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ORIGINAL ARTICLE

# Study of Serum Levels of Melatonin in Children with Congenital Heart Disease Suffering From Heart Failure

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## ABSTRACT

**Background:** Melatonin has been shown to reduce hypertension, protect the ischemic/reperfused heart and decelerate the process of atherosclerosis but the effects of melatonin levels in children with congenital heart disease suffering from heart failure (HF) are not well understood. This study aimed to assess outcome of serum levels of melatonin in children with congenital heart disease suffering from heart failure. **Methods:**This case-control study was conducted at Pediatric Department, Faculty of Medicine, Zagazig University on 40 patients. Case group included children with congenital heart disease suffering from HF; control group of apparently healthy children matched by age & sex. Patients with ROSS score of >2 points were included in the study and divided into three groups according to severity of heart failure: mild (score:3-6), moderate (score:7-9), and severe (score: 10-12). **Results:** children with congestive heart failure had significantly higher serum melatonin level than control children. Receiver operating characteristic (ROC) curve analysis revealed that serum melatonin can differentiate between children with Congestive heart failure (CHF) and healthy controls with an area under the curve (AUC) of 1.0 for serum melatonin with an excellent discrimination ability with optimal sensitivity, specificity, and positive predictive value. **Conclusions:**SerumA melatonin levels play a protective role in children with severe heart failure. It is likely that increasing melatonin levels may act as a compensatory mechanism in pediatric children with CHD with heart failure. We concluded that serum melatonin is a potential prognostic and excellent diagnostic biomarker in children with CHF.

**Keywords :**Melatonin, Congenital Heart Disease, Heart Failure.

## INTRODUCTION

The most prevalent congenital defect, congenital heart disease (CHD), affects 1.35 million newborns worldwide each year. More than 25% of people with deformed hearts have palliative or corrective surgery, which can lead to problems, and those with complicated CHD need lifetime care **[1]**.

It has been noted that there are issues with learning, focus, and stamina, as well as negative body image and inadequate sociability. Up to 90% of children with congenital heart disease now survive into adulthood thanks to recent improvements in medical care. But this also highlights the need to comprehend the growing health concerns that young adult patients are expressing about

the heredity of CHD and how it affects long-term objectives **[2]**.

Most patients born with a congenital heart defect will live to adulthood because of the significant advancements made in cardiothoracic surgery, paediatric cardiology, and critical care medicine in the last several decades. An estimated 1 million adults with CHD, or a frequency of 3 per 1000, lived in the European Union in 2014. This particular patient population has a high rate of morbidity and mortality, which will significantly affect how care is organized and how much it costs **[3]**.

Patients with congestive heart failure may have a variety of contributing causes. Cardiac function may be compromised by valvar abnormalities, shunt lesions, inflow or outflow tract obstruction, arrhythmia, persistent structural defects, aberrant loading conditions, or cyanosis. Myocardial fibrosis, unfavourableremodelling, and subsequent neurohumoral activation will cause a steady decline in cardiac function and the heart failure clinical syndrome **[4].**

Heart failure (HF) is becoming more common in patients with congestive heart failure (CHD); it is a growing strain on healthcare systems and death rates, particularly in young children. As a result, a deeper comprehension of the most effective methods for assessing and handling HF is needed. While improvements in adult HF diagnosis and therapy have been made, pediatric HF patients do not have the same level of awareness **[5].**

The effects of melatonin (N-acetyL-5-methoxytryptamine), a secretory product of the human pineal gland, on the cardiovascular system are widely recognized. Melatonin protects the heart in two ways: through receptor-mediated processes and through receptor-independent mechanisms **[6]**. Hemodynamic stress, free radicals, nitric oxide (NO) availability, and lipid profiles are all impacted by melatonin, which may also change the hypertrophy of cardiomyocytes. This study aimedto assess outcome of serum levels of melatonin in children with congenital heart disease suffering from heart failure**.**

## SUBJECTS AND METHODS

This case-control study was conducted at Pediatric Department, Faculty of Medicine, Zagazig University on 40 patients with congenital heart disease suffering from HF; during the period from January to December2022. Written informed consent was obtained from all relatives of participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University (ZU-IRB). The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

**Inclusion criteria** weremale and female, age from 2 months 6 years and pediatric patient with congenital heart disease cyanotic or acyanotic suffering from heart failure.Any patients with other causes of heart failure,age less than 2 months or more than 6 years and heart failure due to other causes rather than CHD were excluded.

