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Evaluation of ADH4 gene expression and hematological parameters as biomarkers for the pathogenesis of ITP in the pediatric

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ABSTRACT: This study investigates the role of the ADH4 gene expression and hematological biomarkers in the pathogenesis of Immune Thrombocytopenic Purpura (ITP) in pediatric patients. The study involved 100 children, 50 with ITP and 50 healthy controls, to evaluate blood parameters and ADH4 gene expression when Real-Time PCR. Results showed the mean white blood cell (WBC) count was significantly lower in ITP patients (8.11 ± 0.73) compared to controls (11.94 ± 0.69), Similarly, lymphocyte counts were significantly reduced in ITP patients (3.29 ± 0.43) versus controls (5.65 ± 0.42), The platelet count was markedly lower in ITP patients (26.18 ± 2.77) compared to controls (277.40 ± 10.74), On the contrary, The results show there was a non-significant difference between ITP patients and healthy individuals according to both neutrophil count and hemoglobin (Hb) levels ($P < 0.05$), while, ADH4 gene expression was significantly higher in ITP patients shown The mean 13.29, 1.00 between the ITP patients and Control respectively, suggesting its involvement in immune dysregulation. These findings highlight the potential of the ADH4 gene and some hematological parameter as a biomarker and therapeutic target in ITP, emphasizing the need for personalized treatment approaches

Keywords: Immune Thrombocytopenic, ADH4 gene, hematological, ITP pediatric

1. INTRODUCTION

Immune thrombocytopenia purpura (ITP) is an acquired hematological autoimmune disorder characterized by platelet destruction and impaired production and formation of antiplatelet autoantibodies, leading to rushed platelet destruction with premature removal of platelets from the circulation by phagocytes [1]. The pathogenesis mechanism is complex, affecting many immune system components and causing peripheral destruction of platelets and disruption of central platelet agglutination and platelet production in the bone marrow, while pediatric ITP is often acute [2], the platelet count fluctuations, a feature that may help to distinguish ITP from other causes of thrombocytopenia [3], as a decreased number of platelets less than 150 ×109 /L in the circulating blood [4] Since the causes of ITP are unknown and

multifactorial, as inhibiting platelet production is influenced by drugs, infections, malignancy, or autoimmune diseases, and genetic diseases [22].

Studies indicate that, often, the Pediatric thrombocytopenia, which affects 1-5/100,000 children annually, affects immune-mediated destruction of platelets. While most cases resolve spontaneously, 20% become chronic, requiring vital biomarkers for early intervention [5]. Therefore, possible to consider identifying metabolism-related differentially expressed genes as potential biomarkers for the pathogenesis of ITP and hematological diseases using bioinformatic analyses. Genetic predisposition, particularly in immune regulation genes, remains underexplored, such as ADH4, encoding an enzyme in retinol metabolism, is implicated in autoimmune diseases [6]. Therefore, determining the Retinoic acid, one of the metabolites of retinol, modulates T regulatory cells and immune tolerance [7]. Refers. Some hypothesize that ADH4 variants decrease metabolism of retinol, supporting the autoimmunity in ITP [5].

This study evaluates Alcohol Dehydrogenase 4 (ADH4) gene polymorphisms and hematological biomarkers in pediatric ITP through genetic screening and hematological profiling. Blood parameters in pediatric ITP reflect complex immune interactions, as was mentioned by [8]. Addition of the importance of surveillance, Neutrophil, Lymphocytes, MPV, PDW, and Retinal platelets enhance diagnostic and prognostic accuracy, Personal management guidance [9], Future studies should standardize the measurements and explore new biomarkers.

2. MATERIAL AND METHOD

The study was carried out in the Hemato Oncology Center and Al-Karama Teaching Hospital period from September 2024 and February 2025. Collect 100 samples (50patient of ITP and 50 as control). To get consent, all participants in the current study were informed about the goals and methodology. ITP diagnosed by specialized physicians. The Current test included hematological parameters, complete blood count (CBC) and Total RNA of all samples was extracted following the protocol provided by the manufacturer Bioneer/ Korea. Testing was performed using a complete blood cell count (CELL-DYN) device. Ruby, after adding 2 ml of blood into the EDTA K3 anticoagulant tube, the sample was gently shaken and placed directly in its designated place in the CELL-DYN) machine and the start command was given. The device then automatically reads the results. When the results appeared, print instructions were given, according to the German company Abbott Laboratories. The task this study, for thrombocytopenia, such as the basic parameters obtained from a blood complete count (CBC) were white blood cells (WBCs), hemoglobin (HB), Lymphocytes, Neutrophils, and platelets (PLT). While, in genetic screening using the quantitative Real-Time PCR, was used in quantifying the ADH4 gene expression analysis, which was normalized by the housekeeping gene (GAPDH). This method was carried out according to the method described by [10], using a kit the total RNA Extraction Kit AccuZolTM from a company Bioneer /Korea, the result was calculated the expression analysis (fold change) was analyzed by using the Livak method, as described by Schmittgen [11]

