







# Clinical Epidemiology, Treatment Outcome and Mortality Rate of Newly Diagnosed Immune Thrombocytopenia in Adult Multicentre Study in Malaysia

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**Background:** Immune thrombocytopenia (ITP) is well characterized in Western, European and other Asia-Pacific countries. Nevertheless, the clinical epidemiology, treatment pattern and disease outcome of ITP in Malaysia are still limited and not well known.

**Objective:** This study aimed to describe the clinical epidemiology, treatment outcome and mortality of ITP patients in haematology tertiary multicentre in Malaysia.

**Methods:** Clinical and laboratory data of newly diagnosed adults with ITP by a platelet count  $<100 \times 10^9/L$  from January 2010 to December 2020 were identified and analyzed.

**Results:** Out of 500 incident ITP, 71.8% were females with a striking age preponderance of both genders among those aged 18–29 years. The median age was 36 years. The median platelet count was  $17.5 \times 10^9/L$ , 23.0% had a secondary ITP, 34.6% had a Charlson's score  $\geq 1$ , 53.0% had bleeding symptoms including 2.2% intracranial bleedings (ICB). *Helicobacter pylori* screening was performed in  $<5\%$  of cases. Persistency and chronicity rates were 13.6% and 41.8%, respectively. Most (80.6%) were treated at diagnosis onset and 31.2% needed second-line treatment. Throughout the course of ITP, 11.0% of patients died; 3.0% and 8.0% with bleeding and non-bleeding related ITP.

**Conclusion:** This study confirms the epidemiology of ITP is comparable with worldwide studies. Our incidence is high in the female, Malay ethnicity, primary ITP and events of cutaneous bleeding at ITP onset with 18–29 years predominance age group for both genders. The frequency of persistent and chronic ITP is inconsistent with published literature. Corticosteroids and immunotherapies are the most prescribed first-line and second-line pharmacological treatments. Thrombopoietin receptor agonist medications (TPO-RAs) usage is restricted and splenectomy is uncommon. Our mortality rate is similar but ITP related bleeding death is fourth-fold lower than previous studies. Mortality risks of our ITP patients include age  $\geq 60$  years, male, severe bleeding at presentation,  $CCI \geq 1$  and secondary ITP.

**Keywords:** epidemiology, immune thrombocytopenia, mortality, treatment outcome

## Introduction

Immune thrombocytopenia (ITP) formerly described as idiopathic or immune thrombocytopenic purpura<sup>1</sup> is an acquired autoimmune bleeding disorder secondary to premature platelet destruction, decelerated platelet production or a combination of both leading to thrombocytopenia and life-threatening bleeding in some patients.<sup>2–5</sup> In the last several years, the basic understanding of the pathophysiology of ITP has significantly improved but the epidemiology and clinical course of ITP have not been well investigated in the general population, particularly in the Asian population. The

current literature includes a limited number of published studies, each of which describes a relatively small number of ITP patients.<sup>6</sup> ITP is an old disease characterized by bleeding disorder comprises heterogeneous clinical characteristics and response to therapy. Isolated thrombocytopenia (defined as platelet count  $<100 \times 10^9/L$ ) without an evident predisposing etiology is considered primary ITP as opposed to secondary ITP that is associated with coexisting systemic disease.<sup>7,8</sup> ITP remains the exclusion of other causes of thrombocytopenia as no gold standard test to confirm ITP diagnosis. In adult ITP patients, bleeding is the most significant cause of morbidity, mortality and decision to start treatment.<sup>9</sup> Treatment is indicated if the platelet counts less than  $20 \times 10^9/L$  to  $30 \times 10^9/L$ , even in the absence of bleeding manifestation. However, the risk factors that influence bleeding such as older age (eg  $>65$  years), type of ITP, previous bleeding history, exposure to anticoagulants or antiplatelet drugs, the presence of comorbidities such as renal impairment and the risk of trauma from daily activities should be assessed before a decision to start treatment.<sup>10–13</sup>

First-line therapy for ITP is based on oral corticosteroids, plus administration of intravenous immunoglobulin (IVIg) in case of severe bleeding.<sup>11,14</sup> Majority of patients will respond to initial corticosteroid treatment but relapse after the dose is reduced. Only about one-third of treated patients can expect a long-term response.<sup>15</sup> Although chronic refractory patients are a minority, they appear to be at the highest risk of severe bleeding and mortality.<sup>16–18</sup> ITP becomes persistent (lasting  $>3$  months) or chronic (lasting  $>12$  months) in about 70% of adult cases.<sup>19</sup> Various corticosteroid-sparing agents are used in these cases such as splenectomy, rituximab or thrombopoietin receptor agonists (TPO-RAs) such as eltrombopag or romiplostim.<sup>11,14,20</sup> Splenectomy is now frequently delayed until late in the disease course as it is an effective treatment for steroid-refractory or steroid-dependent ITP.<sup>21,22</sup>

Although ITP disease has been studied for more than a century, its robust clinical epidemiological data is not well known in Malaysia. This retrospective study was conducted to analyze the clinical epidemiology, treatment outcome and mortality of newly diagnosed adult ITP patients in the tertiary hospitals in Malaysia. To the best of our knowledge, this is the first article involving a multicentre study on the clinical epidemiology, treatment outcome and mortality of adult ITP in Malaysia at present.

