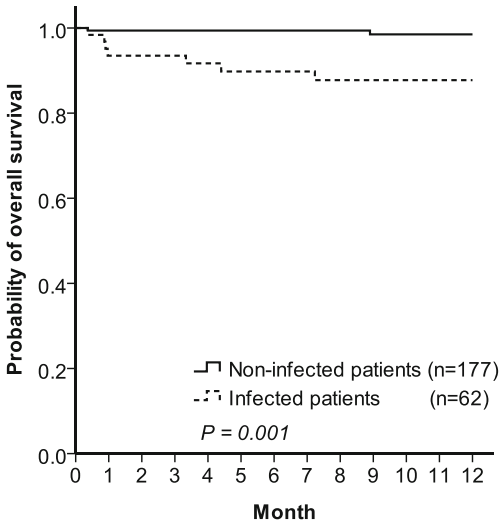

Fig. 1 One-year Kaplan–Meier survival curve for immune thrombocytopenia patients who developed an infection within 6 months of diagnosis, compared to those who remained infection free

Effect of low ALC on time to infection event

To further analyze the contribution of low ALC (less than 1×10^9/l) on the time to infection event, cumulative incidence of infection event was generated by the Kaplan–Meier method. As shown in Fig. 2, the time to infection event is significant faster in those of low ALC, compared with those of higher ALC (P=0.032). Cox proportional

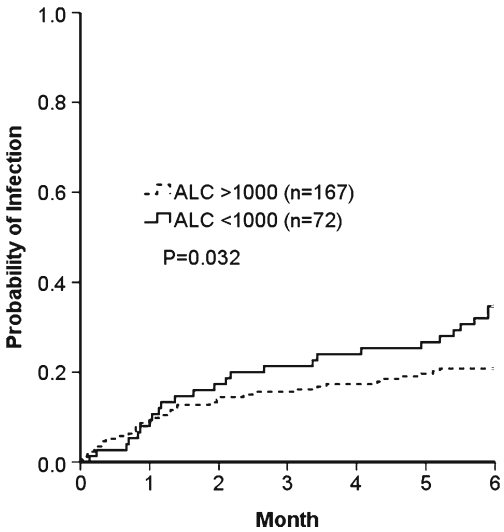

Fig. 2 Kaplan–Meier curve for time to infection event after diagnosis

hazards analysis showed that patient with low ALC had higher risk of infection as compared with those with higher ALC (HR 1.723, 1.040~2.853).

Discussion

ITP has previously been shown to be associated with an increased risk of infection relative to normal populations [3]. Therapy for ITP typically involves the use of steroids and/or other immunosuppressive agents that might contribute to the increased risk of infection. Interestingly, our study demonstrated that a low ALC may be an important risk factor for infection in ITP patients. Moreover, the mean ALC value and the proportion of lymphopenia at time of ITP diagnosis were not significantly differed from those at time of infection among ITP patients with infections suggesting that a low ALC may be a reliable predictive factor for risk of infections in ITP patients. Nevertheless, the mechanisms beneath a low ALC and the association with risk of infections remain unknown, and further studies are necessary. It is possible that ALC may be a surrogate marker, reflecting an underlying immune deficiency and/or dysfunction. There is growing evidence that T cells play a vital role in the onset of ITP [19–28]. As the immune system undergoes dysregulation, predisposed individuals develop a Th1/Th2 imbalance that favors the induction of organ-specific autoimmunity [21]. A reduced number of CD4+ CD25+ T-regulatory cells, which elicit peripheral tolerance and downregulate T-effector cell responses, have also been reported in ITP patients [24, 26]. Several studies have demonstrated that ALC is a good predictor of CD4 count, which in turn is a strong predictor of opportunistic infection in human immunodeficiency virus-positive patients [29–32]. Furthermore, treatment with steroids has been shown to induce lymphopenia [33–36], which may further complicate a preexisting low ALC status. In this study, we have identified a new risk factor associated with infection in patients with ITP, but further studies will be required to confirm this and to elucidate the underlying mechanisms.

The CR rate after initial steroid treatment for ITP was previously reported to be 51.9 % [37], while in our study it was 65.7 %. However, compared with this previous study, the infection risk in our study was higher (25.9 %), which was probably related to the older median age (61 years) in our patient group (a total of 112 patients (46.8 %) were older than 65 years in our study). Moreover, old age was a univariate risk factor associated with infection in our study, although it showed only a borderline significance in multivariate analysis. Aging of the immune system, or immunosenescence, may render the elderly more susceptible to infection and associated mortality [38]. Furthermore, immunosenescence usually involves thymus involution, which is thought to contribute to autoimmune diseases including ITP [39, 40].

Refractory ITP is known to increase the risk of bleeding [41] and mortality, with a reported mortality rate in refractory disease of about 15–20 % [12]. Bleeding and infection both contribute to the death of patients with ITP [1], although the infection-attributable mortality in patients with ITP may vary and is not well-defined. Our study demonstrated that patients who suffered an infection after treatment had a significantly poorer 1-year survival than those who did not develop an infection (Fig. 1). This suggests that the dose of steroid or other immunosuppressive agents should be reduced as soon as a treatment response has been achieved in order to avoid additional infections. Furthermore, if combination chemotherapy is being considered, the short- and long-term risk should be weighed against the potential benefits.

Our study had several limitations. First, the retrospective design and relatively small patient number may have failed to identify other potentially important risk factors. Second, the steroid treatment varied according to each individual's clinical condition. It is therefore difficult to be sure of an association between the cumulative steroid dosage and duration and infection risk, especially in elderly patients. In addition, other viral infections such as cytomegalovirus and Epstein–Barr virus were not routinely screened during the disease course of ITP. Moreover, common viral infections such as "common cold" or flu are generally self-limited and may be resolved before detection, therefore causing difficulty in documentation.

In conclusion, our results show that ITP patients with an infection occurring within 6 months of diagnosis have a poorer 1-year survival than patients who do not succumb to infection. Furthermore, a low ALC may be associated with an increased risk of infection within this period. In addition to monitoring for bleeding, individualized management with cautious monitoring and surveillance for the onset of infection is also needed if better outcomes are to be achieved.

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Conflict of interests The authors declare no conflict of interest.

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