

Original Research Article

## Interleukin 7 in Primary Immune Thrombocytopenia: A Case Control Study

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### ABSTRACT

**Introduction:** Primary immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia without any underlying cause. Until recently, the abbreviation ITP stood for idiopathic thrombocytopenic purpura, but current awareness for the immune-mediated nature of the disease, and the absence or minimal signs of bleeding have led to a revision of the terminology. Concepts surrounding the mechanisms of thrombocytopenia in ITP have shifted from the traditional view of increased platelet destruction mediated by auto antibodies to more complex mechanisms in which both impaired platelet production and T cell-mediated effects play a role. Interleukin-7 (IL-7) is a key factor for thymocyte survival and lymph node maturation. Recent studies indicate its important role in autoimmunity; polymorphisms in the IL-7 receptor (IL-7R $\alpha$ ) have been associated with increased risk for autoimmune disease and blocking IL-7R $\alpha$  antibodies showed therapeutic efficacy in several autoimmune mouse models.

**Aim:** To evaluate the level of IL-7 in primary immune thrombocytopenia for possibility of being adopted as a reliable marker for ITP.

**Materials and Methods:** A total of 65 children were enrolled in the study; 50 ITP patients (35 active and 15 in remissions) diagnosed according to recent IWG criteria in The Pediatric Clinic of ASUH and 15 healthy subjects were taken as control group. All were assessed for plasma and BM levels of IL-7 by ELISA.

**Results:** Our study revealed a significant decrease in plasma IL7 level in both whole ITP patients and active ITP groups than control group, but IL7 level in BM of all patient groups show no significant difference over control. Plasma IL7 has a diagnostic utility in ITP at certain cut-offs.

**Conclusion:** IL7 can be relied upon as a diagnostic marker for ITP at cut-off (15 pg/ mL). However, its role in prognosis needs further investigations.

**Keywords:** ITP, IL-7, primary immune thrombocytopenia.

### INTRODUCTION

Immune thrombocytopenia (ITP) is a common hematologic disorder characterized by isolated thrombocytopenia. ITP presents either as a primary form characterized by isolated thrombocytopenia (platelet count  $< 100 \times 10^9/L$ ) in the absence of other causes or disorders that may be associated with thrombocytopenia, or a secondary form in

which immune thrombocytopenia develops in association with another disorder that is usually immune or infectious. [1]

An International Working Group (IWG) consensus panel of both adult and pediatric experts in ITP recently provided guidance on terminology, definitions, and outcome criteria for this disorder. IWG on ITP proposed the designation "Immune

Thrombocytopenia” instead of idiopathic thrombocytopenic purpura (retaining the abbreviation ITP); this terminology recognizes the immune pathogenesis of ITP and probability of absence of purpura or bleeding manifestations. [2]

The IWG also defines ITP as newly diagnosed (diagnosis to 3 months), persistent (3 to 12 months from diagnosis), or chronic (lasting for more than 12 months). “Severe ITP” refers to the presence of bleeding symptoms at presentation, or the development of new bleeding symptoms while on therapy, requiring additional intervention. “Refractory ITP” designates cases of immune thrombocytopenia that have not responded to splenectomy or have relapsed thereafter, and are severe or pose sufficient risk of bleeding to require ongoing therapy. [2]

The pathology of ITP is heterogeneous and complex. The pathogenesis of ITP involves loss of tolerance to glycoproteins expressed on platelets and megakaryocytes. Epitope spreading may explain the fact that many patients have antibodies against more than one glycoprotein. Anti-platelet glycoprotein antibodies cause thrombocytopenia through two mechanisms: 1) reducing the survival of circulating platelets, and 2) inhibiting the production of new platelets by bone marrow megakaryocytes. [1]

Besides auto-reactive B lymphocytes secreting anti-glycoprotein antibodies which considered as the primary immunologic defect in ITP, abnormality of cellular immunity, such as increased Th1/Th2 ratio, T-cell-mediated platelet lysis and reduced numbers and poor functions of circulating regulatory T cells (Tregs), has also been widely demonstrated in ITP. [3]

Interleukin 7 (IL-7), a member of IL-2 family, is produced by bone marrow stromal and epithelial cells. [4] It acts through a receptor that is comprised of two chains: IL-7R alpha (CD127) and gamma chain (CD132). IL-7R is highly expressed on resting T cells except CD4+CD25+