## Methods

### Study Design

All consecutive adult patients with newly diagnosed ITP from January 2010 to December 2020 were identified through the discharge codes (International Classification of Diseases, 7th–10th). Codes D69.3 (immune thrombocytopenia) from the 10th revision of the International Classification of Diseases (ICD-10) was used in this retrospective, observational multicentre study. All data were retrieved from the database of the International Centre for Casemix and Clinical Coding for Hospital Canselor Tuanku Mukhriz, Universiti Kebangsaan Malaysia Medical Centre (HCTM, UKMMC), Kuala Lumpur, Malaysia and from the database of new cases in Haematology Department, Ampang Hospital, Selangor, Malaysia. Diagnosis of ITP was validated using medical records and Integrated Laboratory Information System (ILMS). There was no duplicated data between the two registries of patients included in this study.

### Study Population

An adult was defined as a patient by an age of 18 years and above. Platelet count  $<100 \times 10^9/L$  without a secondary cause was defined as ITP in our study as outlined by Rodeghiero et al.<sup>19</sup> We obtained information on patients' demographic and clinical data which includes age, gender, ethnicity, hospital visits, date of ITP diagnosis, platelet count and bleeding types at presentation, laboratory values, types and initiation date of pharmacological therapy and duration of ITP-treatment from the registered data and medical records.

### Definitions

Phases of ITP disease were defined according to the International Working Group (IWG); 1. Newly diagnosed ITP: from the time of diagnosis up to 3 months; 2. Persistent: between 3 and 12 months from diagnosis; 3. Chronic phase: disease duration of more than 12 months.<sup>23,24</sup> We defined treatment outcome to ITP treatments following American Society of Haematology (ASH) terminology: Complete response (CR): platelet count  $\geq 100 \times 10^9/L$  and absence of bleeding;

Response (R): platelet count  $\geq 30 \times 10^9/L$  and at least 2-fold increase the baseline count and absence of bleeding; No response (NR): platelet count  $< 30 \times 10^9/L$  or less than 2-fold increase of baseline platelet count or bleeding; Loss of CR or R: platelet count below  $100 \times 10^9/L$  or bleeding (from CR) or below  $30 \times 10^9/L$  or less than 2-fold increase of baseline platelet count or bleeding (from R).<sup>19</sup>

## Mortality

The outcomes of the patients including the date of death were recorded. For patients who passed away during the observation period, the cause of death was investigated by manually reviewing their medical records to identify diagnoses listed at the time of death. These were grouped into ITP related to bleeding and ITP with no specific bleeding.

## Statistical Analysis

Patients' clinical characteristics were analyzed using simple descriptive statistics, mean  $\pm$  standard deviation or median and range for quantitative variables and percentages, n [%] for qualitative or categorical variables. All potential risk associations were assessed by Pearson chi-square test for categorical data. Data were considered statistically significant at  $p$ -values  $< 0.05$ . Mortality relative risk was computed by odds ratio (OR) and 95% confidence interval (CI) for observed number of deaths. Statistical Package for the Social Sciences (IBM-SPSS) version 27 was used to perform all data analysis.

## Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki. As this is a retrospective study, informed consent is not required. The study was approved by the Universiti Kebangsaan Malaysia Medical Research and Ethics Committee (UKM MREC FF-2021-080) and National Medical Research Register (NMRR-20-2969-57701), regional ethical board in Malaysia. Permission to obtain data was approved by the respective unit and was kept anonymized and confidentiality was maintained using coding.

## Results

### Patient Selection

In a database of 740604 of total admission over the study period, we identified 832 patients with a diagnosis encoded D69.3 ICD-10 at any age. Following exclusion criteria, 330 patients were excluded including 12 with a platelet count at ITP diagnosis of  $\geq 100 \times 10^9/L$  but  $< 150 \times 10^9/L$ . Consequently, only 500 patients were included in the study.

### Clinical Epidemiology at ITP Diagnosis

In total, 500 adult patients with newly diagnosed ITP were included in the cohort. Demographic characteristics of ITP patients are expressed in [Table 1](#). The median age at ITP diagnosis of the entire population was 36 years, range 18–84 years. The incidence was more common in females, 359 (71.8%) with a median age of 35 years (18–84 years). The male-to-female ratio was 1:2.5. Male patients were slightly older with a median age of 41 years (range 18–82 years). The most frequent age at diagnosis was those aged 18–29 years in both genders ([Figure 1](#)).