2.1 statistical analysis

The statistical analysis. Data were collected, summarized, analyzed and presented using the statistical package for social sciences (SPSS) version 26 and Microsoft Office Excel 2010. In a manner, an independent sample t-test, One-way ANOVA test with Chi-square test was used to study the association between any two categorical variables. Pearson correlation was used to evaluate the correlation between any 2 numeric variables and the results were expressed as correlation coefficient (r) and the level of significance (P), The level of significance was considered at a P-value of less than 0.05 and highly significant level at 0.01 or less [12]

3. RESULT AND DISSECTION

The present study enrolled 50 patients with Immune thrombocytopenic purpura (ITP) and 50 healthy control individuals, reveals significant insights into the hematological profile associated with ITP, where. The levels of some blood parameters in ITP patients and healthy individuals were measured and compared. The results were demonstrated in (Table 1) and (Fig1). Mean levels of White Blood Cells count were 8.11 ± 0.73 and 11.94 ± 0.69, in ITP patients and healthy control induvial, respectively; the level was lower in the ITP patient group comparison with the healthy group, and the difference was non-significant (P = 0.001). Agree with the results from previous studies that indicate variations in immune response among ITP patients [13][14].

Similarly, lymphocyte counts were significantly reduced in ITP patients (3.29 ± 0.43) versus controls (5.65 ± 0.42), therefore the difference was a significant (P=0.001) As appear in (Table 1) and (Fig1). supporting the notion of lymphopenia in ITP, which has been documented in various pediatric cohorts [15][16]. Neutrophil counts and hemoglobin levels showed no significant differences, which is consistent with reports suggesting that ITP primarily affects platelet counts without significantly altering other blood parameters [17] [18]. However, the current results appear that there is non-significant difference between ITP patients and healthy controls depending on the number of neutrophils and hemoglobin (Hb) levels (P < 0.05)

Table 1. - Mean levels of some blood parameters in ITP patients and healthy control

Parameters	ITP Patients *n* = 50	Control (Healthy) *n* = 50	*P- value*
White Blood Cells count			
Mean± SE	**8.11 ± 0.73**	**11.94 ± 0.69**	**0.001 † S**
Range	1.59 – 17.78	4.50- 19.26	
Lymphocytes count			
Mean± SE	**3.29 ± 0.43**	**5.65 ± 0.42**	**0.001 † S**
Range	0.43 – 9.55	2.79- 10.69	
Neutrophil count			
Mean± SE	**5.70 ± 0.77**	**4.89 ± 0.31**	**0.336 † NS**
Range	0.87 -24.50	1.80-8.80	
Hemoglobin (Hb) (g/dl)			
Mean± SD	**11.77 ± 0.93**	**11.60 ± 0.54**	**0.610 † NS**
Range	8.10 -14.70	8.20-13.30	
Platelet Count (thousand/ µl)			
Mean± SE	**26.18 ± 2.77**	**277.40 ± 10.74**	**0.001 † S**
Range	3.00 -87.00	168.00-435.00	

n: number of cases; SE: standard error; †: independent samples t-test; S: significant at P ≤ 0.05. NS: not significant at P > 0.05

Regarding the important part of comparison, the present results show the mean levels of platelet in ITP patients were markedly lower in ITP patients (26.18 ± 2.77) compared to controls (277.40 ± 10.74) As shown in (Table 1) and (Fig1), reaffirming the diagnostic hallmark of ITP [17][6]. These findings highlight the importance of comprehensive blood parameter assessment in diagnosing and managing ITP, as low platelet counts can lead to increased risk of bleeding complications [20][21].

The significant differences in lymphocyte and platelet counts underscore the need for ongoing research into the underlying mechanisms of thrombocytopenia and immune dysregulation in ITP [22][23][24]. The study's results contribute to the growing body of evidence that emphasizes the necessity for tailored therapeutic approaches based on individual hematological profiles in pediatric ITP patients [5][25].

