

doi: 10.3897/bgcardio.31.e170466

## THE EFFECT OF THERAPY ON ELECTROCARDIOGRAPHY PARAMETERS IN CHILDREN WITH IRON DEFICIENCY ANEMIA AND MINOR THALASSEMIA COMPARED WITH THE HEALTHY CHILDREN

N. M. Noori<sup>1</sup>, G. M. Aliabad<sup>2</sup>, T. Boryri<sup>3</sup>, A. Teimouri<sup>4</sup>

<sup>1</sup>Children and Adolescents Health Research Center, Research Institute of Cellular and Molecular Science in Infectious Diseases, Zahedan University of Medical Science's – Zahedan, Iran

<sup>2</sup>Pediatric ward, School of Medicine, Iran University of Medical Sciences – Tehran, Iran

<sup>3</sup>Department of Midwifery, School of Nursing and Midwifery, Pregnancy Health Research Center, Zahedan University of Medical Sciences – Zahedan, Iran

<sup>4</sup>Children and Adolescents Health Research Center, Research Institute of cellular and Molecular Science in Infectious Diseases, Zahedan University of Medical Science's – Zahedan, Iran

## ЕФЕКТЪТ НА ТЕРАПИЯТА ВЪРХУ ЕЛЕКТРОКАРДИОГРАФСКИТЕ ПАРАМЕТРИ ПРИ ДЕЦА С ЖЕЛЯЗОДЕФИЦИТНА АНЕМИЯ И ЛЕКА ТАЛАСЕМИЯ В СРАВНЕНИЕ СЪС ЗДРАВИ ДЕЦА

Н. М. Нури<sup>1</sup>, Г. М. Алиабад<sup>2</sup>, Т. Борири<sup>3</sup>, А. Теймури<sup>4</sup>

<sup>1</sup>Изследователски център за здравето на деца и юноши, Изследователски институт по клетъчна и молекулярна наука в областта на инфекциозните болести, Медицински университет в Захедан – Захедан, Иран

<sup>2</sup>Педиатрично отделение, Медицински факултет, Ирански университет по медицински науки – Техеран, Иран

<sup>3</sup>Катедра по акушерство, Факултет по медицински сестрински грижи и акушерство, Изследователски център по здравето на бременните жени, Медицински университет в Захедан – Захедан, Иран

<sup>4</sup>Изследователски център за здравето на деца и юноши, Изследователски институт по клетъчни и молекулярни науки в областта на инфекциозните болести, Медицински университет в Захедан – Захедан, Иран

### Abstract.

**Introduction:** Iron deficiency anemia (IDA) and minor thalassemia (MT) are common hematologic disorders in children that may affect cardiovascular function. **Objectives:** The goal of the study was to determine whether ECG abnormalities in these populations are clinically significant and potentially reversible. **Material and methods:** This prospective, randomized clinical trial aimed to evaluate electrocardiographic (ECG) changes in 135 children aged 5-18 years, equally divided into IDA, minor thalassemia, and healthy control groups. ECG parameters such as QT interval, corrected QT interval (QTc), P-wave dispersion (PWd), Tpe interval, and Tpe/QTc ratio were assessed before and after Iron supplementation in the IDA group. **Results:** Pre-treatment, the IDA group showed significantly lower hemoglobin, ferritin, and serum Iron levels, along with elevated TIBC and marked ECG abnormalities including prolonged QTc, P-wave dispersion, Tpe interval, and increased Tpe/QTc ratio, indicating higher arrhythmogenic risk. Following Iron supplementation, the IDA group demonstrated significant improvements in hematological parameters and normalization of ECG indices. In contrast, the MT and control groups exhibited stable hematologic and ECG profiles throughout the study. Statistical analysis confirmed significant pre- to post-treatment improvements in IDA patients, while no significant ECG changes were observed in MT or control groups. These findings suggest that ECG abnormalities in IDA are reversible with appropriate treatment, highlighting the importance of early diagnosis and intervention to prevent cardiac complications in pediatric populations. **Conclusion:** These findings highlight the importance of early detection and treatment of IDA to mitigate cardiac complications in pediatric populations.

### Key words:

electrocardiography, iron deficiency anemia, minor thalassemia, children

**Address for correspondence:** Prof. Noor Mohammad Noori, Professor Pediatric Cardiology, e-mail: dr\_noori\_cardio@yahoo.com, ORCID: 0000-0002-0732-6412; Prof. Ghasem Miri Aliabad, Professor Pediatric Hematology and Oncologist, e-mail: ghmiri1357@gmail.com, ORCID: 0000-0002-9112-5567; Tahereh Boryri, Instructor of Midwifery, e-mail: Boryri\_tahereh@yahoo.com, ORCID: 0000-0001-7897-1884; Alireza Teimouri, Assoc. Prof. in Demography, e-mail: alirezateimouri260@gmail.com, ORCID: 0000-0002-8356-4260

**Резюме.** **Въведение:** Желязодефицитната анемия (ЖДА) и леката таласемия (ЛТ) са често срещани хематологични заболявания при деца, които могат да повлияят на сърдечно-съдовата функция. **Цел:** Целта на проучването беше да се определи дали ЕКГ аномалиите при тези популации са клинично значими и потенциално обратими. **Материал и методи:** Това проспективно, рандомизирано клинично проучване имаше за цел да оцени електрокардиографските (ЕКГ) промени при 135 деца на възраст 5-18 години, разделени поравно в групи с ЖДА, лека таласемия и здрави контроли. ЕКГ параметри като QT-интервал, коригиран QT-интервал (QTc), дисперсия на P-вълната (PWd), Тре-интервал и съотношение Тре/QTc бяха оценени преди и след приема на желязни добавки в групата с ЖДА. **Резултати:** Преди лечението групата с ЖДА показва значително по-ниски нива на хемоглобин, феритин и серумно желязо, заедно с повишени нива на TIBC и отчетливи ЕКГ аномалии, включително удължен QTc, дисперсия на P-вълната, Тре-интервал и повишено съотношение Тре/QTc, което показва по-висок риск от аритмия. След приема на желязни добавки групата с IDA показва значително подобрение в хематологичните параметри и нормализиране на ЕКГ индексите. За разлика от това групата с ЛТ и контролната група показаха стабилни хематологични и ЕКГ профили през целия период на проучването. Статистическият анализ потвърди значително подобрение при пациентите с ЖДА преди и след лечението, докато при ЛТ или контролната група не бяха наблюдавани значителни промени в ЕКГ. Тези резултати демонстрират, че аномалиите в ЕКГ при ЖДА са обратими с подходящо лечение, което подчертава важноста на ранната диагностика и интервенция за предотвратяване на сърдечни усложнения при педиатричната популация. **Заключение:** Получените резултати подчертават важноста на ранното откриване и лечение на ЖДА за намаляване на сърдечните усложнения при педиатричната популация.