Ethnic background is presented in [Table 1](#). The percentage of patients was higher in Malays and smaller in the other groups. Other ethnicities include Indonesian, Siamese, Myanmar, Australian and African. Two hundred and five patients (41%) cases had one or more comorbidities including hypertension, diabetes mellitus, autoimmune disease, renal and heart disease. We observed 173 patients had Charlson comorbidity index (CCI) of  $\geq 1$  (14.2% had a CCI of  $\geq 3$ ).

Out of all cohort patients, only 19 patients were on antiplatelet drugs and 13 patients were exposed to the anticoagulant, but none had exposure to non-steroidal anti-inflammatory drugs (NSAIDs). A total of 385 patients with primary ITP and 115 with secondary ITP were diagnosed on both participating sites. The secondary causes were related to other conditions including autoimmune disease (n = 79, 15.8%), viral infections (n = 22, 4.4%), malignancy (n = 6, 1.2%) and drug-induced (n = 8, 1.6%). Eight patients were identified with Evans syndromes.

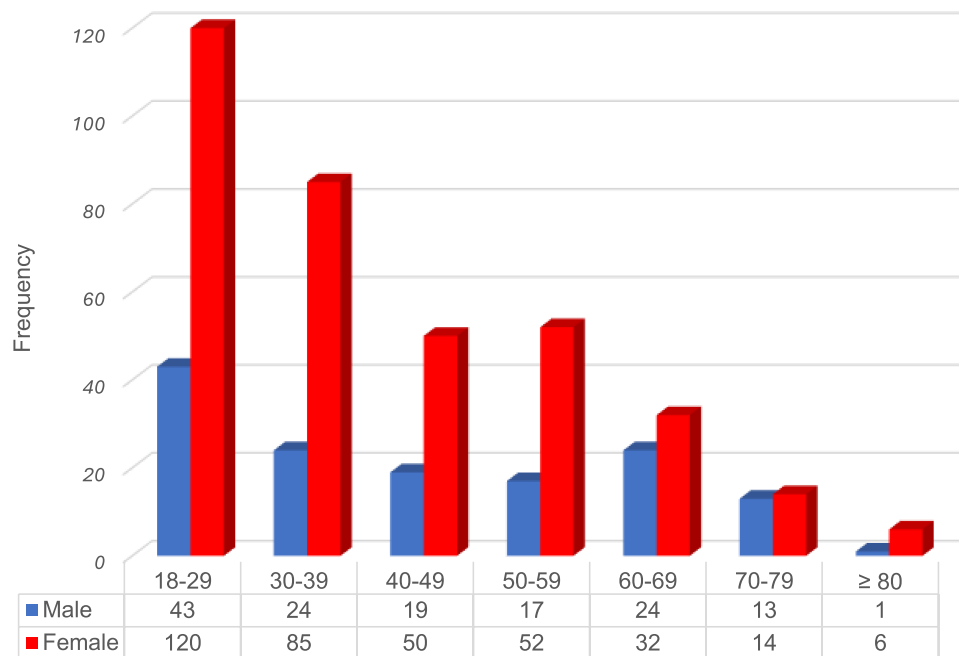
**Table 1** Demographic Characteristics of ITP Patients

Variables	Study Subjects, n (%)
Total number of patients	500 (100)
Age at diagnosis, year	
18–29	163 (32.6)
30–39	109 (21.8)
40–49	69 (13.8)
50–59	69 (13.8)
60–69	56 (11.2)
70–79	27 (5.4)
≥ 80	7 (1.4)
Sex	
Male	141 (28.2)
Female	359 (71.8)
Ethnic background	
Malay	274 (54.8)
Chinese	122 (24.4)
Indian	68 (13.6)
Others	36 (7.2)
Charlson comorbidity index (CCI)	
0	327 (65.4)
1	48 (9.6)
2	54 (10.8)
≥ 3	1 (14.2)
Concomitant drugs	
Antiplatelet	19 (3.8)
Anticoagulant	13 (2.6)
NSAIDS	0 (0.0)
Type of ITP	
Primary	385 (77.0)
Secondary	115 (23.0)
Platelet count at presentation ( $\times 10^9/L$ ), median	17.5 [0–99]
Bleeding symptoms at ITP diagnosis	
Yes	265 (53.0)
No	235 (47.0)