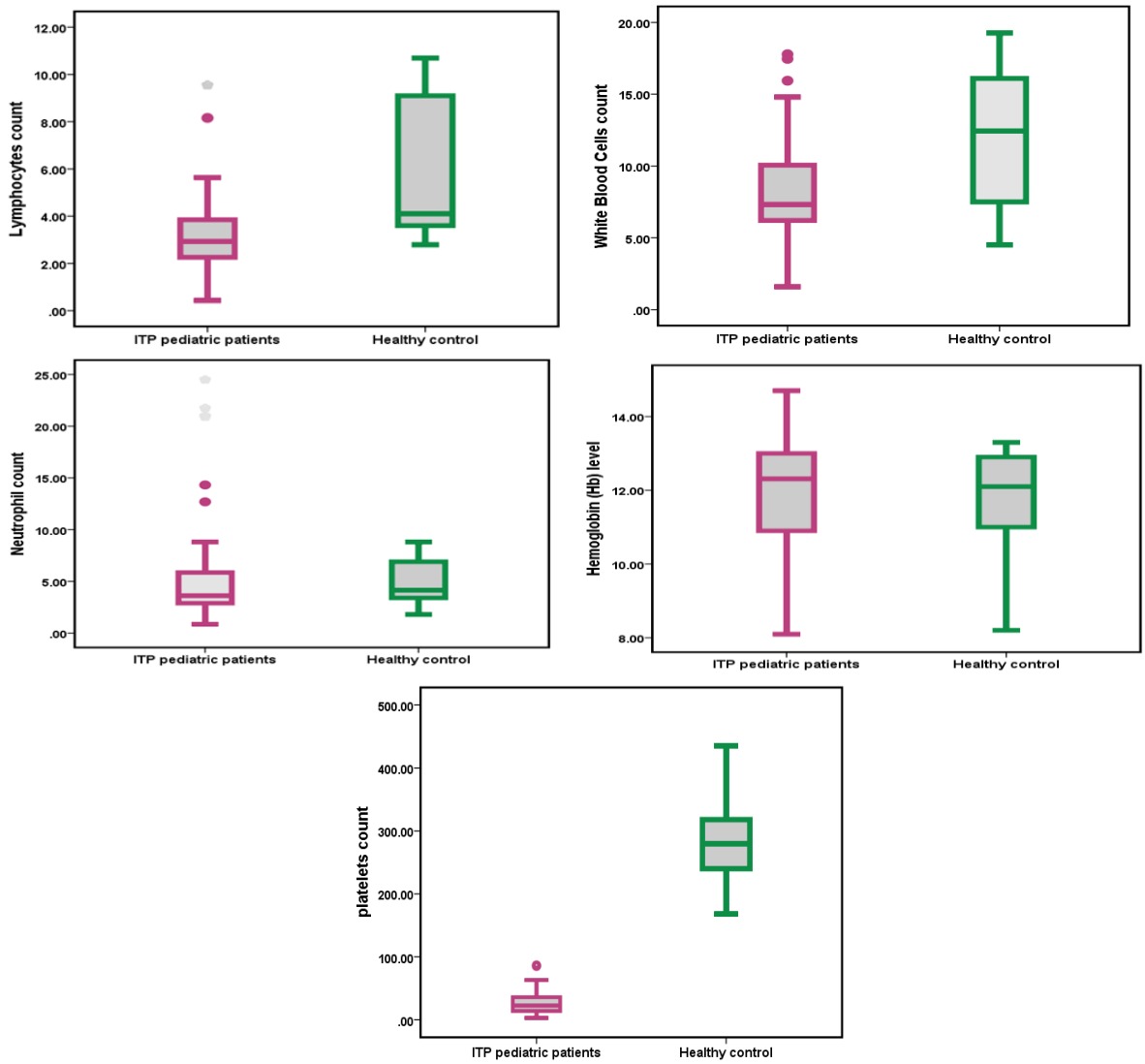

Fig1: comparative mean levels of some blood parameters in ITP patients and healthy