**Ключови думи:** електрокардиография, желязодефицитна анемия, лека таласемия, деца

**Адрес за кореспонденция:** Проф. Нур Мохамад Нури, професор по детска кардиология, e-mail: dr\_noori\_cardio@yahoo.com, ORCID: 0000-0002-0732-6412; Проф. Гасем Мири Алиабад, професор по педиатрична хематология и онкология, e-mail: ghmiri1357@gmail.com, ORCID: 0000-0002-9112-5567; Тахерех Борири, инструктор по акушерство, e-mail: Boryri\_tahereh@yahoo.com, ORCID: 0000-0001-7897-1884; Алиреза Теймури, доцент по демография, e-mail: alirezateimouri260@gmail.com, ORCID: 0000-0002-8356-4260

## INTRODUCTION

Electrocardiography (ECG) is a simple, non-invasive, and highly informative tool that allows clinicians to evaluate how the heart's electrical system is functioning. In children, even small ECG changes can provide early clues about hidden health issues, including blood-related disorders such as iron deficiency anemia (IDA) and minor thalassemia (MT). Although these conditions primarily affect the blood, growing evidence shows that they can also influence heart function [1, 2].

IDA is the most common nutritional disorder among children. It typically develops when the body does not receive enough iron from the diet, has difficulty absorbing it, or requires more iron during periods of rapid growth. When iron levels drop, the production of hemoglobin the molecule in red blood cells that carries oxygen also decreases. Consequently, tissues receive less oxygen, leading to symptoms such as fatigue, pale skin, and an increased heart rate. Over time, as anemia becomes more severe, the heart must work harder to meet the body's oxygen needs, which may cause subtle but important cardiovascular changes [3, 4].

On an ECG, children with IDA may present with a faster heart rate or a prolonged QT interval, indicating that the heart takes longer to recharge between beats. This delay can raise the risk of developing irregular heart rhythms, such as Torsades de Pointes. Other ECG findings, including ST-segment depression, T-wave inversion, or mild alterations in PR or QRS intervals, may represent early effects of chronic anemia on heart muscle performance [5].

Minor thalassemia, on the other hand, is an inherited blood disorder that causes the body to produce abnormal hemoglobin. Most affected children appear healthy, yet persistent anemia forces the heart to work harder to ensure sufficient oxygen delivery. Some studies have noted mild ECG abnormalities in these children, such as QT prolongation and T-wave changes. These alterations may arise from a combination of anemia, oxidative stress, and in cases involving transfusions mild iron overload [6-8].

Despite increasing awareness of these cardiac effects, few studies have specifically examined ventricular repolarization parameters such as QT and QTcd, Tpe interval, and Tpe dispersion in children with IDA or MT compared to healthy peers. Understanding these

differences could help identify early electrical changes in the heart before more serious complications develop [9, 10]. Researchers have emphasized the need for larger, well-designed studies to clarify how these ECG changes relate to the risk of future cardiac events [11].

If left untreated, IDA may progressively impair heart function and elevate the risk of arrhythmias [12]. Encouragingly, effective treatment and correction of anemia can help the heart recover and reduce these risks. Establishing reliable ECG reference values for healthy children can also assist clinicians in recognizing early warning signs in those with anemia.

The present study aims to determine whether the ECG abnormalities observed in children with IDA and MT are clinically meaningful and whether they improve with appropriate treatment. These findings may contribute to a more comprehensive and preventive approach to managing pediatric anemia and its potential cardiovascular consequences.

## METHODS

### Study Design and Population

This prospective, randomized, and blinded clinical trial was conducted on children with blood disorders of Iron Deficiency Anemia (IDA) and Minor thalassemia (MT) to evaluate the electrocardiographic (ECG) changes in pediatric patients both before and after treatment, compared to healthy controls. The study run on patients who referred to Ali Asghar pediatric hospital affiliated to the Zahedan University of medical sciences between 2020 and 2021. A total of 135 children aged 5-18 years were equally shared and enrolled into three groups of: (1) IDA, (2) MT, and (3) healthy controls after considering the exclusion criteria.

### Inclusion and Exclusion Criteria

Participants in this study were pediatric patients aged 5 to 18 years who had been diagnosed with either IDA or MT. Diagnosis of IDA was based on hemoglobin levels below 13 g/dL in boys and below 12 g/dL in girls, while children with MT were identified through hemoglobin electrophoresis showing HbA<sub>2</sub> levels greater than 3.5%. Exclusion criteria were carefully defined to eliminate confounding factors and included patients with other types of anemia, hematologic disorders, cardiac, renal, gastrointestinal, or endocrine diseases, as well as infections or malignancies. Children who had used medications affecting iron absorption, received iron or anti-inflammatory treatments prior to enrollment, or demonstrated poor adherence to prescribed iron therapy were also excluded. The control group consisted of healthy children with no history of anemia or chronic illness. For all study groups, additional exclusion criteria included known cardiovascular disease or

congenital heart defects, ongoing infections or inflammatory conditions, iron or folate supplementation within the past three months, a history of blood transfusion in the previous six months, and any electrolyte imbalances or metabolic disorders.