Tregs. [5]

IL-7 is critical for T-cell development, survival, proliferation, differentiation and inhibition of apoptosis. In addition, IL-7 could significantly promote the production of Th1 cytokines like IL-2, interferon-g (IFN- $\gamma$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), while slightly induce the Th2 cytokines, IL-4 and IL-5. IL-7 also could stimulate the cytotoxic activity mediated by CD8+ T cells; it may be able to accelerate the progression of autoimmunity. [6]

Interest in the role of IL-7 in autoimmune diseases and its potential as a therapeutic target has soared in recent years. [7] It is reported that IL-7 R $\alpha$ -blocking antibodies could reverse the clinical signs of experimental autoimmune encephalomyelitis and type one diabetes. [8]

Hence, this study aimed to evaluate the role of IL7 in immunopathogenesis of primary immune thrombocytopenia through assessing plasma and BM levels and correlating their levels with active and remission phases.

## MATERIALS AND METHODS

This study was conducted on fifty ITP patients attending The Hematology Pediatric Clinic of Ain Shams University Hospitals during the period from June 2015 to March 2016. The age of patients ranged from 1.5m-15y with median of 5 years and the male to female ratio was 1.2:1. The diagnosis was based on the IWG criteria; thrombocytopenia (platelet count  $<100 \times 10^9/L$ ), normal or increased marrow megakaryocytes, and no secondary immune or non-immune abnormalities that could account for the thrombocytopenic state. Fifteen age and sex matched healthy child who were subjected to bone marrow examination due to clinically suspected hematological diseases and finally were found to be normal were taken as the control group. Bone marrow aspiration was done after written informed consent from parents.

**The patient groups were further divided into:**

**I. Active ITP patients (platelet count <100 × 10<sup>9</sup>/L):**

This group included 35 patients. They were 21 males and 14 females with a male to female ratio 1.5:1.

**II. ITP patients in remittent phase (platelet count > 100 × 10<sup>9</sup>/L):**

This group included 15 ITP patients. They were 6 males and 9 females with male to female ratio 1:1.5.

**All individuals included in this study were subjected to the following:**

1- Detailed history about the onset of the disease, bleeding manifestations, course of the disease, recent viral infection and exclusion of any cause of secondary ITP such as SLE.

2- Thorough clinical examination with special emphasize on clinical signs of bleeding such as bruising or purplish areas on the skin, mucous membranes or gums, menorrhagia, blood in urine or stool and any associated splenomegaly.

3- Laboratory investigation:

a) Complete blood count (CBC) on LH750 Beckman Coulter-Miami, Florida, USA and Leishman stained peripheral blood smear.

b) Bone marrow examination by direct puncture of PSIS obtaining both bone marrow slide smears and bone marrow samples on EDTA vacutainer tubes.

4- Measurement of IL7 level in peripheral blood plasma and bone marrow using WKEA MED SUPPLIES of human IL-7 ELISA kit; An in vitro enzyme-linked immunosorbent assay for the quantitative measurement of human IL-7 according to the manufacturer's instructions.

**Statistical methods:** IBM SPSS statistics (V. 22.0, IBM Corp., USA, 2013) was used for data analysis. Data were expressed as Mean±SD for quantitative parametric measures in addition to Median Percentiles for quantitative non-parametric measures and both number and percentage for categorized data. The following tests were done:

1. Comparison between two independent groups for non-parametric data using Wilcoxon Rank Sum test.
2. Comparison between more than 2 patient groups for non-parametric data using Kruskal Wallis test.
3. Ranked Sperman correlation test to study the possible association between each two variables among each group for non-parametric data.
4. Chi-square test to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data. The probability of error at 0.05 was considered significant, while at 0.01 and 0.001 are highly significant.
5. Diagnostic validity test: It includes: a. the diagnostic sensitivity: TP/TP+FN. b. The diagnostic specificity: TN/TN+FP. c. The predictive value for a +ve test: TP/TP+FP. d. The predictive value for a -ve test: TN/TN+FN. e. The efficacy or the diagnostic accuracy of the test: TP+TN/ TP+FN+TN+FP. The ROC was constructed to obtain the most sensitive and specific cutoff for each technique. To evaluate the most discriminating markers between the compared groups, AUC can also be calculated.

