Primary versus secondary immune thrombocytopenia in adults; a comparative analysis of clinical and laboratory attributes in newly diagnosed patients in Southern Pakistan

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ABSTRACT

Back ground: Immune thrombocytopenic purpura (ITP) is a hemorrhagic diathesis, characterized by platelets destruction alongside impaired production. Patients from Asian regions often exhibit distinctive characteristics in comparison to the western patients. We accomplished this study to evaluate the prevalence of primary versus secondary ITP along with the comparative analysis between them. The secondary objective was to determine the etiological spectrum of secondary ITP.

Methods: We illustrate the results of a large cohort of newly diagnosed adults ITP from southern Pakistan. The study extended from January 2009-December 2013. Complete blood counts, HbsAg, Anti-HCV, ANA, stool for Helicobacter-pylori were done on all. HIV, TSH, anti-dsDNA, RA factor, APLA and direct coombs test were evaluated in cases where indicated.

Results: A total of 417 patients were included with a mean age of 40.95±14.82 years. Primarily disease was observed in the 3rd decade of life. Male to female ratio was 1:1.5. Mean platelets count was 46.21±27.45x10^9/l. At diagnosis 43.16% (n=180) patients had hemorrhagic manifestations whilst 56.8% (n=237) were asymptomatic. None of the patient presented with visceral, retropharyngeal or intracranial bleed. The prevalence of secondary ITP was substantially higher (64.8%) as compared to primary ITP (35.2%). Secondary ITP was predominantly seen in HCV reactive patients (24.4%) followed by helicobacter-pylori infection (11%). Nevertheless 16.4% patients had underlying autoimmune disorders. Providentially no study subject was found to be HIV reactive.

Conclusions: Our study revealed predominance of secondary ITP. However bleeding manifestations and degree of thrombocytopenia were high in primary-ITP. Infectious etiology followed by autoimmune disorders is mainly implicated for secondary ITP in our setting.

KEY WORDS:
ITP, Secondary, Primary, HCV, Helicobacter pylori

INTRODUCTION

ITP is a heterogeneous acquired bleeding diathesis, resulting from platelets sensitization by autoantibodies leading to accelerated destruction along with impaired platelet production owing to immune disturbance. [1] An estimated overall incidence of adult's ITP is variable from 1.6-3.9 per 100, 000 individuals per year. [2] Predominantly it's a disease of female, with female to male ratio of 1.7. [3] Recent studies on ITP indicate increasing incidence and prevalence of disease with increasing age. [2]

The adults ITP is often insidious and reveals diversity in the clinical course. These patients typically seek medical care mainly for mucocutanaeous or subcutanaeous bleed, although clinical picture is variable from asymptomatic to rarely life threatening bleed. Though platelets counts are indicator for treatment, but sole platelet counts are not reliable predictor of the disease outcome nor are the goal to achieve the normal platelets but to prevent the symptomatic bleeding. Despite the substantial advancement in the meticulous etiology, ITP still remains as a disease of exclusion. [4]

Recently ITP international working group has reported the three phases of disease as newly diagnosed ITP (≤3months), persistent disease (3 months -1 year) and chronic ITP (> 1 year) 5. ITP can be further segregated as being either primary (idiopathic) or secondary ITP. [5]

Secondary causes are being increasing acknowledged in the pathogenesis of ITP. Autoantibodies may be triggered by underlying infections that cross react with platelets antigen or may have immune complexes which binds to platelets Fcγ receptors. [4] Secondary ITP share a common feature of self reacting antiplatelets antibodies with primary ITP but reveals deviation in respect to pathobiology. [4]

Secondary ITP can be drug induced or be a manifestation of human immunodeficiency virus, hepatitis C virus, helicobacter pylori, lymphoproliferative disorder or auto immune-rheumatological disorders, Evan syndrome and others.[3] The estimated prevalence of secondary ITP may vary greatly universally. In the United state an estimated ~20% of ITP cases are secondary to underlying disorders. [6] Varied

This article was accepted: 14 August 2016
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prevalence of secondary ITP has been reported world widely due to wide disparity in prevalence of infectious disorders, autoimmune diseases and malignancies distribution globally.