3.1 CORRELATION BETWEEN BLOOD PARAMETERS IN ITP PATIENTS

While shown, the correlations between some blood parameters (white blood cells, lymphocytes, neutrophils, hemoglobin, and platelets) in thrombocytopenia patients are shown in (Tables 2). The present results observed show there was significant positive correlation between WBC count and lymphocyte count (r=0.426 and p=0.001), as well as WBC count and neutrophil level (r=0.363 and p=0.001), suggest a potential interplay in immune system functioning, indicating

that as WBC counts increase, lymphocyte and neutrophil levels may also rise [16][23][26], Furthermore, the significant correlation between lymphocyte and platelet counts (r=0.312, p=0.027) may highlight a relationship between immune modulation and thrombocytopenia in ITP [27][28]. But the present results show the non-significant correlation between all other parameters in ITP patients. Finally, these findings underscore the complexity of ITP pathology, where immune dysfunction can manifest in various hematological parameters [29][30]

Table 2: Correlation of some blood parameters in thrombocytopenia patients

Parameters	blood parameters									
	WBC		Lymphocyte		Neutrophil		HGB		Platelets	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*p*	*r*	*P*
WBC	1									
Lymphocyte	0.426	0.001*	1							
Neutrophil	0.363	0.001*	-0.023	0.872	1					
HGB	0.003	0.984	0.027	0.850	0.140	0.331	1			
Platelets	-0.027	0.855	0.312	0.027*	-0.212	0.138	0.077	0.597	1	

r: Pearson correlation.

3.2 Evaluation of ADH4 gene expression

In this study, a quantitative analysis of RT-PCR the Done to analyses the Expression of ADH4 and Compare the expression between the clear health control group with the ITP patients' group. The change in gene expression was calculated using a relative quantitative measurement [11]. This is based on the Normalize Ct values for calculation ΔCt and represents the difference between the average Ct values of the ADH4 cDNA amplification replica for each case and the case of GAPDH. The plots of each run, including amplification plots and detachment curves, were recorded. Fig (2) appperance the amplification diagrams and detachment curves for gene ADH4.

While the part of the study focused on determining the roles of ADH4 in ITP in the pediatric population of Wasit throughout the evaluation of the folding change of gene expression (2-ΔΔct) in ITP patients and comparing them with healthy individuals, in addition, this part of the study aims to detect the roles of these genes in developing the severity of ITP.

In the calculate the relative expression of the ADH4 gene in all groups study, 2-ΔCt scores were applied. A calibrator was used, which was one of the control samples. with high expression of ADH4. As shown in Table (3), the mean of 2-ΔCt values of the control group was (-0.003) and that for ITP patients was (-2.94). When calculating, the gene expression was significantly higher in the ITP patients' group than the control group. Fold number in the ITP group was 13.29, as shown in Table 3

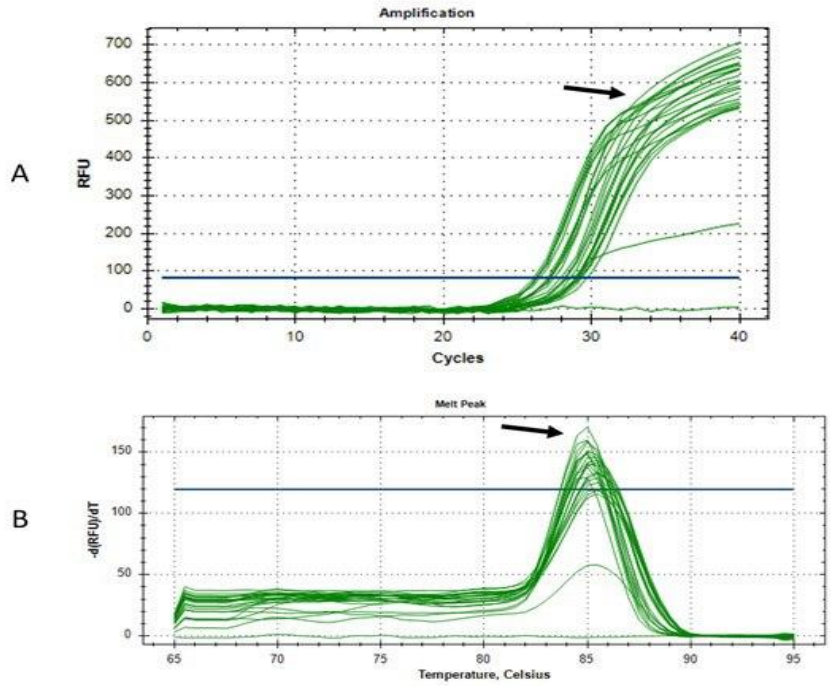

Fig 2 amplification ADH4 gene plots by RT-PCR. both ITP and healthy groups. Image was taken directly from Agilent qPCR machine

The investigation of gene expression profiles in pediatric patients with Immune Thrombocytopenic Purpura (ITP) provides substantial insights into the roles of ADH4 in the pathophysiology of this disorder. This upregulation suggests that these genes may be involved in the immune dysregulation and inflammatory processes characteristic of ITP [31][32]. The high diagnostic accuracy of ADH4, with an area under the curve of 1.000 for the gene [17][33].