## RESULTS

**Table 1: Demographic, clinical and laboratory findings for each group**

		Active	Remittent	Control
Age	Median (IQR)	5 (0.3- 15)	5 (0.3- 15)	7.5 (2- 13)
Sex	Male (n%)	21 (60%)	6 (40%)	8 (53.3%)
	Female (n%)	14 (40%)	9 (60%)	7 (46.7%)
Symptoms	Negative (n%)	6 (17%)	15 (100%)	
	Positive (n%)	29 (83%)	0 (0%)	
Plt x10 <sup>9</sup> /L	Median (IQR)	8 (1 - 61)	119 (112 - 568)	218.5 (178 - 455)
Hb g/dl	Median (IQR)	11.5 (8.4-13.1)	8.3 (5.5-9)	12.2 (11-13.6)
TLC x10 <sup>9</sup> /L	Median (IQR)	7.7 (1.9 - 28)	12 (4 - 21.6)	7.8 (4 - 11)
BM IL7 pg/mL	Median (IQR)	20 (5-35)	20 (5-25)	17.5 (6-35)
Plasma IL7 pg/mL	Median (IQR)	10 (5 - 20)	10 (5-15)	17.5 (5-30)

This study was carried out on 50 patients (35 active ITP patients + 15 ITP patients in remission) and control group included 15 age and sex matched subjects. The demographic, clinical and laboratory findings for each group are represented in table 1.

**Comparative study between whole patients and control groups:** revealed a

highly significant decrease in platelet count & Hb concentration and a highly significant increase in TLC in whole patient group over control group. It also showed a significant decrease in plasma IL7 of whole patients over control group ( $P < 0.01$ ). Conversely, there was a non-statistically significant difference regarding BM IL7 ( $p > 0.05$ ) Table 2.

**Table (2): Statistical comparison between the control group and the whole patient groups regarding the studied parameters**

		Control group n = 15	Patients group n = 50	Test	6p-value	Sig
Age(year)	Median (IQR)	7.5 (2- 13)	5 (0.3- 15)	-0.71	0.477	NS
Sex (%)	Male [n (%)]	8 (53.3%)	27 (54%)‡			
	Female [n (%)]	7 (46.7%)	23 (46%)‡			
Hb g/dl	Median (IQR)	12.2 (11-13.6)	10.3 (5.5-13.1)	-2.609*	0.009	HS
Plt x10 <sup>9</sup> /L	Median (IQR)	218.5 (178 - 455)	16 (1 - 568)	-4.236*	0.000	HS
TLC x10 <sup>9</sup> /L	Median (IQR)	7.8 (4 - 11)	9.6 (1.9 - 28)	-.97*	0.332	NS
BM IL7 pg/mL	Median (IQR)	17.5 (6-35)	20 (5-35)	-0.389*	0.697	NS
Plasma IL7pg/mL	Median (IQR)	17.5 (5-35)	10 (5 - 25)	-2.411*	0.016	S

\* Data were presented as median and IQR and compared using Wilcoxon Rank Sum Test.

‡ Data were presented as number and percentages and compared together using Chi-square test

**Comparative study between active and control groups:** revealed a highly significant decrease in platelet count and a significant decrease in plasma IL7 level in

active ITP patients group over control group ( $p < 0.01$ ). A non-statistically significant difference was observed as regard BM IL7 ( $p > 0.05$ ) Table 3.

**Table (3): Statistical comparison between the control group and active patient groups regarding the studied parameters**

		Control group n = 15	Active group n = 35	Test	p-value	Sig
Age(year)	Median (IQR)	7.5 (2- 13)	5 (0.3- 15)	-1.395*	0.163	NS
Sex (%)	Male [n (%)]	8 (53.3%)	21 (60%)‡			
	Female [n (%)]	7 (46.7%)	14 (40%)‡			
Hb g/dl	Median (IQR)	12.2 (11-13.6)	11.5 (8.4-13.1)	-1.66*	0.096	NS
Plt x10 <sup>9</sup> /L	Median (IQR)	218.5 (178 - 455)	8 (1 - 61)	-4.57*	0.000	HS
TLC x10 <sup>9</sup> /L	Median (IQR)	7.8 (4 - 11)	7.7 (1.9 - 28)	-0.31*	0.756	NS
BM IL7 pg/mL	Median (IQR)	17.5 (6-35)	20 (5-35)	-0.55*	0.579	NS
PlasmaIL7 pg /mL	Median (IQR)	17.5 (5-35)	10 (5 - 20)	-2.32*	0.02	S

\* Data were presented as median and IQR and compared using Wilcoxon Rank Sum Test.