In certain parts of the world *Helicobacter* pylori (HP) prevalence ranges from 1% in the US to as high as 60% in Japan and Italy, which varied the prevalence of ITP-HP globally. 6 Similarly secondary ITP-HIV has been variable from 5 to 30 % and likewise antiphospholipid antibodies (APLAs) have been found in 10% to as high as 70% of patients with ITP.[7, 8]

The divergent pathophysiology, natural history and responsiveness to the treatment in diverse etiological causes of secondary ITP necessitate the accurate diagnosis. The optimal targeted treatment of the underlying disorder is the main goal; as it will not only eradicate the primary disease but would also be eliminating the secondary ITP.

One prior study reported from Pakistan mainly addressed clinico-haematological features of ITP and described its association only with autoimmune disorders in the small series of 44 patients.[9] The relatively small sample and merely autoimmune association in that study might not reflect the actual picture in our population.[9] This prompted us to explore the frequency of primary versus secondary adults ITP and determines the comparative analysis with respect to clinical and laboratory attributes between them. Our secondary objective is to determine the underlying etiological spectrum of secondary ITP in a large cohort of Pakistani patients.

MATERIALS AND METHODS

Patients: This is cross sectional single center study, extended from Jan 2009 to Dec 2013 at a tertiary care center. Patients were diagnosed as ITP on the basis of careful history, physical examination, complete blood count and peripheral smear examination. All the newly diagnosed untreated adolescent and adults patients (age ≥ 13 years) were enrolled during the study duration. Thrombocytopenia was defined as having platelets count $<100x10^9/l$ [5]. An informed consent was obtained from all the participating patients.

Patients with other causes of thrombocytopenia (bone marrow failure syndrome, inherited thrombocytopenia, post chemotherapy/radiotherapy, pancytopenia, hypersplenism, myelodysplasia, acute leukemias, thrombotic thrombocytopenia, disseminated intravascular coagulopathy) were excluded from the study.

Ethical approval of the study was given by ethical and research committee of Liaquat National Hospital, taken prior to the study.

Methods: Demographical data including age, gender, medical and drug history were recorded. Mycobacterium tuberculosis and drug induced ITP were documented by positive medical and drug history (with normal bone marrow). Patients with suspected drug induced ITP were follow-up for 6 weeks after stopping suspected drug, and document as drug induced ITP if recovered. Viral fever was recognized if found to had febrile illness with thrombocytopenia and atypical lymphoid cells (>5%) in the peripheral smear (with normal marrow). Lymphoproliferative disorders (LPD) was diagnosed by lymph node biopsy and immunhistochemistry. Those patients with LPD were enrolled who presented to OPD with thrombocytopenia with normal marrow production.

Complete blood counts, serology for HbsAg, Anti-HCV, ANA, TSH and stool for *Helicobacter* pylori were done on all patients. Whereas anti-dsDNA, RA factor and APLAs (anticardiolipin and lupus anticoagulant) were done (at single instance) if ANA was found to be positive. Direct coombs test were evaluated in cases where peripheral smear showed anemia (hemolytic type) with thrombocytopenia to diagnosed Evans syndrome. Serology for HIV was done if patient had any history of high risk behavior.

Hematological parameters included hemoglobin/hematocrit, mean corpuscular volume (MCV), total leukocytic count (TLC), platelets and mean platelets volume (MPV) were determined by automated Cell Dyne Ruby (Abott Diagnostic, USA). Manual platelets counts were determined by improved Neubaur chamber if smears revealed giant/large platelets and repeated in sodium citrate anticoagulant if smears revealed pseudothrombocytopenia. Patients with pseudothrombocytopenia were excluded from the study. Serology for anti-HCV, HbsAg, HIV antibodies (type I & II) were done by Architect i1000SR, (Abbott Diagnostic, USA). Patients with chronic hepatitis (with hypersplenism) were excluded. Direct coombs test were done by column agglutination gel technique (Diamed). Helicobactor-Pylori infection was documented by Helicobactor-pylori stool antigen (HpSA) enzyme immunoassay method. TSH was determined by Elecsys 2010 Japan, by immunoassay. RA factor, ANA and double stranded anti ds-DNA were detected by Automatic ELISA analyzer - ETI-Max 3000 by EIA technique. Antiphospholipid antibodies include anticardiolipin antibodies were documented by ETI-Max 3000 instrument while lupus anticoagulant was detected by coagulation analyser by clotting assay. Bone marrow examination was carried out in patients above 60 years and in those where it was deemed necessary.