The study participants are classified into two groups: Study group;which consisted of 30

pediatric patients with congenital heart disease (with heart failure), selected randomly from cardiology department, Zagazig University Hospitals, they are 18 male and 12 female, their age ranged from 2 months to 6 years. They were subdivided into three subgroups according to the severity of the heart failure depending on the ROSS classification. **Control group;**that included 10 children apparently healthy selected from outpatient clinic, Pediatric Department Zagazig University Hospitals properly matched with study group in age and sex.

All participants were subjected to full history taking included age, sex, gestational age, birth height, birth weight and order. General examination to detect pallor, cyanosis, orthopnea, abnormal movements, clubbing, pulse and blood pressure were done. Anthropometric measurements including weight and height with plotting them in to the standard growth charts was measured. Local cardiac examination to detect Pericardial bulge, cardiac pulsations, scar of previous operation, thrills, dullness and auscultation of the heart sounds and murmurs. Other system examination includes abdomen (hepatomegaly) and chest. Severity of HF according to Modified Ross's Clinical score for diagnosis of HF in pediatric cardiac patients was assessed.

Investigations included Complete blood count (hemoglobin percentage, hematocrit value, white blood cells count and platelets count). (Fyfnex-K-21), Liver function tests (SGPT, SGOT) (Cobas-6000) and Kidney function tests (Serum Urea and creatinine) (Cobas-6000). Measurement of plasma melatonin by enzyme-linked immunosorbent assay (ELISA).

**Melatonin test principle**

The kit uses a double- antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Human Melatonin (MT) in samples. Add Melatonin in (MT) to monoclonal antibody enzyme well which is precoated with human melatonin (MT) monoclonal antibody, incubation; then, add melatonin (MT) antibodies labled with biotin, and combined with streptavidin- HRP to form immune complex; then carry out incubation and washing again to remove the uncombined enzyme. Then add chromogen solution A, B, the color of the liquid changes into the blue, and at the effect of acid, the color finally becomes yellow. The chroma of color and the concentration of the human substance melatonin (MT) of sample were positively correlated.

Radiological investigations plain X-ray chest P-A view was done.

**Electrocardiogram (ECG)**:

Commonly, 10 electrodes attached to the body were used to form 12 ECG leads, with each lead measuring a specific electrical potential difference. Transthoracic complete M-mode, two-dimensional echocardiography was done in supine position for all patients and healthy individuals. Transthoracic examination was performed in the parasternal log – axis view, left ventricular end – systolic (LVES) and left ventricular end diastolic (LVED) dimensions were measured to all enrolled patients. Ejection fraction (EF) and fractional shortening (ES) of the left ventricle were estimated.

## STATISTICAL ANALYSIS

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded and entered. Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 26. Independent samples t-test, Mann-Whitney U test, Fisher's Exact Test, ANOVA, Welch's one way ANOVA test, Kruskal-Wallis H test (nonparametric alternative to the one-way ANOVA. Dunn's multiple comparison tests, Pearson's correlation and A receiver operating characteristic (ROC) curve. The level statistical significance was set at $P < 0.05$. Highly significant difference was present if $P \leq 0.001$.

## RESULTS

Table 1; showed that no significant differences were found in age and gender distribution between children with congestive heart failure than control children ($P>0.05$). No significant difference in proportion of immunization among the studied children ($P=0.56$). However, proportion of children with a poor nutrition status and motor delay are significantly higher in children with CHF than normal children ($P<0.001$, each).

Mean heart rate ($P=0.012$) and respiratory rate ($P<0.01$) were significantly higher in in children with congestive heart failure than control children. Compared to control children, children with CHF had significantly higher WBCs ($P=0.018$) and significantly lower hematocrit ($P=0.006$). While other laboratory findings were not significantly different between controls and children with CHF (table 2).