‡ Data were presented as number and percentages and compared together using Chi-square test

**Table (4): Statistical comparison between the control group and remittent patient group regarding the studied parameters**

		Control group n = 15	Remittent group n = 15	Test	p-value	Sig
Age(year)	Median (IQR)	7.5 (2- 13)	5 (0.3- 15)	-0.91*	0.294	NS
Sex (%)	Male [n (%)]	8 (53.3%)	6 (40%)‡			
	Female[n(%)]	7 (46.7%)	9 (60%)‡			
Hb g/dl	Median (IQR)	12.2 (11-13.6)	8.3 (5.5-9)	-3.79*	0.000	HS
Plt x10 <sup>9</sup> /L	Median (IQR)	218 (178 -455)	119 (112 - 568)	-2.282*	0.023	S
TLC x10 <sup>9</sup> /L	Median (IQR)	7.8 (4 - 11)	12 (4 - 21.6)	-2.05*	0.04	S
BM IL7 pg/mL	Median (IQR)	17.5 (6-35)	20 (5-25)	-0.077*	0.938	NS
PlasmaIL7pg/mL	Median (IQR)	17.5 (5-35)	10 (5-15)	-1.846*	0.065	NS

\* Data were presented as median and IQR and compared using Wilcoxon Rank Sum Test.

‡ Data were presented as number and percentages and compared together using Chi-square test

**Comparative study between remittent and control groups:** revealed a highly significant decrease in Hb concentration

( $p < 0.001$ ), a significant decrease in platelet count ( $p < 0.05$ ) and a statistically significant increase in TLC in ITP patients of remittent

phase over control group. A non-statistically significant difference was detected as regard BM IL7 and plasma IL7 between both groups ( $p > 0.05$ ) Table 4.

**Correlation study between BM & plasma IL7 level and CBC parameters (TLC, Plt, Hb):** revealed that there was a highly significant negative correlation between BM IL7 level and platelets count among patients

in active phase ( $p < 0.001$ ) Figure 1 and a statistically significant positive correlation ( $p < 0.05$ ) between plasma IL7 and platelets count among patients in both active and remittent phase Figure 2. It also revealed a statistically highly significant negative correlation between BM IL7 and TLC among patients in remittent phase ( $p < 0.001$ ).