### Treatment

The typical dosage of ferrous sulfate, Tablet 200 mg with the 50mg elemental Iron (Made in Iran, DaruPakhsh) that used 4-6 mg of elemental Iron per kilogram of body weight per day, divided into 2 doses in 3 months. Ferrous sulfate is best to be taken with empty stomach to optimize absorption, but if gastrointestinal discomfort arises, it can be consumed with a small amount of food. It is important to avoid taking it alongside dairy products, calcium supplements, or anti-acids, as these can hinder Iron absorption. Hemoglobin levels and serum ferritin checked monthly to monitor the treatment's effectiveness. Additionally, potential side effects, such as gastrointestinal issues like constipation or nausea, monitored and managed through dietary adjustments or alternative formulations if was necessary. The treatment for children with minor thalassemia primarily focused on supportive care, as these patients usually do not require specific medical therapy. The mainstay of management include folic acid supplementation) Iran Daru( 1 mg daily) to support red blood cell production and prevent megaloblastic changes.

### Blood Sample Collection and Measurements

To diagnose and monitor IDA in children, hematological parameters including hemoglobin (Hb), ferritin, serum Iron, and total Iron-binding capacity (TIBC) were measured before treatment and after 3 months of therapy. A total of 5 mL of venous blood was collected from each participant to perform all required tests. For Hb measurement, whole blood was collected in an EDTA tube and analyzed using an automated hematology analyzer. Ferritin, serum iron, and TIBC were determined from serum samples obtained after clotting and centrifugation, using standard assay kits or automated analyzers according to the manufacturers' instructions. All results were recorded in appropriate units (Hb in g/dL, ferritin in ng/mL, serum Iron in µg/dL).

### Electrocardiography

At the time of diagnosis and at the end of Iron treatment, every child underwent electrocardiography (ECG). The 12-lead ECG was recorded at a paper speed of 50 mm/second and a gain of 10 mm/mV using a Cardiofax V device (Nihon Kohden Corporation, Tokyo, Japan) while the patient was in a supine position. During the recording, patients were allowed to breathe normally but were instructed not to speak. All measurements were taken manually using a magnifying glass,

and the mean values were obtained by averaging the results of three consecutive measurements.

P-wave duration was measured in lead II from the beginning to the end of the P wave. P wave dispersion was calculated by subtracting the minimum P wave duration from the maximum P-wave duration. QT interval measurement started from the onset of the Q wave to the end of the T wave. The QTc was calculated using Bazett's formula. QTd was calculated as the difference between the longest and shortest QT intervals. QTcd was found by subtracting the minimum QTc interval from the maximum QTc interval (Fig. 1).

The Tpe interval, measured from the peak of the T wave (highest point) to the end of the T wave, was defined as the intersection between the tangent of the downward slope of the T wave and the isoelectric line (Fig. 2). The Tpe/QTc ratio was calculated based on these measurements, with all Tpe measurements taken from the precordial leads.

### Ethical Approval

This study approved by the ethical committee of the University of Medical Science, Zahedan, Iran, coded as IR.ZAUMS.REC.1399.373 and coded IRCT20250416065355N1 as a clinical trials.

### Statistical Analysis

Continuous variables were summarized using mean  $\pm$  standard deviation (SD), while categorical variables were reported as frequencies and percent-

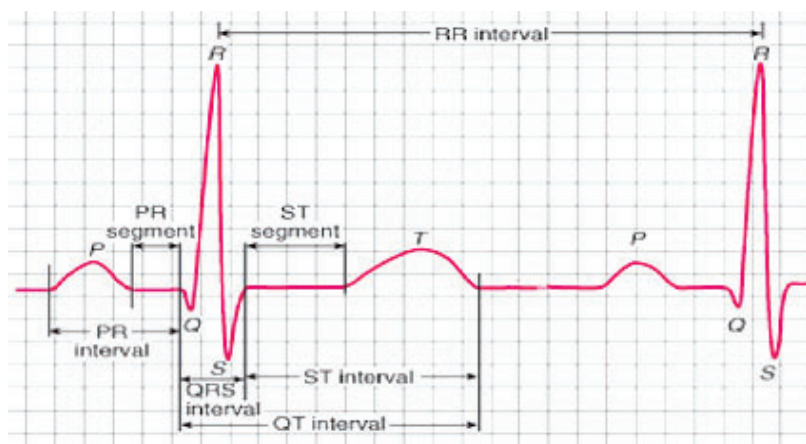
ages. The Shapiro-Wilk test was used to assess the normality of continuous data. Hematological and electrocardiographic parameters were compared among the IDA, MT and control groups both before and after treatment. For comparisons across the three groups, the Kruskal-Wallis test was applied. When significant differences were observed, pairwise comparisons were performed using Dunn's post hoc test with adjustment for multiple comparisons. A p value  $<0.05$  was considered statistically significant.

## RESULTS

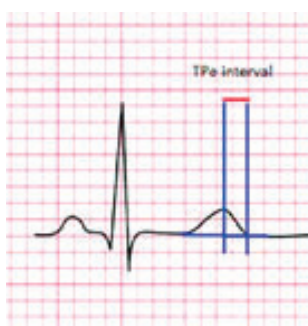
The mean age of participants was 11.69 years (SD = 4.27) in the IDA group, 11.24 years (SD = 3.73) in the MT group, and 11.64 years (SD = 3.65) in the control group. The overall mean age across all groups was 11.53 years (SD = 3.87) with no statistically significant differences ( $F = 0.178$ ,  $p = 0.837$ ).

The sex distribution among participants was relatively balanced across all groups. In the IDA group, 51.1% were girls. The MT group included 48.9% girls, identical to the control group, which also had 48.9% girls. Overall, the total sample consisted of 49.6% girls. The comparison of sex distribution among the groups revealed no statistically significant difference (Contingency Coefficient = 0.021,  $p = 0.971$ ).