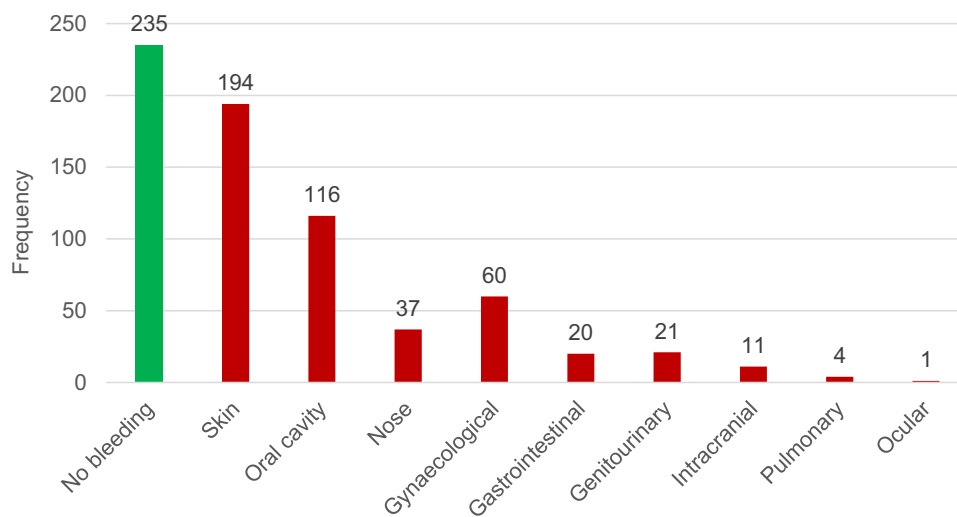
**Abbreviations:** ITP, immune thrombocytopenia; NSAIDS, non-steroidal anti-inflammatory drugs.

Clinical symptoms of bleeding at diagnosis were assessed by location; no bleeding, skin, oral cavity, nose, gynaecological, gastrointestinal tract (GIT), genitourinary, intracranial, pulmonary, and ocular (Figure 2). Bleeding manifestations (any site) were observed more frequently in females (194 patients, 73.2%) than in males (71 patients, 26.8%) ( $p = 0.458$ ) but no difference in age between males and females (peak at age 18–28 years). Multiple sites ( $\geq 1$  site) of bleeding have been observed in 134 patients of the bleeding subgroup with cutaneous bleeding as the most common presentation.

The median platelet count at diagnosis was  $17.5 \times 10^9/L$  (range 0–99  $\times 10^9/L$ ) and 257 (51.4%) patients showed value  $< 20 \times 10^9/L$  at presentation. The distribution of the platelet count at initial diagnosis is shown in Figure 3. If data are analyzed in patients with a presenting platelet of  $< 20 \times 10^9/L$ , bleeding occurred in 190 (71.7%) of cases ( $p < 0.001$ ). ICB occurred in 11 of cases (2.2%) ( $p = 0.002$ ), by which 2 patients with the platelet of  $\geq 20 \times 10^9/L$ . The mean age of patients with intracranial hemorrhage was 40 years. The median platelet at diagnosis was  $7.0 \times 10^9/L$  (range 1–23  $\times 10^9/L$ ). Among them, only one patient died due to massive ICB after 5 days of admission. No association was found between risk



**Figure 1** Distribution of age and gender of ITP patients.



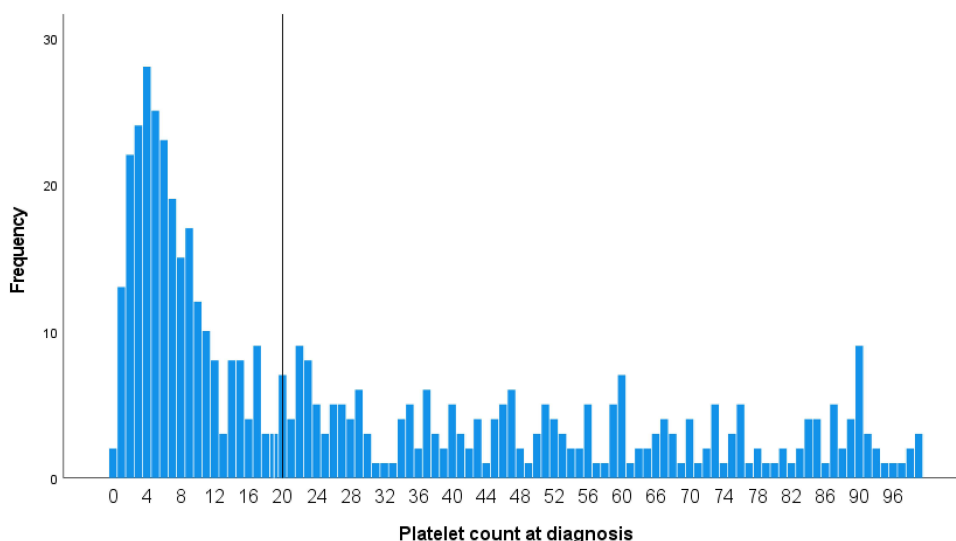
**Figure 2** Bleeding symptoms at presentation by anatomical site.

of ICB and any of the following; age, gender, ethnicity, comorbidity, type of ITP or drug exposure except for platelet counts ( $p = 0.041$ ).

Bone marrow examinations were performed in 134 (26.8%) cases, more often in patients who needed corticosteroids in contrast to other treatments. An antiphospholipid antibody, rheumatoid factor and *Helicobacter pylori* (*H.pylori*) testing were performed in less than 50% of patients. Antinuclear antibody (ANA) was the frequently positive laboratory test, while testing for *H. pylori* was not routinely done in ITP patients (Table 2).