Table 3; Children with congestive heart failure has significantly higher serum melatonin level than control children ($P<0.001$).

Table 4; Almost all of children of CHF had combined cardiac lesions. Pulmonary hypertension represents the highest proportion among the three categories.

Table 5; showed that there were statistically significant differences in proportions of feeding problems ($P=0.011$) and excessive sweating ($P=0.03$) among children with congestive heart failure stratified according to modified ROSS classification. While proportion of cyanosis and family history of CHF were similar between these children ($P>0.99$ and $P=0.3$, respectively).

Table 6; showed that there were no statistically significant differences in anthropometric measurements of children with congestive heart failure stratified according to modified ROSS classification ($P>0.05$).Liver and kidney functions findings were not significantly different among children with congestive heart failure stratified according to modified ROSS classification ($P>0.05$). Serum melatonin level was significantly different among children with serum melatonin level stratified according to modified ROSS classification ($P=0.038$).

Table 7; showed that there were significant negative correlation between age and serum melatonin level was noted ($P=0.003$). While significant positive correlations between heart rate ($P=0.007$), respiratory rate ($P=0.003$), AST enzyme

activity (*P*=0.005), and serum melatonin levels. While no significant correlations between other parameters and serum melatonin levels in children with congestive heart failure stratified according to modified ROSS classification (*P*>0.05).

**Table (1):**Baseline characteristics, Immunization, nutritional status, and motor development of the studied children of the studied children

| Baseline characteristics | Controls n=10 | Cases n=30 | Test of significance | P-value |
|---|---|---|---|---|
| **Age (months)** | | | Mann-Whitney U test (Z)=1.01 | 0.32 |
| median(range) | 37(5-48) | 20(2-72) | | |
| **Gender**, n(%) | | | Fisher's exact test | >0.99 |
| Girls | 4(40) | 12(40) | | |
| Boys | 6(60) | 18(60) | | |
| **Immunization,*n*(%)** | | | Fisher's exact test | 0.56 |
| **No delay** | 10(100) | 26 (86.7) | | |
| **Delay** | 0(0) | 4(13.3) | | |
| **Nutritional status,*n*(%)** | | | Fisher's exact test | **<0.001** |
| **Poor** | 0(0) | 27 (90) | | |
| **Good** | 10(100) | 3(10) | | |
| **Motor development, *n*(%)** | | | Fisher's exact test | **<0.001** |
| **No delay** | 10(100) | 10(33.33) | | |
| **Delay** | 0(0) | 20(66.67) | | |

**Table (2):**Vital signsand Complete blood countof the studied children

| Vital signs | Controls n=10 | Cases n=30 | Test of significance | P-value |
|---|---|---|---|---|
| **Heart rate (beat/min)** | | | Independent samples t-test=2.7 | **0.012** |
| **mean±SD** | 101±12 | 118±25 | | |
| **Respiratory rate (cycle/min)** | | | Independent samples t-test=4.7 | **<0.001** |
| **mean±SD** | 29±5 | 40±10 | | |
| **WBCs ($\times10^3$ /$mm^3$)** | | | Independent samples t-test=2.5 | **0.018** |
| **mean±SD** | 10.8±2.4 | 13.5±4.3 | | |
| **RBCs ($\times10^6$/$mm^3$)** | | | Independent samples t-test=0.9 | 0.4 |
| **mean±SD** | 4.1±0.4 | 4.3±0.9 | | |
| **Hemoglobin (g/dL)** | | | Independent samples t-test=1.3 | 0.21 |
| **mean±SD** | 11.3±0.9 | 10.7±1.5 | | |
| **Hematocrit (%)** | | | Independent samples t-test=2.9 | **0.006** |
| **mean±SD** | 35.3 ±4.6 | 31.5 ±3.1 | | |
| **MCV (fL)** | | | Independent samples t-test=0.12 | 0.91 |
| **mean±SD** | 78.3±6.2 | 78.6±7.2 | | |

| Vital signs | Controls | Cases | Test of significance | P-value |
|---|---|---|---|---|
| | n=10 | n=30 | | |
| **Platelet Count ($\times10^3/mm^3$)** | | | Independent samples t-test=٠.33 | 0.74 |
| **mean±SD** | 299.8±106.4 | 287.6±96.3 | | |