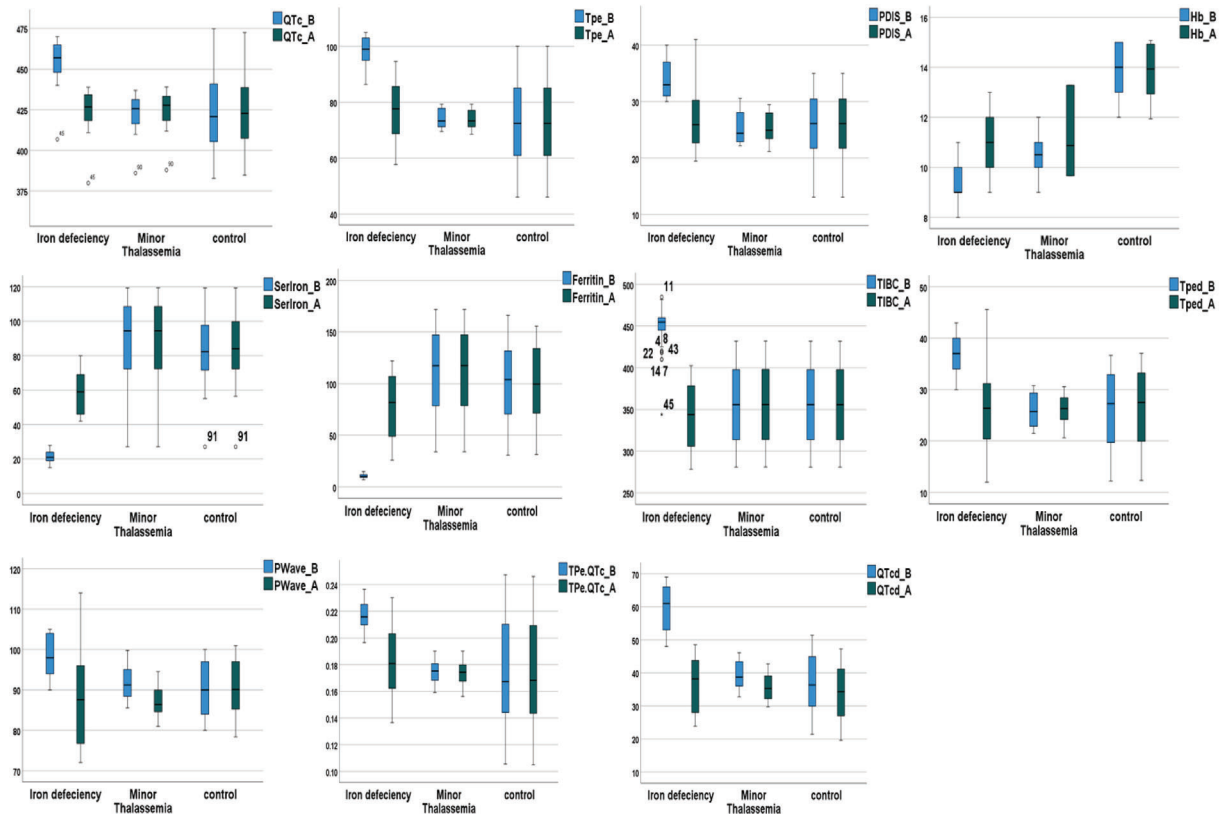
Figure 3 illustrated that prior to treatment, children with IDA had the lowest mean (SD) hemoglobin (HB)



**Fig. 1.** Schematic Representation of ECG Waves and Intervals (PR, QRS, ST, QT, and RR) on a Standard Electrocardiogram



**Fig. 2.** Measurement of the TPe Interval on a Standard Electrocardiogram (ECG) Trace



**Fig. 3.** Comparison of Hematological and Electrocardiographic Parameters in Iron Deficiency and Minor Thalassemia Before (B) and After Intervention/Time (A)

levels 9.27 (0.91), ferritin 10.38(2.12), and serum Iron 21.42 (3.63), alongside the highest TIBC 449.78 (25.12), compared to the minor thalassemia and control groups.

ECG parameters in the IDA group also showed marked abnormalities, including elevated QTc of 455.28 (11.57), QTcd of 59.60 (6.69), Tpe of 98.76 (4.57), Tped of 36.8 (3.95), P wave duration of 98.13 (5.29), PDIS 34.16(3.20), and Tpe/QTc ratio of 0.22 (0.01), suggesting greater electrical instability. After treatment, the IDA group showed significant improvement: HB rose to 11.12 (1.36), serum Iron increased to 58.98  $\mu\text{g/dL}$  (13.38), ferritin improved to 79.47 (31.93), and TIBC declined. Concurrently, ECG indices improved, with reductions in QTc of 425.14 (10.81), QTcd of 36.02 (7.75), Tpe of 77.11 (10.56), Tped of 26.19 (8.29), and Tpe/QTc of 0.18 (0.02). In contrast, the minor thalassemia and control groups showed stable hematological and ECG values across both time points.

Kruskal-Wallis test results between the three groups before treatment in the Table 1 showed significant differences ( $p < 0.001$ ) among the three groups of participants across all hematological and ECG parameters. The IDA group had the lowest mean ranks for hemoglobin (30.94), ferritin (23.00), and serum Iron (23.09), and the highest for TIBC (109.62), P wave (94.37), P wave dispersion (108.52), QTc (106.69), QTcd (112.42), Tpe (110.08),

Tpedb (108.20), and Tpe/QTc (105.31), reflecting more severe hematological deficits and cardiac electrical abnormalities. After treatment, while differences in hemoglobin, ferritin, and serum Iron remained significant ( $p < 0.001$ ), the IDA group's mean ranks notably improved (e.g., hemoglobin = 46.47), and TIBC no longer differed significantly ( $p = 0.220$ ), indicating recovery in Iron status. Importantly, all ECG parameters showed no significant differences post-treatment ( $p = 0.251-0.801$ ), suggesting that the cardiac electrical abnormalities observed in IDA children were largely resolved with therapy.