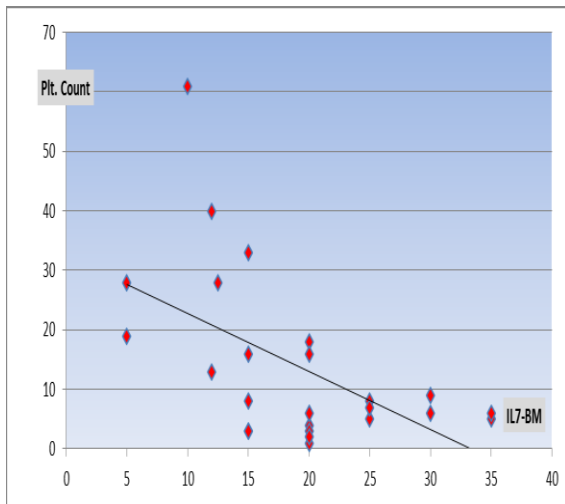


Fig. (1): Correlation study between IL7 BM and Plt. Count among active group

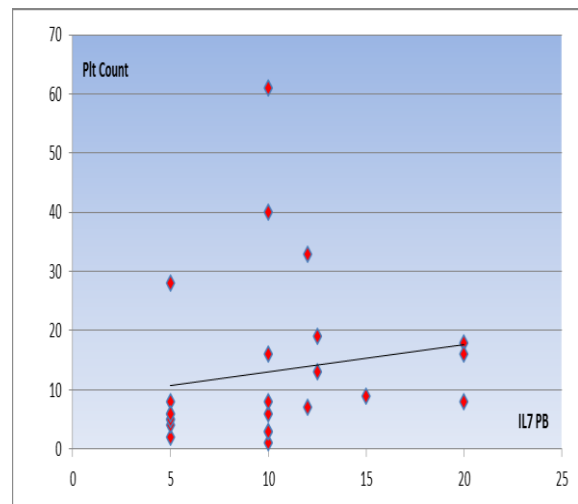


Fig. (2): Correlation study between IL7 PB and Plt. Count among active group

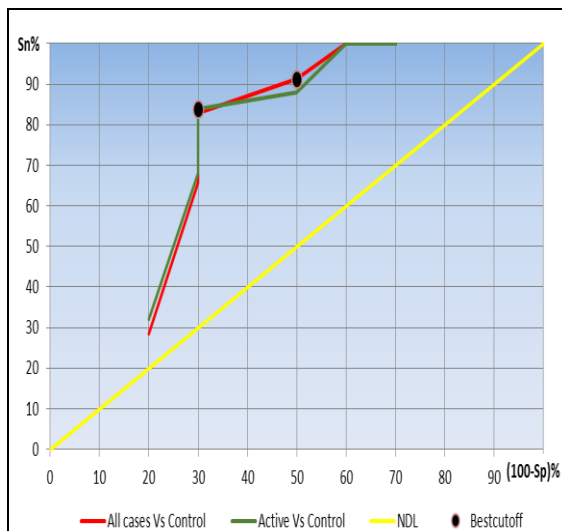


Fig. (3): ROC curve analysis showing the diagnostic performance of IL7 PB for discriminating patients groups from control

Receiver operating characteristic curve (ROC) analysis was applied to assess the diagnostic utility of plasma IL7 level in detecting active ITP patients. Our result showed that the best cut off value for plasma IL7 was 12.5 pg/ mL which succeed to sharply discriminate between active ITP

patients and healthy controls with 84% sensitivity 70 % specificity, 63.6% negative predictive value, 87.5% positive predictive value and 80% efficacy (AUC: 0.886). While the best cut off value for plasma IL7 which succeed to discriminate between all ITP patients and healthy controls was 15 pg/ mL with 91.4% sensitivity 50 % specificity, 62.5% negative predictive value, 86.5% positive predictive value and 82.2% efficacy (AUC: 0.884) Figure 3 knowing that the normal serum level of IL-7 is 10-20 pg/mL.

## DISCUSSION

Primary immune thrombocytopenia presents as isolated thrombocytopenia (platelet count  $< 100 \times 10^9/L$ ) in the absence of other causes or disorders that may be associated with thrombocytopenia. It is usually self-limited in children, with approximately 80% of cases resolving within 6-12 months.

The pathogenesis of ITP involves humoral immunity resulting in loss of



tolerance to glycoproteins expressed on platelets and megakaryocytes and cellular immunity contributes significantly to the pathogenesis of ITP via alterations in T cell subsets and decreased numbers and activity of regulatory T cells are common. Cytotoxic T cells may also mediate toxicity against platelets and megakaryocytes.

IL-7 is implicated in the pathogenesis of primary ITP due to its role in lymphocyte development, survival and cytotoxicity. Hence, this study aimed to evaluate the role of IL7 in immunopathogenesis of primary immune thrombocytopenia through assessing its plasma and BM levels and correlating them with active and remission phases.

This study was conducted on 50 ITP child, 35 of them were in active phase of the disease and 15 patients in remission phase. These patients were compared to 15 age and sex matched apparently healthy control child. In the current study, the age of patients ranged from 1.5m-15y with median of 5 years and the male to female ratio was 1.2:1.

In this work, plasma IL7 level was statistically significant lower in patient with active disease [10(5-20) ng/L] in comparison to control group [17.5(5-30) ng/L] with ( $p=0.02$ ) in agreement with Hui-Yuan Li et al. [3] who conducted their study on 83 ITP patients and 47 healthy control subjects. They evaluated the clinical significance of plasma and BM cytokine levels in ITP patients and demonstrated that plasma IL7 concentrations measured in patients at the onset of their disease [42.36 $\pm$ 4.63 pg/mL] ( $p<0.001$ ) were lower in comparison to normal controls [76.42  $\pm$  1.8 pg/mL].