Table (3): Comparison of (Ct, $2^{-}\Delta$ct and folding) between patients and healthy controls

All group	*Mean Ct of ADH4 gene*	*Mean Ct of GAPDH*	*$^{\Delta}$Ct of ADH4*	*$2^{-\Delta Ct}$*	*Fold of gene expression*
ITP patients	23.72	23.13	0.36	-2.94	13.29*
Control	26.84	23.54	3.30	-0.003	1.0

The ability to distinguish ITP patients from healthy controls using these biomarkers is particularly significant in clinical practice, where accurate diagnosis can lead to timely and appropriate treatment interventions [20][25]

The comparison of ADH4 gene expression between ITP patients and healthy control subjects has been carried out and the results were demonstrated in Table 4. The mean of ADH4 gene expression was 13.29 ± 3.51, and 1.00 ± 0.21 in ITP patients and healthy control, respectively; the mean levels were higher in ITP patients compared to healthy control, and the difference was highly significant ($P < 0.001$). Therefore, ADH4, known for its role in alcohol metabolism and oxidative stress response, may contribute to the pathophysiological landscape of ITP by influencing cellular responses to inflammation and stress [34][35]. The significant fold change in ADH4 expression (13.29 in ITP patients vs. 1.00 in controls) underscores its potential relevance in the disease process, suggesting that elevated ADH4 levels may reflect an adaptive response to the inflammatory milieu seen in ITP [36][37].

Table (4): Comparison of mean of *ADH4 gene expression* between patients and healthy controls

Groups	Mean	SD	SE	p-value
ITP patients	13.29	3.51	0.74	0.001**
Control	1.00	0.21	0.11	

SD: standard deviation; SE: standard error; †: one way ANOVA; **: significant at $P < 0.05$

The correlation between gene expression parameters and other parameters in patients with ITP was shown in Tables (5). There is a positive correlation between the ADH4 gene (r=0.560 and p=0.001), but the present results show a non-significant correlation between other parameters.

further elucidate the interconnectivity of immune regulation and inflammation in ITP [38][39]. The logistic regression analysis suggests that the upregulation of ADH4 may enhance the expression, indicating a potential regulatory mechanism at play [3][40]. Understanding the pathways through which ADH4 influence immune responses could provide novel therapeutic targets for ITP, particularly in cases where traditional treatments are ineffective [17][21]

Table (5): Correlation between gene expression parameters and other parameters in patients with ITP

Parameters	*ADH4 gene*	
	r	***P***
ADH4 gene	1	
WBC	-0.086	0.552
Lymphocyte	-0.251	0.081
Neutrophil	-0.253	0.077
HGB	-0.008	0.957
platelets	-0.120	0.406

***r*: correlation coefficient**.

Future studies should focus on elucidating the precise mechanisms through which these genes interact with immune pathways and contribute to platelet destruction in ITP [41] [42] Additionally, exploring the potential for targeting ADH4 pathways in therapeutic contexts may yield new strategies for managing ITP, particularly in cases that are resistant to conventional treatments [43][44]. Furthermore, the integration of gene expression profiling into clinical practice could enhance personalized medicine approaches, allowing for tailored treatment options based on individual molecular profiles [6] [32][42] [45[46]. Overall, this study underscores the importance of ADH4 as potential biomarkers and therapeutic targets in ITP, providing a foundation for future research aimed at unraveling the complexities of this disorder and improving patient outcomes through innovative treatment strategies, Finally, a recommendation. Therefore, possible to increase studies about gene variants that predispose children to ITP by altering immune-metabolic pathways, and gene expression levels can predict platelet recovery or chronicity, and detect relationships between the hematological parameters and genes in ITP progression. The potential impact of this research includes improved early diagnostic differentiation of ITP, and to help reduce the extent of ITP.

4. CONCLUSION

The study demonstrated the gene expression of ADH4 and the pathways by which hematological parameters affect immune and platelet functions in ITP. The function of this gene may use a potential biomarker to diagnose ITP. This could pave the way for novel therapeutic approaches ultimately improving management strategies for the affected.

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