Table 2 showed that before treatment, children with IDA had significantly worse hematological and electrocardiographic parameters compared to both the MT and control groups. Hemoglobin levels differed across all three groups, with the most pronounced difference between IDA and control (Adj.  $p < 0.001$ ). Ferritin, serum Iron, and TIBC were significantly worse in the IDA group versus both MT and control (Adj.  $p < 0.001$ ), while no differences were found between MT and control. Similarly, all ECG parameters – including P wave, PDIS, QTc, QTcd, Tpe, Tpedb, and Tpe/QTc were significantly elevated in IDA compared to both MT and control (Adj.  $p < 0.001$ ), but not between MT and control (Adj.  $p = 0.281$  to 1.00), indicating a unique cardiac burden in IDA. After treatment, hemoglobin improved in the IDA group, as re-

flected by the lack of significant difference between IDA and MT (Adj.  $p = 0.609$ ), though IDA vs. control and MT vs. control remained significant (Adj.  $p < 0.001$ ). Ferritin and serum Iron remained significantly lower in the IDA group compared to both MT and control (Adj.  $p < 0.001$  to  $0.034$ ), while MT and control differences stayed non-significant. These findings highlight marked baseline impairments in IDA patients, with post-treatment recovery most evident in hemoglobin levels, while Iron stores and serum Iron remained suboptimal.

Table 3 showed that treatment led to markedly different responses between the IDA and MT groups. In the IDA group, Wilcoxon signed-rank analysis revealed strong and consistent improvements in all hematologic parameters, with significant increases in hemoglobin, ferritin, and serum Iron ( $Z = -6.09$  to  $-6.56$ ,  $p <$

$0.001$ ), and a significant reduction in TIBC ( $Z = -6.26$ ,  $p < 0.001$ ). Electrocardiographic parameters also improved significantly, including reductions in P wave duration, PDIS, QTc, QTcd, Tpe, Tped, and Tpe/QTc ratio ( $Z = -3.17$  to  $-6.56$ ,  $p \leq 0.002$ ), indicating enhanced cardiac conduction and reduced arrhythmogenic risk. In contrast, the MT group showed modest but significant hematologic gains ( $Z = -4.399$  to  $-5.841$ ,  $p < 0.001$ ), particularly in ferritin and serum Iron, while TIBC also declined favorably. However, ECG parameters in MT patients remained unchanged, with all  $p$ -values  $> 0.05$ , suggesting limited or no cardiac electrical impact. Overall, the IDA group exhibited both hematologic recovery and substantial ECG improvement post-treatment, while the MT group demonstrated hematologic gains without notable cardiac changes.

**Table 1. Comparison of hematological and electrocardiographic parameters among iron deficiency anemia, minor thalassemia, and control groups using the Kruskal-Wallis Test before and after**

Variables	Groups of participants	Before Treatment			After Treatment		
		Mean Rank	$\chi^2$	p value	Mean Rank	$\chi^2$	p
Hemoglobin	Iron deficiency	30.94	102.02	$< 0.001$	46.47	48.78	$< 0.001$
	Minor Thalassemia	60.50			56.93		
	control	112.56			100.60		
Ferritin	Iron deficiency	23.00	90.51	$< 0.001$	49.47	17.96	$< 0.001$
	Minor Thalassemia	94.80			84.18		
	control	86.20			70.36		
Serum Iron	Iron deficiency	23.09	91.65	$< 0.001$	33.76	54.14	$< 0.001$
	Minor Thalassemia	97.16			91.51		
	control	83.76			78.73		
TIBC	Iron deficiency	109.62	76.49	$< 0.001$	59.78	3.02	0.220
	Minor Thalassemia	47.84			72.96		
	control	46.53			71.27		
PWAVE	Iron deficiency	94.37	30.93	$< 0.001$	61.49	2.30	0.316
	Minor Thalassemia	56.74			73.97		
	control	52.89			68.54		
PDIS	Iron deficiency	108.52	73.17	$< 0.001$	73.29	1.28	0.527
	Minor Thalassemia	44.42			64.49		
	control	51.06			66.22		
QTC	Iron deficiency	106.69	66.04	$< 0.001$	70.44	0.49	0.783
	Minor Thalassemia	48.60			68.73		
	control	48.71			64.82		
QTcd	Iron deficiency	112.42	87.87	$< 0.001$	70.07	2.39	0.302
	Minor Thalassemia	49.42			73.09		
	control	42.16			60.84		
Tpe	Iron deficiency	110.08	78.19	$< 0.001$	75.36	2.66	0.265
	Minor Thalassemia	47.56			66.47		
	control	46.37			62.18		
Tpedb	Iron deficiency	108.20	71.81	$< 0.001$	69.98	0.44	0.801
	Minor Thalassemia	45.11			64.87		
	control	50.69			69.16		
Tpe / QTC	Iron deficiency	105.31	61.54	$< 0.001$	75.33	2.76	0.251
	Minor Thalassemia	47.91			66.91		
	control	50.78			61.76		

TIBC – Total Iron Binding Capacity, P-wave – duration from the beginning to the end of the P-wave, P wave d – maximum P-wave duration–minimum P-wave duration, QT interval – started from the onset of the Q wave to the end of the T wave, QTc – was calculated using Bazett's formula, QTd – Difference between the longest and shortest QT intervals, QTcd – maximum QTc interval–minimum QTc interval, Tpe interval – measured from the peak of the T wave (highest point) to the end of the T wave, Tped – maximum Tpe interval–minimum Tpe interval

**Table 2. Pairwise Comparisons of Hematological and Electrocardiographic Parameters Between Iron Deficiency Anemia, Minor Thalassemia, and Control Groups Before and After Treatment Using Dunn's Post Hoc Test**