Data analysis: Data was entered and analyzed using SPSS version 21. The results were expressed as mean±SD for quantitative variables and qualitative variables are presented as frequency & percentages. Student't' test was applied for the comparison of mean. Data were considered statistically significant at P-value <0.05. Chi-square test was applied for correlation of secondary and primary ITP with age, gender and bleeding tendency.

RESULTS

Out of 417 patients, 171 (41.01%) were males and 246 (58.99%) were females. The mean age of patients was 40.95±14.82 (range 13 to 75) years. Primarily disease was observed in 3rd decade of life. Male to female ratio was 1:1.5. Bimodal peak, first at 3rd decade and subsequent at 5th decade, are seen excessively in females (figure 1). As

Table I: Clinical manifestations of primary versus secondary ITP

Parameters	Primary ITP n= 147	Secondary ITP n= 270	P- value
Mean age	37.5±14.8	42.8±14.5	0.04
Male; female	1.5 : 2	2: 3	-
Asymptomatic	38.8%	65.6%	0.004
Symptomatic	61.2%	34.4%	0.004
Dry purpura	57.1%	26.7%	0.001
Wet purpura	49.0%	25.6%	0.008
Epistaxis	40.8%	13.3%	0.001
Gum bleeding	32.7%	11.1%	0.003
Bruises	6.1%	2.2%	0.3*
Mennorhagia	6.1%	5.6%	1.0*
Hematuria	4.0%	2.2%	0.6*
Melena	2.0%	2.2%	1.0*

Table II: Laboratory attributes of primary versus secondary ITP

Parameters	Primary ITP n= 147 Mean±SD	Secondary ITP N= 270 Mean±SD	P- value
Hemoglobin (gm/dl)	12.2± 1.4	11.3 ±1.8	0.01
Hematocrit (%)	38.2±1.7	30.5±2.3	0.001
TLC (10^9/l)	8.3 ± 2.8	6.6± 2.8	0.002
Platelets (10^9/l)	31.5±21.9	54.1± 26.9	0.000
MPV (fl)	12.8±1.4	9.6±0.9	0.001
MCV (fl)	83.1± 8.7 fl	86.6 ±8.9 fl	0.06 *

exemplified in figure 2, there has been a gradually increasing incidence over the last 5 years at our tertiary care center.

The mean hemoglobin at presentation was 11.68±1.75g/dl, while mean platelets count was 46.21±27.45x10^9/l. At diagnosis 43.16% (n=180) patients had hemorrhagic manifestations whilst 56.8% (n=237) were asymptomatic at presentation. Cutaneous bleeding was appreciated in 37.4% patients while epistaxis, gum bleeding and mennorhagia were detected in 23%, 18.7% and 5.7% respectively. Luckily we did not found any patient with visceral, retropharyngeal or intracranial bleed. Overall 24.4% had platelets <20x10^9/l, while 33.9% and 41.7% had platelets count between 21-50x10^9/l and >50x10^9/l respectively. Severe thrombocytopenia (<20x10^9/l) was significantly associated with amplified bleeding tendency (P<0.001).

The prevalence of secondary ITP was substantially higher (64.8%) as compared to primary ITP (35.2%). Comparative analysis of clinical and hematological parameters of primary and secondary ITP patients are shown in table I & II respectively. The spectrum of secondary ITP is shown in figure 3.

Of the secondary ITP, 102 patients were HCV reactive (24.4%), followed by helicobacter pylori infection in 45 patients (11%). Nevertheless 16.4% patients had underlying autoimmune disorders, including Evan's syndrome in 18 (4.3%), hypothyroidism 15 (3.5%), APLA in 15 (3.5%) and RA factor in 9 patients (2.1%). Systemic lupus erythromatous (ANA and anti-ds DNA double positivity) was seen in 12 patients (3%). Lymphoproliferative disorder [chronic lymphoid leukemia & NHL (diagnosed by lymph node biopsy and immunohistochemistry)] were detected in 2.1%. Alongside use of medications at the time of presentation was found, in 21 patients (5%). This included anti-inflammatory, anticonvulsants, diuretics and antimicrobials. Mycobacterium tuberculosis was appreciated in 0.7% of secondary ITP. Providentially no study subject was found to be HIV reactive.

Comparative analysis of primary versus secondary ITP revealed statistically significant difference with increased bleeding tendency and low platelets counts in primary entity (P<0.05). Also secondary ITP divulged positive association with advancing age (P<0.05).