## Treatment Exposure at Diagnosis

A total of 403 (80.6%) patients received the first ITP treatment during the study period. Among this subgroup, 246 (61.0%) were presented with bleeding and 157 (39.0%) without bleeding. All patients have recorded platelets count at the



**Figure 3** Platelet count at the time of ITP diagnosis. The vertical line indicates a platelet count of  $20 \times 10^9/L$ .

clinic before the start of treatment. Among the patients who did not need ITP treatment, the mean platelet count was  $60.3 \times 10^9/L$ . The median platelet count at treatment start was  $11.0 \times 10^9/L$  (range  $0-99 \times 10^9/L$ ). Among them, 298 (59.6%) and 234 (46.8%) had platelet counts checked at 3 months and 12 months, respectively, after treatment started. In the subgroup of patients requiring treatment, 77 (19.1%) had severe bleedings and were mostly in the age group 18–29 years. Seventeen (4.2%) patients were aged 60 and above.

Corticosteroids were the most used first-line treatment. Corticosteroids alone were given in 398 patients (98.8%) in which all of them received high-dose prednisolone 1mg/kg at the initial treatment. Intravenous (IV) methylprednisolone was pulsed in 258 (51.6%) patients at starting of therapy while concurrent intravenous hydrocortisone and dexamethasone were given in 0.7% and 0.5% patients, respectively. Out of 104 (20.8%) who received platelet transfusion, 83 (79.8%) was due to platelet  $<20 \times 10^9/L$ , 84 (80.8%) presented with any bleeding and 47 (45.2%) with severe bleeding. Among them, 4 patients with platelet  $>20 \times 10^9/L$  were given platelet transfusion prior to surgical procedures. Second-line therapy is illustrated in Table 3.

## Treatment Outcomes and Mortality

The mean follow-up was 69 months after the first diagnosis. ITP course at 3 and 12 months is observed in the whole cohort by platelet counts. Out of the remaining 97 patients who did not require initial treatment, 15 (15.5%) had normal platelet count  $>100 \times 10^9/L$  at 3 months and 23 (23.7%) at 12 months without any active treatment. Among those who did not require initial treatment, only 2 (2.1%) patients had platelet count  $<30 \times 10^9/L$  at 3 months and none at 12 months monitoring. The initial response to first-line treatment is shown in Table 3. Disease outcome was assessed at the time of

**Table 2** Laboratory Test Results

Test	Positive (%)	Negative (%)	Not Done (%)
Antiphospholipid antibodies	24 (4.8)	39 (7.8)	437 (87.4)
Antinuclear antibodies	129 (25.8)	267 (53.4)	104 (20.8)
Rheumatoid factor	18 (3.6)	47 (9.4)	435 (87.0)
Hepatitis B	14 (2.8)	433 (86.6)	53 (10.6)
Hepatitis C	5 (1.0)	441 (88.2)	54 (10.8)
HIV	11 (2.2)	411 (82.2)	78 (15.6)
<i>Helicobacter pylori</i>	6 (1.2)	8 (1.6)	486 (97.2)

**Abbreviation:** HIV, human immunodeficiency virus.

**Table 3** Treatment Exposure at Diagnosis

Treatment	All ITP, n = 500
General data	
No therapy, number (%)	97 (19.4)
Platelet transfusion at diagnosis, number (%)	104 (20.8)
First-line therapy, number (%)	
IV Methylprednisolone (pulses) + corticosteroids	258 (51.6)
IV Hydrocortisone + corticosteroids	3 (0.6)
IV Dexamethasone + corticosteroids	2 (0.4)
IVIg + corticosteroids	136 (27.2)
Corticosteroids alone	398 (79.6)
Second-line treatments (%)	156 (31.2)
Azathioprine	134 (26.8)
Eltrombopag	27 (5.4)
Danazol	45 (9.0)
MMF	25 (5.0)
Vincristine	3 (2.6)
Cyclosporin	8 (1.6)
Cyclophosphamide	2 (0.4)
Rituximab	35 (7.0)
Splenectomy	9 (1.8)
Initial response rate to first line treatments, with reference to;	All patients, n = 403
At 3 months, number (%)	
Complete response	147 (36.5)
Partial response	91 (22.6)
No response	60 (14.9)
No count (loss of follow-up)	105 (26.1)
At 12 months, number (%)	
Complete response	105 (26.1)
Partial response	75 (18.6)
No response	54 (13.4)
No count (loss of follow-up)	169 (41.9)

**Abbreviations:** IV, intravenous; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil.

analysis according to their platelet count response at least of 3 to 12 months consequence follow-up. Acute ITP was observed in 185 (37.0%) patients, 68 (13.6%) became persistent ITP and 209 (41.8%) progress to chronic ITP (cITP). Another 38 (7.6%) cases were lost to follow-up. Among those who progress to persistent and cITP, 23 (33.8%) and 85 (40.7%) required second-line therapy, respectively.