**CBC:** Complete Blood count, **RBCs:** Red Blood Cells Count, **MCV:** Mean corpuscular volume.

**Table (3):**Serum melatonin level in the studied children

| Serum melatonin level (Pg/dL) | Controls | Cases | Test of significance | P-value |
|---|---|---|---|---|
| | n=10 | n=30 | | |
| | | | Mann-Whitney U test (Z)=4.7 | **<0.001** |
| **median(range)** | 9.2(13.64-23.15) | 46.8(24.1-69.3) | | |

**Table (4):** Etiology of congenital heart disease among children with congestive heart failure stratified according to modified ROSS classification

| Etiology of congenital heart disease, n(%) | Congestive heart failure | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| | n=10 | n=10 | n=10 |
| **Cyanotic** | | | |
| Pulmonary atresia | 1(10) | 1(10) | 0(0) |
| Tetralogy of Fallot | 0(0) | 1(10) | 1(10) |
| Ebstein anomaly | 1(10) | 0(0) | 0(0) |
| Transposition of great arteries | 0(0) | 0(0) | 1(10) |
| **Non-cyanotic** | | | |
| Ventricular septal defect | 3(30) | 4(40) | 5(50) |
| Atrial septal defect | 3(30) | 2(20) | 3(30) |
| Patent ductusarteriosus | 2(20) | 0(0) | 1(10) |
| Coarctation of aorta | 1(10) | 0(0) | 1(10) |
| Atrioventricularseptal defect | 1(10) | 2(20) | 2(20) |
| Dextrocardia | 0(0) | 1(10) | 0(0) |
| Aortic regurge | 0(0) | 1(10) | 2(20) |
| Pulmonary regurge | 0(0) | 0(0) | 1(10) |
| Mitral stenosis | 1(10) | 1(10) | 2(20) |
| Pulmonary hypertension | 4(40) | 5(50) | 8(80) |

**Table (5):**Medical history and early clinical presentation of children with congestive heart failure stratified according to modified ROSS classification

| Medical history/Early clinical presentations | Congestive heart failure | | | Test of significance† | P-value |
|---|---|---|---|---|---|
| | Mild | Moderate | Severe | | |
| | n=10 | n=10 | n=10 | | |
| **Cyanosis,*n*(%)** | | | | 0.23 | >0.99 |
| No | 8(80) | 8(80) | 8(80) | | |
| Yes | 2(20) | 2(20) | 2(20) | | |
| **Feeding problems,*n*(%)** | | | | 8.9 | **0.011** |
| No | 6(60) | 2(20) | 0(0) | | |
| Yes | 4(40) | 8(20) | 10(10) | | |
| **Excessive sweating,*n*(%)** | | | | | |
| No | 7(70) | 6(60) | 0(0) | 12.6 | **0.03** |
| Yes | 3(30) | 4(40) | 10(100) | | |
| **Family history of CHF,*n*(%)** | | | | 3.2 | 0.30 |
| No | 9(90) | 9(90) | 6(60) | | |
| Yes | 1(10) | 1(10) | 4(40) | | |

Fisher's exact test (R× C), bold values indicate statistically significant differences at $P<0.05$.

**Table (6):**Anthropometric measurements, Laboratory findings and Serum melatonin levelof children with congestive heart failure stratified according to modified ROSS classificationof children with congestive heart failure stratified according to modified ROSS classification.