Variables	Sample1-Sample2	Dunn Statistics	p value	Adj. p value
Before treatments				
Hemoglobin	IDA-MT	29.556	< 0.001	0.001
	IDA-Control	81.611	< 0.001	< 0.001
	MT-Control	52.056	< 0.001	< 0.001
Ferritin	IDA-MT	71.800	< 0.001	< 0.001
	IDA-Control	63.200	< 0.001	< 0.001
	MT-Control	8.600	0.297	0.890
Serum Iron	IDA-MT	74.67	< 0.001	< 0.001
	IDA-Control	60.667	< 0.001	< 0.001
	MT-Control	13.400	0.104	0.312
TIBC	IDA-MT	61.778	< 0.001	< 0.001
	IDA-Control	63.089	< 0.001	< 0.001
	MT-Control	1.311	0.874	1.00
PWAVE	IDA-MT	36.422	< 0.001	< 0.001
	IDA-Control	41.378	< 0.001	< 0.001
	MT-Control	4.956	0.548	1.00
PDIS	IDA-MT	64.100	< 0.001	< 0.001
	IDA-Control	57.467	< 0.001	< 0.001
	MT-Control	6.633	0.421	1.00
QTC	IDA-MT	59.267	< 0.001	< 0.001
	IDA-Control	58.067	< 0.001	< 0.001
	MT-Control	1.200	0.884	1.00
QTcd	IDA-MT	61.778	< 0.001	< 0.001
	IDA-Control	71.489	< 0.001	< 0.001
	MT-Control	9.711	0.238	0.716
Tpe	IDA-MT	62.522	< 0.001	< 0.001
	IDA-Control	63.711	< 0.001	< 0.001
	MT-Control	1.189	0.885	1.00
Tped	IDA-MT	63.089	< 0.001	< 0.001
	IDA-Control	57.511	< 0.001	< 0.001
	MT-Control	5.578	0.499	1.00
Tpe / QTc	IDA-MT	57.166	< 0.001	< 0.001
	IDA-Control	54.378	< 0.001	< 0.001
	MT-Control	2.778	0.736	1.00
After Treatments				
HB	IDA-MT	10.467	0.203	0.609
	IDA-Control	54.133	< 0.001	< 0.001
	MT-Control	43.667	< 0.001	< 0.001
Ferritin	IDA-MT	34.711	< 0.001	< 0.001
	IDA-Control	20.889	0.011	0.034
	MT-Control	12.822	0.094	0.281
Serum Iron	IDA-MT	57.756	< 0.001	< 0.001
	IDA-Control	44.978	< 0.001	< 0.001
	MT-Control	12.778	0.121	0.364

TIBC – Total Iron Binding Capacity, P-wave – duration from the beginning to the end of the P-wave, P wave d – maximum P-wave duration–minimum P-wave duration, QT interval – started from the onset of the Q wave to the end of the T wave, QTc – was calculated using Bazett's formula, QTd – Difference between the longest and shortest QT intervals, QTcd – maximum QTc interval–minimum QTc interval, Tpe interval – measured from the peak of the T wave (highest point) to the end of the T wave, Tped – maximum Tpe interval – minimum Tpe interval

**Table 3. Thalassemia: A Wilcoxon Signed-Rank Analysis**

Variables	changes	Iron Deficiency Anemia			Major thalassemia		
		N	Z	P	N	Z	P
HB	Negative	0	-6.09	< 0.001	10	-4.399	< 0.001
	Positive	39			35		
	Ties	6			0		
Ferritin	Negative	0	-6.56	< 0.001	0	-5.841	< 0.001
	Positive	45			45		
	Ties	0			0		
Serum Iron	Negative	0	-6.56	< 0.001	0	-5.842	< 0.001
	Positive	45			45		
	Ties	0			0		
TIBC	Negative	44	-6.26	< 0.001	0	-5.841	< 0.001
	Positive	1			45		
	Ties	0			0		
PWAVE	Negative	33	-3.17	0.002	20	-0.863	0.388
	Positive	11			18		
	Ties	1			7		
PDIS	Negative	41	-5.37	< 0.001	28	-0.073	0.942
	Positive	4			17		
	Ties	0			0		
QTC	Negative	45	-6.56	< 0.001	15	-1.884	0.060
	Positive	0			10		
	Ties	0			20		
QTcd	Negative	45	-6.56	< 0.001	20	-1.867	0.062
	Positive	0			15		
	Ties	0			10		
TPe	Negative	45	-6.56	< 0.001	2	-0.271	0.786
	Positive	0			3		
	Ties	0			40		
Tped	Negative	42	-5.66	< 0.001	21	-0.231	0.817
	Positive	3			24		
	Ties	0			0		
TPe./ QTC	Negative	45	-6.56	< 0.001	11	-1.706	0.088
	Positive	0			16		
	Ties	0			18		

TIBC – Total Iron Binding Capacity, P-wave – duration from the beginning to the end of the P-wave, P wave d – maximum P-wave duration–minimum P-wave duration, QT interval – started from the onset of the Q wave to the end of the T wave, QTc – was calculated using Bazett's formula ,QTd – Difference between the longest and shortest QT intervals ,QTcd – maximum QTc interval – minimum QTc interval, TPe interval – measured from the peak of the T wave (highest point) to the end of the T wave, Tped – maximum Tpe interval–minimum Tpe interval

## DISCUSSION

The study explored electrocardiographic (ECG) alterations in children with iron deficiency anemia (IDA) and thalassemia minor (MT) compared to healthy controls, assessing changes before and after treatment. Significant differences were observed in both hematological and ECG parameters, especially among untreated IDA patients, highlighting the broader cardiovascular effects of anemia. IDA, the most prevalent nutritional deficiency globally, can cause myocardial hypoxia and altered ventricular repolar-

ization, which may normalize after Iron supplementation [11]. In contrast, MT, a genetic condition, typically presents with milder and less reversible ECG changes managed through regular monitoring and folic acid supplementation. Previous studies have shown that parameters like P wave dispersion, QTd, and Tpe interval can serve as predictors of atrial and ventricular arrhythmias in anemic patients, linking anemia severity to electrical instability of the heart [10, 12].

In children, Iron deficiency impairs hemoglobin synthesis, leading to systemic hypoxia. This hypoxia exerts stress on the cardiovascular system, manifest-

ing through sympathetic nervous system activation, increased cardiac output, and subsequent electrophysiological alterations detectable on ECG [13, 14].