At the time of analysis, 445 patients were alive (89.0%) whereby 55 patients had died (11%). Table 4 shows the mortality risk observed in our cohort. The death was two-fold in male patients with a mortality risk of 2.0 (95% CI, 1.2–3.2). When patients were reclassified as young age (<60 years) and old age ( $\geq$ 60 years), the old age had a higher mortality risk 2.8 (95% CI, 1.5–5.1). ITP patients presenting with severe bleeding symptoms suffered a 2.6-fold (95% CI, 1.4–4.9) increased mortality risk. CCI  $\geq$  1 and secondary ITP accelerated the mortality risk by 3.9 (95% CI, 2.2–7.0) and 2.1 (95% CI, 1.2–3.8), respectively.

Causes of death were classified into ITP related and non-ITP related deaths. A total of 15 (3.0%) patients with newly diagnosed ITP died due to bleeding ITP-related deaths during the entire period of follow-up. Among this subgroup, 7 were ICB, 7 with upper gastrointestinal bleeding (UGIB) and one case with epistaxis and massive bleeding. Causes of death considered unrelated to ITP or bleeding ITP consisted of malignancy (6), cardiovascular disease (7), severe infection (15), multiorgan failure (3), multiple underlying comorbid (3), both sepsis and underlying malignancy (1), trauma (1), old age (3) and one (1) undetermined cause of death.

**Table 4** Mortality Risk of ITP Patients

Variables	Dead	Alive	Relative Risk (95% CI)	P value
Age, years				
<60 (n = 410)	36 (8.8)	374 (91.2)	0.4 (0.3–0.7)	0.001
≥60 (n = 90)	19 (21.1)	71 (78.9)	2.8 (1.5–5.1)	
Gender				
Male (n = 141)	24 (17.0)	117 (83.0)	2.0 (1.2–3.2)	0.007
Female (n = 359)	31 (8.6)	328 (91.4)	0.5 (0.3–0.8)	
Initial platelet				
<20 × 10 <sup>9</sup> /L (n = 257)	26 (10.1)	231 (89.9)	0.8 (0.5–1.4)	0.516
≥20 × 10 <sup>9</sup> /L (n = 243)	29 (11.9)	214 (88.1)	1.2 (0.7–2.1)	
Bleeding at diagnosis				
Yes (n = 265)	30 (11.3)	235 (88.7)	1.1 (0.6–1.9)	0.808
No (n = 235)	25 (10.6)	210 (89.4)	0.9 (0.6–1.6)	
Severe bleeding at diagnosis				
Yes (n = 82)	17 (20.7)	65 (79.3)	2.6 (1.4–4.9)	0.002
No (n = 418)	38 (9.1)	380 (90.9)	0.4 (0.3–0.7)	
Charlson comorbid index				
0 (n = 327)	20 (6.1)	307 (93.9)	0.3 (0.2–0.5)	0.000
≥1 (n = 173)	35 (20.2)	138 (79.8)	3.9 (2.2–7.0)	
Type of ITP				
Primary (n = 385)	35 (9.1)	350 (90.9)	0.5 (0.3–0.9)	0.013
Secondary (n = 115)	20 (17.4)	95 (82.6)	2.1 (1.2–3.8)	
Anticoagulant				
Yes (n = 13)	3 (23.1)	10 (76.9)	2.5 (0.7–9.4)	0.159
No (n = 487)	52 (10.7)	435 (89.3)	0.5 (0.2–1.3)	
Antiplatelet				
Yes (n = 19)	2 (10.5)	17 (89.5)	1.0 (0.2–4.2)	0.946
No (n = 481)	53 (11.0)	428 (89.0)	1.0 (0.3–4.0)	

**Abbreviations:** ITP, immune thrombocytopenia; CI, confidence intervals.

## Discussion

Clinical epidemiology, laboratory tests and mortality of newly diagnosed ITP in adults have not been systematically described in previous studies including in Asia and Malaysia. Published research suggests that there are differences in the clinical manifestations of ITP with variable clinical presentations, clinical consequences and treatment responses in different ages.<sup>11,25</sup> Understanding the similarities and differences could affect the clinical practice and may provide a starting point for future study of the underlying etiologies and pathophysiological causes in each age group. The establishment of a regional ITP registry plays an important role to gather all the data, as a valuable resource for studies of rare diseases at the population level, clinical trials, improve treatment, disease burden and outcomes for all ITP patients.<sup>26</sup> In addition, the local population study also will be able to guide future planning of social, health policies and services.<sup>27</sup> Although there are few tertiary centres for referral for haematology cases in Malaysia, the national ITP registry has not yet been established. Currently, Japan is the only country in the Asia-Pacific region that has a national ITP registry.<sup>19,28</sup>

The incidence of ITP is reported in 1.5 to 5 per 100000 persons in the general population for both adults and children.<sup>6,29–33</sup> The incidence of adult ITP patients is illustrated in Table 5. A multimodal incidence with 1 peak seen in childhood whereby the second and third peaks observed in young adults and the elderly.<sup>34</sup> Our study confirms the higher incidence of ITP in females in younger adults as reported by previous population-based literature but not in the elderly (>65 years). The prevalence of ITP in men and women in the elderly is almost even in previous studies.<sup>4,6,18</sup> We identify only one predominance peak of age at 18–29 years old for both genders. We did not see any multimodal peak as