DISCUSSION

ITP affects individuals of all ages, with the peak incidence during childhood and in the elderly age. The present study illustrated that ITP is constantly found in younger age group, as our patients mainly presented in the 3rd decade of life. When compared with earlier reports, our results are in concurrence with a local study published from Pakistan with the median age of 30 years.[9] Previous studies have found an increased incidence and prevalence of ITP with the increasing age. However peak age group is ≥60 years in developed countries.[10] Perhaps this disparity may be clarified by obvious difference between two racial groups based on genetics makeup, immune status and environmental factor with underlying infective etiology and also the higher average age in western countries. ITP, relatively affected females in our series and this predominance was comparable to that reported in international and regional studies.[10-12]

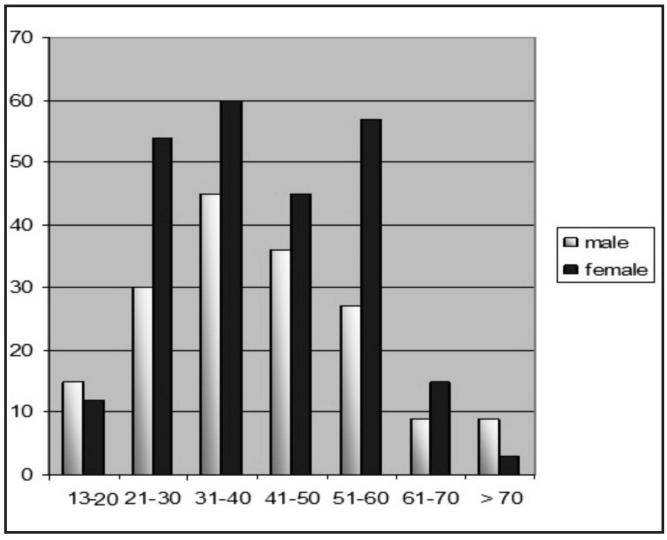

Fig. 1: Age group with gender distribution.

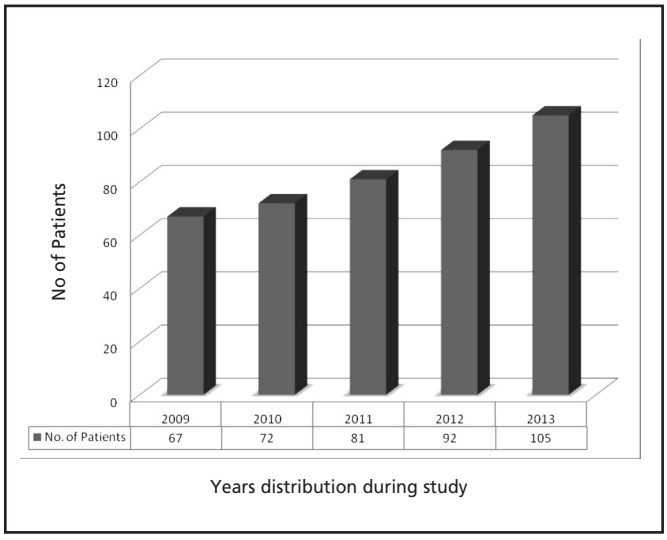

Fig. 2: ITP incidence over 5 years.

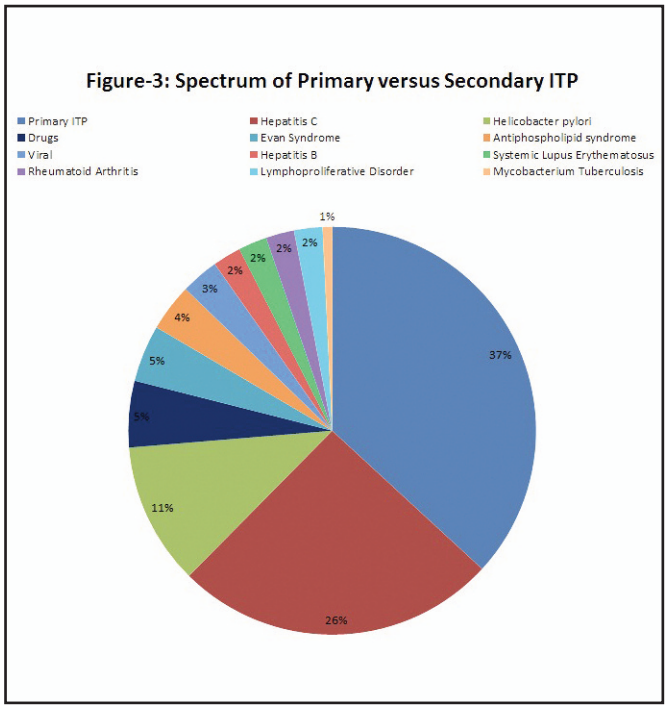

Fig. 3: Spectrum of primary versus secondary ITP.