However, plasma IL7 in remittent group [10(5-15) ng/L] show no significant difference from control group [10(5-20) ng/L] ( $p=0.065$ ) in contrast to Hui-Yuan Li et al. [3] revealed a statistically significant decrease of plasma IL7 in patients of remittent group [66.63 $\pm$ 5.1pg/mL] ( $p=0.048$ ) in comparison to normal controls [76.42  $\pm$  1.8 pg/mL].

On measuring of IL7 in BM, both active [20(5-35) ng/L] and remittent groups [20(5-25) ng/L] showed no significant difference in comparison to control group [17.5(5-30) ng/L]; ( $p=0.579$ ) in active group, ( $p=0.938$ ) in remittent group.

This finding was comparable to that reported by Hui-Yuan Li et al. [3] who also assayed BM IL7 concentration from ITP patients and control subjects but it didn't show any difference [ITP patients: 150 $\pm$ 35.7pg/mL, controls: 159.6  $\pm$ 47.8pg/mL] ( $p=0.870$ ).

In our study, on correlating plasma IL7 with CBC parameters (Hb, TLC, PLTs), we found a highly significant positive correlation with platelet count in active group ( $p=0.000$ ) and a significant correlation ( $p=0.023$ ) in remission group.

This coincides with Hui-Yuan Li et al. [3] who also analysed the relationship between plasma IL7 and CBC parameters which showed a significantly positive correlation with platelets count ( $p=0.029$ ).

Our findings were also in consistent with a study done by Fumihiko Kimura et al. [9] on cyclic thrombocytopenia, a rare disorder characterized by alternating thrombocytopenia and thrombocytosis in regular intervals with proposed autoimmune mechanism, who serially measured serum level of IL7 weekly for 3 months. They found that IL-7 showed a significant positive correlation between IL-7 level and platelet count ( $P<0.0001$ ). IL7 level was below the minimum detected value (6 pg/mL) at thrombocytopenic nadir and the peak coincided with the maximum platelet count.

Concerning the other CBC parameters, we found a highly statistically significant decrease of hemoglobin concentration in remittent group over active group ( $p=0.000$ ). This can be explained by development of the full picture of anemia after the active phase of the disease (3 months).

TLC showed a statistically significant increase in remittent group ( $p=0.04$ ), which can be explained by the

compensatory up-regulation of T cell to restore plasma IL7 to its normal level, indicating presence of regulatory role for IL7 on T lymphocyte and vice versa.

The same proposal was adopted by Hui-Yuan Li et al. [3] who suggested that the down-regulated IL7 in active ITP patients may be as a result of negative-feedback of up-regulated auto-reactive T cells, since the auto-reactive T cell from ITP patients are resistant to apoptosis and expands more quickly than that of healthy controls.

Based on the immunological basis of ITP, our results were in agreement with churchman et al. [10] who assayed IL7 in patients of rheumatoid arthritis (RA); Serum IL-7 was measured in 90 RA patients (age range 23 to 79 years). Their result revealed that Serum IL-7 was reduced in RA independently of systemic levels of inflammation; ranged from 2.5 to 22.9 pg/mL (median 10.7 pg/mL) similar to plasma IL-7 level in active ITP group in our study [10(5-20) ng/L].

Comparing IL-7 with other cytokines that is implicated in immunopathogenesis and prognosis of ITP; Del vecchio et al. [11] demonstrated that the elevated serum level of IL10 in active, remittent and chronic groups than healthy control suggested that they could be good diagnostic markers in ITP. Lubna M Tag [12] revealed that IL-2 is a good prognostic factor in chronic ITP through assessing the increased level of both IL-2 and IFN- $\gamma$  when compared to acute ITP or control.

In the current study, the diagnostic reliability of IL7 level was calculated using different cut off levels. We set 12.5pg/ml as the best cut off value which succeeds to sharply discriminate between active ITP patients and healthy controls with 84 % sensitivity 70 % specificity, 62.5% negative predictive value and 86.5 % positive predictive value.

While the best cut off value for plasma IL7 which succeed to discriminate between all ITP patients and healthy controls was 15 pg/ mL with 91.4% sensitivity 50 % specificity, 62.5% negative

predictive value, 86.5% positive predictive value and 82.2% efficacy.

## CONCLUSION

In conclusion, plasma IL-7 measurement is candidate marker for diagnosis of ITP. However, its role as a prognostic marker for the progression of the disease needs further investigations.

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