**Table 5** Incidence of Adult ITP Patients in General Population

Year	Study	Country	Design	Incidence	Year of Studied
1999	Frederiksen et al <sup>38</sup>	Denmark	Retrospective by ICD code	2.68	1973–1995
2009	Marieke Schoonen et al <sup>6</sup>	England	Retrospective by administrative data	3.90	1990–2005
2010	Terrell et al <sup>30</sup>	Europe	Critical review of published reports	3.30	1966–2009
2010	Kurata et al <sup>28</sup>	Japan	Retrospective by registered data	2.16	2004–2007
2014	Michel et al <sup>39</sup>	France	Retrospective by cohort study	4.00	2009–2012
2017	Lee et al <sup>40</sup>	Korea	Retrospective by registered data	1.50	2010–2014
2018	Hung et al <sup>41</sup>	Taiwan	Retrospective by registered data	2.00	2006–2013

described in European<sup>4</sup> and Japanese studies.<sup>28</sup> It has previously been reported that most cases of adult ITP occur between 20 and 40 years old in female patients and that it is less common after 50 years old.<sup>35–37</sup> These epidemiological data were similar in our study, instead not only in female but also in male patients. The incidence of ITP was found to be higher in Malay (54.9%) ethnicity. This is most likely contributed by the Malay being the highest ethnicity group in Malaysia.

This study demonstrated that infective screening (hepatitis B, hepatitis C and HIV) is frequently done (>80%) in our practice compared to autoimmune antibodies screening (<10% except ANA test). The antiphospholipid antibody, ANA and rheumatoid factor were not performed in all patients, restricting the analysis to exclude secondary causes and may underestimate the incidence. Furthermore, ANA provides information about the baseline risk of thrombosis which is associated with systemic lupus erythematosus (SLE)<sup>42</sup> or antiphospholipid syndrome (APS).<sup>43</sup> ITP patients concomitant with APS have an increased risk of thrombotic complications which may be higher if given TPO-RAs medications. For ITP patients at risk of thrombotic complications, there is limited evidence for the use of anticoagulation but stopping anticoagulation can result in more harmful outcomes than continuing anticoagulation.<sup>44</sup> Positive *H. pylori* testing is common with increasing age and the prevalence of pathogenic strains can depend upon the country of birth. The overall prevalence rate of *H. pylori* infection was 35.9% in Malaysia and differs in the different regions within Malaysia. The Malay populations have the lowest prevalence of *H. Pylori* infection (11–29%) compared to Indians and Chinese, 49–52.3% and 26.7–57.5%, respectively.<sup>45,46</sup> Despite the fact that the prevalence of *H. pylori* infection is high in Malaysia, the screening test by *H. pylori* serology and confirmation of active infection with a C14 urea breath test is not routinely done in our study (<5.0%). Moreover, eradication of *H. pylori* may rise a platelet count up to 50% of ITP patients with *H. pylori*-positive based on studies that were mostly conducted in Japan.<sup>47,48</sup> Our frequency of secondary ITP (23%) is almost equal to the estimated incidence (~20%) by the expert opinion.<sup>41,49–51</sup> In contrast, the prevalence of secondary ITP was substantially higher (64.8%) as compared to primary ITP (35.2%) in Pakistan.<sup>52</sup> Our data also support that the female patients have a higher association with autoimmune disorders ( $n = 67$ , 18.6%) for secondary ITP, which may be an explanation for the greater number of women with ITP.

The incidence of bleeding events (53.0%) is in following previous French and the United Kingdom (UK) cohorts.<sup>12,53,54</sup> Figure 2 presents the incidence of bleeding according to the site of bleeding at presentation. Estimated incidence, the weighted proportion of ICB and severe non-ICB bleeding have been reported in 1.4% (95% CI, 0.9–2.1%) and 9.6% (95% CI, 4.1–17.1%), respectively, in adults with ITP.<sup>55</sup> The event of bleeding and rarity of serious bleeding at ITP onset in our cohort study is comparable with previous studies. Nonetheless, the incidence of ICB is higher but fewer GIT bleeding cases (2.2% and 4.0% respectively) compared to <1% for ICB and ~6.0% for GIT in the past.<sup>54,56,57</sup> There was no association of ICB with age, gender, ethnicity, comorbidity, type of ITP or drugs exposure except for platelet counts ( $p = 0.041$ ). The incidence of persistent and chronic disease in our study is smaller (<50%), inconsistent with France and Swiss populations.<sup>58–60</sup> Interestingly, the persistent disease (13.6%) is much lower but higher rate of cITP (41.8%) in our population compared to Taiwanese population (24% persistent and 12.3% cITP). Our study demonstrated that 23 (18.0%) and 8 (6.3%) of partial response and no response ITP patients, respectively, at 3 months monitoring has switched into remission status at 12 months follow-up ( $p < 0.001$ ). Out of 23 partial response who became remission,

only 6 (26.1%) patients needed second-line treatment while 2 patients did not require further therapy among no response cases.