| | Congestive heart failure | | | Test of significance | P-value |
|---|---|---|---|---|---|
| | Mild | Moderate | Severe | | |
| | n=10 | n=10 | n=10 | | |
| **Anthropometric measurements** | | | | ANOVA $F$=0.053 | 0.95 |
| **Body weight (kg)** | | | | | |
| mean±SD | 11.3±5.8 | 10.7±2.8 | 10.9±3.7 | | |
| **Height (cm)** | | | | ANOVA $F$=0.14 | 0.87 |
| mean±SD | 79.2±21.5 | 83±13.6 | 82.8±19.0 | | |
| **Liver function test** | | | | ANOVA $F$ =0.063 | 0.94 |
| ALT (IU/L) | | | | | |
| mean±SD | 24.5±8.4 | 23.2±8.7 | 23.2 ±10.2 | | |
| AST (IU/L) | | | | ANOVA $F$ =2.6 | 0.096 |
| mean±SD | 25.2±8.5 | 22.2±10.2 | 30.7±6.6 | | |
| Kidney function test | | | | Kruskal Wallis H test=1.4 | 0.49 |
| Serum creatinine (mg/dL) | | | | | |
| median(range) | 0.3(0.1-0.9) | 0.22(0.11-0.56) | 0.33(0.17-0.6) | | |
| Blood urea (mg/dL) | | | | Kruskal | 0.42 |

| | Congestive heart failure | | | Test of significance | P-value |
|---|---|---|---|---|---|
| | Mild | Moderate | Severe | | |
| | n=10 | n=10 | n=10 | | |
| median(range) | 12.05(5.6-57) | 20.3(8.5-39.70) | 14.9(7.40-37) | Wallis H test=1.7 | |
| **Serum melatonin level (Pg/dL)** | | | | Kruskal Wallis H test=6.5 | **0.038** |
| median(range) | 29.9(24.1-66.7) | 46.8(24.9-64.6) | 62.4(27.1-69.3) | | |

**Table (7):**Correlation between serum melatonin levels and other relevant parameters of children with congestive heart failure stratified according to modified ROSS classification

| | Serum melatonin levels (pg/dL) | |
|---|---|---|
| | Pearson correlation coefficient (r) | P-value |
| Age (months) | -.522 | 0.003 |
| Weight (kg) | -.183 | 0.33 |
| Height (cm) | -.012 | 0.95 |
| Heart rate (ppm) | .479 | 0.007 |
| Respiratory rate (cycle/min) | .526 | 0.003 |
| WBCs ($\times 10^3$ /$mm^3$) | -.053 | 0.78 |
| RBCs ($\times 10^6$/$mm^3$) | -.117 | 0.54 |
| Hemoglobin (g/dL) | .027 | 0.89 |
| Hematocrit (%) | .086 | 0.65 |
| MCV (fL) | .068 | 0.72 |
| Platelet Count ($\times 10^3$ /$mm^3$) | .127 | 0.51 |
| AST (IU/L) | .496 | 0.005 |
| ALT (IU/L) | .213 | 0.26 |
| Serum creatinine (mg/dL) | .256 | 0.17 |
| Blood urea (mg/dL) | -.222 | 0.24 |
| EF% | -.107 | 0.57 |
| FS% | -.219 | 0.24 |

EF%: Ejection Fraction, FS%: Fractional shortening
Bold values indicate statistically significant differences at P<0.05.

## DISCUSSION

A structural anomaly of the heart and major vessels that exists from birth is known as congenital heart disease (CHD). At ≈1% of all live births, it is the most prevalent birth defect. Heart failure arises from disruption of the regular heart development routine. A combination of final anatomical and physiological characteristics has been used to classify CHD **[8].**

Although hemodynamic management of CHD has improved Significant cardiac and extracardiac co-morbidities negatively impact the quality of life for a large number of CHD patients. Individuals with palliated or corrected congenital heart disease (CHD) are susceptible to arrhythmias and heart failure. The associated neuro-developmental deficits (NDD) may have the biggest influence on the quality of life for people with congestive heart failure (CHD)**[9].**

An independent hereditary component

is present, even though the increased prevalence of HF in CHD is generally thought to come from a volume or pressure overload, whereby the starting point is a defective heart. This second pathway outlines a purely genetic component, independent of hemodynamic Stress that results in both cardiac deformity and a cardiomyopathy that leads to heart failure. Hinton clarified that many of the mechanisms linked to the development of the heart in utero are also involved in the structure and stability of the heart **[4].**