Mucocutaneous bleeding is the most common disease manifestation related to the degree of thrombocytopenia; nearly all bleeding manifested at platelets counts of $<30x10^9/l$.[2] In the current study 43.1% patients had bleeding manifestations which appears high when compared with the study from Intercontinental Cooperative Immune Thrombocytopenia Study Group which reported 23% adults having sign of active bleeding at the disease presentation.[13] Relatively high prevalence of bleeding was also detected in studies from UK and China on elderly ITP; 72% and 87.8% patients respectively.[14,15] Hemorrhagic events have most frequently been seen in elderly patients; 10.4% of patients >60 years, compared to 0.4% under 40 years, at similar platelets counts.[16] Similarly we detected 28.2% of patients >60 years to had bleeding tendency while hemorrhagic tendency was 14.8% in patients <60 years.

We did not found any patient with visceral, retropharyngeal or intracranial bleed which is very unique finding as this is tertiary care center where mostly very ill patients are presented. This may be attributed to functionally active giant's platelets however this needs to be authenticating in the future studies. Fatal hemorrhage in ITP is luckily uncommon, with the incidence of 1.6-3.9 cases per hundred per year.[17] In our experience none of the patient presented with visceral, retropharyngeal or intracranial bleed. Recently Intercontinental cooperative immune thrombocytopenia study group reported, 1.8% adult patients had intracranial bleed compared with 0.6% in children's with newly diagnosed ITP.[13] Relatively high prevalence of intracranial bleed could be the manifestation of low mean platelets counts ($24.5x10^9/l$) in their cohort compared with our results ($46.2x10^9/l$).

Primary ITP, a diagnosis of exclusion, is identified in 35.2% patient in our cohort. Ayesh MH et al from Jordan reported 56.7% patients were diagnosed as having primary ITP.[18] In contrast to our findings, prior studies reported from United State and France revealed significantly high prevalence of primary ITP in ~ 80% of patients.[6,19]

Present study reported the preponderance of secondary ITP (64.8%) in an Asian population. Cines DB identified merely 20% of patients as having secondary ITP.[6] Similarly Moulis G from France determined 18% adult's with secondary ITP in a large population based study recently.[19] Compared to developed countries an elevated secondary ITP prevalence is noted in Asian patients which might be the reflection of high infectious disease (HCV/ *H pylori*) burden in the developing countries.

Hepatitis C virus (HCV) is the most common chronic viral infection worldwide, affecting 100 million peoples.[6] Cumulative reports from 6 cross sectional showed that 20% of

ITP patients had serological evidence of HCV.[7] The pathogenesis of HCV-ITP is multifactorial. Antiplatelets glycoproteins antibodies are frequent, secondly anti-viral antibodies cross react with platelets surface GP-IIIa antigen. Furthermore infection of megakaryocytes resulting in impaired platelets production as well.[6, 20] One of every four (24.4%) patients was infected with HCV virus in our series. Relatively very low prevalence of HCV positivity has been reported from western studies. In one it is accountable in only 3% patients of ITP.[13] Our study suggests a major role played by HCV infection and contributing as a main infectious burden in the disease pool compared with the western world.