The rate of patients treated at the onset of ITP diagnosis (80.6%) was in accordance with the recent study by Grimaldi-Bensouda et al (87.4%).<sup>60</sup> Corticosteroids remain the most frequently used first-line treatment followed by IVIg. A scoring system such as Khellaf's bleeding score >8 has been recommended by the French group to aid clinicians in adding IVIg to corticosteroids particularly in patients with life-threatening bleeding when a rapid increase in platelet counts is required.<sup>61,62</sup> This practice can also be implemented among Malaysian physicians. The use of anti-D Ig in the Asia-Pacific region is uncommon due to its ability to cause hemolysis and lack of availability in many countries in Asia.<sup>63,64</sup> None of the patients was given anti-D Ig in our study. Second-line therapy (31.2%) is less frequently used in our population as compared to French nationwide population-based study (47.1%).<sup>20,51</sup> Recent ASH ITP guidelines recommend TPO-RAs rather than rituximab,<sup>65</sup> however, our rate of TPO-RAs usage is not as high as reported in ITP World Impact Survey (iWISH study).<sup>66</sup> TPO-RAs such as eltrombopag or romiplostim are an option in patients after failure of steroids and splenectomy, prior to the use of rituximab and also can reduce the use of concomitant ITP medication.<sup>67–70</sup> Nevertheless, long-term treatment should be used with caution as the most frequent adverse effects were headache, thrombocytosis and the risk of fibrosis in the bone marrow.<sup>69,71</sup> Splenectomy is hardly practiced nowadays and was performed in only 9 (1.8%) of our refractory patients, as compared to 6–34% in the other countries.<sup>6</sup> Splenectomy is not advisable in secondary ITP associated with an autoimmune or connective tissue disease since a subsequent flare of the connective tissue disease may necessitate immunosuppression. Asplenic patients have a higher risk of infection and the use of immunosuppressants is associated with poor survival in these patients.<sup>72</sup>

The mortality rate (11.0%) in our cohort is relatively consistent with the UK study (12.1%) but slightly lower compared to Netherland's study (15.8%). Mortality risks of our ITP patients include age  $\geq 60$  years, male, severe bleeding at presentation, CCI  $\geq 1$  and secondary ITP. Surprisingly, platelet counts at ITP onset and medications (anticoagulant and antiplatelet) were not related to mortality risk in our study population. Of the 55 ITP patients for whom a cause of death was recorded, 3% died due to bleeding, which is a very small proportion than reported previously (~13.0%).<sup>53,73</sup> This is probably due to established guidelines from the ITP-IWG and ASH on ITP management, with the inclusion of eltrombopag, romiplostim and rituximab in the treatment of cITP. Newer agents such as sutimlimab, fostamatinib and decitabine were shown promising results in recent a ITP study.<sup>74</sup>

The strengths of our study include the ability to include all cases of adult ITP during the study period. Thus, there is no selection bias of a certain group of ITP patients. The records from the computerized database were able to provide a relatively large number of cases. The study findings are comparable with other studies worldwide because we used IWG definitions and standardized terms and definitions. Nevertheless, this study has some limitations. As this study was done retrospectively in the tertiary hospital of haematology centres, the data were restricted which may contribute to analysis discrepancies. The local national ITP registry is not available in Malaysia, thus the completeness of the data registry cannot be exactly assessed. Consequently, the results cannot be extended to other regions or countries, particularly regarding laboratory results and treatment exposure.

## Conclusions

In conclusion, this study confirms the epidemiology of newly diagnosed adults ITP is comparable with nationwide studies. Our study population demonstrated the high incidence in the female, Malay ethnicity, primary ITP and events of cutaneous bleeding with a predominance 18–29 years age group for both genders. Corticosteroids and immunotherapies are the most prescribed first-line and second-line pharmacological treatments. Splenectomy and TPO-RAs prescriptions are infrequent. Our mortality rate is even, but ITP-related bleeding death is fourth-fold lower than reported before. Mortality risks of our ITP patients include age  $\geq 60$  years, male, severe bleeding at presentation, CCI  $\geq 1$  and secondary ITP.

## Future Directions

This study has paved the way for the development of a local national ITP registry or a population-based surveillance system. This registry will enable us to obtain data which is useful for standardization of local clinical practice, explore

new research and novelty findings in ITP patients in Malaysia including study for possible platelet disorders in refractory and cITP group. It is also our hope that with this data/registry, we are able to pave easier access to TPO-RAs that will benefit all individuals diagnosed with ITP.

## Data Sharing Statement

Study data are available on request from the corresponding author.

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## Disclosure

The authors report no conflict of interests.

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