Patil et al. [15], and Kumar et al. [10] emphasized that hypoxia from chronic anemia enhances sympathetic drive, which can lead to changes in ventricular repolarization such as QT prolongation, T-wave inversion, and reduced QRS voltage. Our study corroborated these physiological mechanisms. Children with untreated IDA demonstrated statistically significant prolongation of the QTc interval, QTcd, and Tpe, as well as increased Tpe/QTc ratio and P wave dispersion (PDIS). These parameters reflect increased heterogeneity in atrial and ventricular repolarization and are known to predict a higher risk of arrhythmias. Kumar et al. [10] similarly reported that lower hemoglobin levels were associated with more pronounced ECG changes, particularly in patients with cardiomegaly or increased cardiothoracic ratios. The association between systemic hypoxia and repolarization heterogeneity highlights the potential arrhythmogenic risk in pediatric IDA, even in the absence of overt cardiac pathology.

Biochemically, our IDA cohort exhibited significantly reduced levels of hemoglobin, ferritin, and serum Iron, alongside elevated TIBC, consistent with a classic profile of Iron depletion. Bouri et al. [16] highlighted TIBC as a sensitive marker reflecting the body's attempt to enhance Iron transport under deficient states, thereby reconfirming our findings. Importantly, our post-treatment analysis revealed notable improvements in both hematological and ECG parameters in the IDA group. In this regard, QTc and QTcd values normalized significantly, as did indices like Tpe and Tpe/QTc ratio. These results support the reversibility of electrophysiological alterations following Iron repletion.

Savarese et al. [17], Singer et al. [18], and Moscheo et al. [13] have all emphasized that correction of Iron deficiency not only restores hematologic values but also stabilizes myocardial electrophysiology. Notably, Findikli and Tutak [19] and Kwon et al. [20] observed that children with the lowest baseline ferritin and hemoglobin levels exhibited the most significant ECG abnormalities and demonstrated the most marked improvements following Iron therapy. These findings align closely with our observations and suggest that early detection and prompt treatment are crucial in preventing potential long-term cardiac remodeling. Furthermore, our findings reinforce the argument by Triphaus et al. [21] who stressed that maintaining adequate hemoglobin levels is essential for optimal myocardial oxygenation and electrical stability. The improvement seen in dispersion indices following treatment underscores the value of integrating cardiovascular monitoring in the routine care of pediatric IDA patients.

Falahati et al. [22] also advocated for the use of bioavailable Iron formulations like ferrous gluconate to ac-

celerate recovery, which is relevant in the context of clinical decision-making regarding Iron supplementation. Thalassemia minor, characterized by chronic microcytic hypochromic anemia due to defective  $\beta$ -globin synthesis, is generally considered a clinically benign condition [23]. Our study supports this understanding, showing that although hemoglobin levels were significantly lower in thalassemia minor children compared to healthy controls, serum Iron, ferritin, and TIBC did not differ significantly, indicating that anemia in thalassemia minor is genetically mediated rather than driven by Iron deficiency [24]. Correspondingly, pre-treatment ECG parameters including QTc, QTcd, Tpe, Tped, and PDIS showed no significant differences between MT patients and healthy controls, suggesting no increased risk of repolarization abnormalities or arrhythmogenicity in this population.

Kolios et al. [25] conducted a study on the EKG abnormalities and arrhythmic risk markers in adult patients with beta thalassemia major and found that the majority of patients, had prolonged QT and QTc intervals, as well as increased QTd and QTcd despite the absence of overt systolic dysfunction. Akarsu et al. [26] reported that MT patients exhibited electrocardiographic changes similar to those in IDA, especially in QT and QTc intervals, despite normal Iron levels. This suggests that factors beyond Iron deficiency, such as genetic or structural influences, may affect cardiac repolarization in MT. Elevated QT dispersion in MT further indicates subtle ventricular repolarization disturbances, even in clinically mild anemia, challenging the notion that MT is entirely electrophysiologically benign and implying that cardiac monitoring might be warranted in some cases. Similarly, Karadeniz et al. [9] reported that otherwise healthy children with low serum ferritin ( $<15$  ng/mL) showed significantly increased P wave duration, QT and Tpe intervals, as well as increased dispersions of PW, QT, QTc, and Tpe compared to children with higher ferritin levels. These findings underscore that low Iron stores, even without overt anemia, are associated with changes in ECG parameters that reflect ventricular repolarization heterogeneity and may increase arrhythmia risk. Given these distinctions, routine ECG screening appears particularly important in children with IDA especially in moderate to severe cases or when treatment is delayed while in children with thalassemia trait, cardiovascular surveillance may be best reserved for those with additional risk factors or clinical symptoms. Future studies with larger cohorts and extended follow-up are needed to clarify any potential long-term cardiac risks associated with Beta Thalassemia Trait and to investigate the influence of specific genetic variants on cardiac outcomes.

## STUDY LIMITATIONS

The main limitation of this study was the relatively small sample size, which may have limited the ability to

detect subtle or rare ECG abnormalities and reduced the generalizability of the findings to the broader pediatric population.

## CONCLUSION

From the study, it was concluded that children with Iron Deficiency Anemia (IDA) and Minor Thalassemia (MT) had significant differences in both hematological and electrocardiographic parameters compared with healthy children before treatment. Children with IDA had markedly lower hemoglobin, ferritin, and serum iron levels, along with prolonged QT, QTc, QTcd, Tpe, and P wave durations, reflecting early alterations in cardiac electrical activity due to chronic anemia. Children with MT also showed some hematological and ECG abnormalities, but these were generally less pronounced than in the IDA group. After treatment, children with IDA demonstrated significant improvements in blood indices and normalization of most ECG parameters, indicating that correction of iron deficiency effectively reversed both biochemical and cardiac electrical disturbances. In contrast, children with MT showed smaller hematological improvements and minimal changes in ECG parameters, consistent with the genetic nature of their condition and the limited effect of supportive treatments such as folic acid. Overall, the study concluded that iron deficiency had reversible effects on cardiac function, whereas MT produced subtler, largely persistent ECG changes, highlighting the importance of early detection and treatment of IDA to prevent potential cardiovascular complications.