Helicobacter pylorus (HP), a gram-negative microaerophilic bacterium that inhabits the gastrointestinal tissues, shows strong association with ITP.[21] Successful eradication therapy resulting in durable platelets recovery strengthens this association. However success rate is variable in different geographical areas.[6] Pathogenesis has been linked to molecular mimicry where *HP* antibodies cross react with platelets surface antigen.[21] *HP* positivity was encountered in 11% of our patients. The incidence of *Helicobacter pylorus* ranges from 1% in the US to as high as 60% reported from Italy and Japan, while the intermediate frequency of *HP* that is 31%, was determined in ITP patients previously.[6, 13]

Systemic autoimmune disorders like systemic lupus erythematosus, antiphospholipid syndrome and rheumatoid arthritis patients are prone for developing ITP.[22] The underlying mechanism is unclear, more likely due to immune dysregulation as many features are common between them.[23] Mild to moderate thrombocytopenia develops in one-third patients with SLE while 2% to 5% ITP patients have underlying SLE as a causative factor.[6,10] Our results are analogous with 3% positivity for SLE in secondary ITP. Pathophysiology includes antibodies against platelets glycoprotein, surface phospholipid, thrombopoietin and its receptor.[6] Similarly approximate one-third patients with Antiphospholipid syndrome develop moderate thrombocytopenia.[10] The proposed contributory mechanism is APLA binding with anionic epitopes on GP-IIIa surface antigen.[6] Around 10-70% patients with ITP have contributory APLA antibodies.[24] Intercontinental cooperative immune thrombocytopenia study group reported 6% ITP patients had APLA antibodies, similarly we detected 3.5% of patients had underlying APLA antibodies.[13]

Evan's syndrome, the combination of ITP and autoimmune hemolytic anemia is established in 4.3% of secondary ITP patients in the present study. Previously reported prevalence of Evan syndrome in ITP was 0.7-2% that is comparatively low compared to our results.[6]

Drug induced ITP is another identifiable cause of secondary ITP. First case affiliated with quinine was reported about 140 years ago. Since than numerous drugs have been identified to cause immune thrombocytopenia.[4,25] Various mechanisms have been postulated for drug induced immune thrombocytopenia.6 Kuhne T *et al* reported 17 out of 340 (5%) patients with adults ITP, had history of underlying certain medication.[13] The estimated prevalence in our study (5%) is parallel to that reported earlier.[13] We follow these patients for 4-6 weeks time and virtually all patients counts were recovered which confirmed the diagnosis.

The common neoplasms linked with ITP are the hematopoietic malignancies but uncommonly reported with solid tumors.[6] Regarding lymphoproliferative disorders (LPD), previously reported prevalence ranged between 1-5% in the secondary ITP, which may be correlated with decreased survival and poor prognosis.[10] Our results are also similar with 2.1% positivity as a causating factor in secondary ITP.

Fortunately, Human immunodeficiency virus infection is not problematic in our country as no positive case is reported in this series, though it is challenging in some countries where prevalence in general population is high. HIV-ITP was reported in 5 to 30% of infected patients.[7] Suppressed platelets production and accelerated platelets clearance are well established underlying mechanisms.[6]

Mycobacterium tuberculosis and hepatitis B positivity associated with ITP are very rare finding but regularly reported in the literature.[26-28] We detected in HBV and mycobacterium infections as 2.1% and 0.7% of patients respectively. This is the pertinent findings of our study due to the high prevalence of these infections in our local population.

Limitation of the study needs to be mentioned firstly we did not have a follow up of all patients to determined the outcomes, secondly certain test were not done includes β-2 microglobulin for APLA, testing for viral infections and an autoimmune profile for hypothyroidism, which may fluctuate the current findings. We recommend that future studies must incorporate these tests to determine more accurate findings.

Lastly there is a convincing rationale why the diagnosis of primary ITP necessitates the exclusion of others etiological thrombocytopenia, including definitive identification of underlying cause in secondary ITP. The optimal therapy of the underlying disease (HCV, H.pylori, NHL) is likely to ameliorate thrombocytopenia along with eradication of disease. In conditions where cure of disease is not possible (autoimmune diseases, APLA) treatment for thrombocytopenia is likely to provide relief to patient with improvement in quality of life.

CONCLUSION

There is a substantial finding of predominance of secondary ITP in an Asia region compared with western countries where primary ITP is the major chunk. There is predominance of bleeding tendency and pronounced thrombocytopenia in the primary entity. Moreover HCV and helicobacter pylori infections are implicated for elevated incidence of secondary ITP in our part of world. The study briefed the demographic, clinical and laboratory aspects in adult's ITP, which serve as a base for designing future prospective clinical trials.

ACKNOWLEDGEMENT

The authors are thankful to all patients participated in this study. Authors are grateful to Mr Danish from Department of Biostatistics, Liaquat National Hospital for statistical analysis for this manuscript.

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