**Acknowledgements:** The Authors would like to express their sincere gratitude to the participants and their parents who consented to participate in our research.

**Conflicts of interest:** The authors declare that there are no conflicts of interest regarding the publication of this study. All authors affirm that they have no affiliations, financial interests.

## References

1. Ansari MY, Qaraqe M, Charafeddine F et al. Estimating age and gender from electrocardiogram signals: a comprehensive review of the past decade. *Artificial Intelligence in Medicine*. 2023;146:102690.
2. Chaparro CM, Suchdev PS. Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries. *Ann N Y Acad Sci*. 2019;1450(1):15-31. doi:10.1111/nyas.14092.
3. Aksu T, Ünal Ş. Iron Deficiency Anemia in Infancy, Childhood, and Adolescence. *Turk Arch Pediatr*. 2023;58(4):358-362. doi:10.5152/TurkArchPediatr.2023.23049.
4. Obeagu EI. Iron homeostasis and health: understanding its role beyond blood health - a narrative review. *Ann Med Surg (Lond)*. 2025 ;87(6):3362-3371. doi: 10.1097/MS9.0000000000003100.
5. Ceasovschi A, Şorodoc V, Covantsev S et al. Electrocardiogram Features in Non-Cardiac Diseases: From Mechanisms to Practical Aspects. *J Multidiscip Healthc*. 2024;17:1695-1719. doi:10.2147/JMDH.S445549.
6. Sadiq IZ, Abubakar FS, Usman HS et al. Thalassemia: Pathophysiology, Diagnosis, and Advances in Treatment. *Thalassemia Reports*. 2024; 14(4):81-102. <https://doi.org/10.3390/thalass-rep14040010>
7. Akiki N, Hodroj MH, Bou-Fakhredin R et al. Cardiovascular Complications in  $\beta$ -Thalassemia: Getting to the Heart of It. *Thalassemia Reports*. 2023; 13(1):38-50. <https://doi.org/10.3390/thalass-rep13010005>
8. Zhou Y, Cao Y, Fang Z et al. Research on the clinical factors of cardiac Iron deposition in children with beta-thalassemia major. *Eur J Pediatr*. 2024;183(2):875-882. doi:10.1007/s00431-023-05300-w.
9. Karadeniz C, Özdemir R, Demiroglu M et al. Low Iron stores in otherwise healthy children affect electrocardiographic markers of important cardiac events. *Pediatric cardiology*. 2017;38:909-14
10. Kumar N, Gupta SK, Singh RK. Electrocardiographic Changes in Anemic Patients: Diagnostic Value and Correlation with Hematological Severity. *Eur J Cardiovasc Med*. 2025;15:664-9.
11. Pantopoulos K. Oral Iron supplementation: new formulations, old questions. *Haematologica*. 2024 ;109(9):2790-2801. doi:10.3324/haematol.2024.284967.
12. Ghandi Y, Ghahremani B, Habibi D et al. Assessment of transmural dispersion of repolarization in children with mitral valve prolapse. *J Tehran Heart Cent* 2020;15(2):64-8.
13. Martens P. The effect of iron deficiency on cardiac function and structure in heart failure with reduced ejection fraction. *Cardiac Failure Review*. 2022;8:e06.
14. Moscheo C, Licciardello M, Samperi P et al. New insights into Iron deficiency anemia in children: a practical review. *Metabolites* 2022;12(4):289.
15. Patil SV, Kshirsagar NS, Mohite RV. Nutritional anemia: prevalence, causes, and interventions in the pediatric population. *Obstet Gynecol Forum*. 2024;34(3).
16. Bouri S, Martin J. Investigation of Iron deficiency anaemia. *Clin Med (Lond)*. 2018;18(3):242-4.
17. Savarese G, von Haehling S, Butler J et al. Iron deficiency and cardiovascular disease. *Eur Heart J*. 2023;44(1):14-27.
18. Singer CE, Vasile CM, Popescu M et al. Role of Iron deficiency in heart failure: clinical and treatment approach: an overview. *Diagnostics (Basel)*. 2023;13(2):304.
19. Fındıklı HA, Tutak AS. Evaluation of the platelet indices in patients with subclinical hypothyroidism. *Arch Clin Biomed Res*. 2018;2(6):227-32.
20. Kwon JM, Cho Y, Jeon KH et al. A deep learning algorithm to detect anaemia with ECGs: a retrospective, multicentre study. *Lancet Digit Health*. 2020;2(7).
21. Triphaus C, Judd L, Glaser P et al. Effectiveness of pre-operative Iron supplementation in major surgical patients with Iron deficiency: a prospective observational study. *Ann Surg*. 2021;274(3).
22. Falahati V, Ghasemi A, Ghaffari K et al. Comparison of the effect of ferrous sulfate and ferrous gluconate on prophylaxis of Iron deficiency in toddlers 6-24 months old: a randomized clinical trial. *J Educ Health Promot*. 2022;11:368.
23. Noori NM, Mahjoubifard M, Mohammadi M et al. Comparison of QT dispersion with left ventricular mass index in early diagnosis of cardiac dysfunction in patients with  $\beta$ -thalassemia major. *Iran Red Crescent Med J* 2014; 16: e11698.
24. Ahmadpanah M, Asadi Y, Haghghi M et al. In Patients with Minor Beta-Thalassemia, Cognitive Performance Is Related to Length of Education, But Not to Minor Beta-Thalassemia or Hemoglobin Levels. *Iran J Psychiatry*. 2019;14(1):47-53.
25. Kolios G, Korantzopoulos P, Vlahos AP et al. Electrocardiographic abnormalities and arrhythmic risk markers in adult patients with beta thalassemia major. *Int J Cardiol* 2016; 221: 932-6.
26. Akarsu S, Kasar T, Yilmaz E.  $\beta$ -Talasemi Taşıyıcılarında Ventriküler Depolarizasyon ve Repolarizasyon Farklı mıdır? *Fırat Tıp Dergisi/Fırat Med J* 2022; 27(1): 6-10.