The function of melatonin (N-acetyl-5-methoxytryptamine) in human health and disease has garnered significant attention in the field of cardiovascular research. Hoseini and associates demonstrated that it carries out its typical role as an endogenous synchronizer, or chronobiotic, regulating circadian and seasonal cycles and fostering sleep. As a multifunctional chemical, it also possesses numerous biological activities, such as antioxidant, anti-inflammatory, anti-excitatory, immune-modulator, vasomotor, and metabolic qualities[10]. Endogenous melatonin has a significant role in a number of metabolic and cardiovascular conditions that may exacerbate heart failure **[10]**.

This study composed of 30 patients with different types of CHD with cyanotic or non cyanoyic disease all complicated with heart failure and also 10 healthy controls of the same age to assess outcome of serum levels of melatonin in children with congenital heart disease suffering from heart failure.

Regarding the demographic data of our studied patients, the majority were males with median age 37 months among controls and 20 months among cases. No significant differences were found in age and gender distribution between children with congestive heart failure than control children.No significant difference in proportion of immunization among the studied childrenwas also found. However, proportion of children with a poor nutrition status and motor delay are significantly higher in children with CHF than normal children.No significant differences in proportions of nutritional status and motor development of children with congestive heart failure stratified according to modified ROSS classification.

The demographic information from a recent Wu research that was comparable to ours was in agreement. The median age of children with heart failure was 0.5 years, and the majority were male (interquartile range 0.31- 116 11.33 years) with 31 patients aged less than 1 year (66%), 7 patients between 1 to 3 years (15%), 1 patient between 4 to 7 years (2%) and 8 patients 117 aged > 8 years (17%) **[11].**

The mean heart rate and respiratory rate of the children with congestive heart failure we evaluated were found to be considerably greater than those of the control group.

Contrary to our results, mean heart rate and respiratory rate were within high normal limits in the results of **Wu and Yi[11],** on the other hand, the body weight and height were lesser in children with congestive heart failure and these findings came to be in agreement with us**.**

Compared to control children in our study, children with CHF had significantly higher WBCs and significantly lower haematocrit (HCT) other laboratory findings were not significantly different between controls and children with CHF.

In agree of us **Barron et al. [12]** found that WBCs count was higher and haematocrit (HCT) was lower among their patients. The cause of that may be referred to the occurrence of anemia in the selected cases.

**Sharmin et al. [13]** cleared many mechanisms that may explain the association between CHF and elevations in WBC count in a vicious circle. WBC count may be elevated in those children due to recurrent chest infections. However, multiple studies have also shown that tumor necrosis factor-α, one of the many proinflammatory cytokines produced by leukocytes, is implicated in myocyte dysfunction, which means that a higher WBC count may exacerbate heart failure.

Our studied children with congestive

heart failure had significantly higher serum melatonin level than control children.

Contrary to our findings**, Kimak et al. [14]** found that individuals with both acute and chronic heart failure had lower levels of circulating melatonin and pineal melatonin secretion.

However, some data indicate that in certain pediatric HF patients, biomolecules such as melatonin can be elevated in response to sickness, almost as an adaptive response to the illness. These conclusions turned out to be at odds with our findings **[15].**

Regarding the aetiology of congenital heart disease among our studied children with congestive heart failure stratified according to modified ROSS classification, almost all of children of CHF had combined cardiac lesions. Pulmonary hypertension represents the highest proportion among the three categories.

**DuranandMandras [16]** shown that pulmonary hypertension (PH) has a worse prognosis and is a common occurrence in heart failure (HF). In order to maximize treatment, it becomes crucial to accurately identify these patients. It is critical that doctors are aware of the most recent classification of PH in left heart disease as well as on going and planned clinical trials.

Our findings demonstrated that there were statistically significant differences in proportions of feeding problems and excessive sweating among children with congestive heart failure stratified according to modified ROSS classification. Proportion of cyanosis and family history of CHF were similar between these children.

Hsu and Pearson analyzed the clinical manifestations of heart failure in children. In agreement with us, they reported several feeding problems and excessive sweating among the studied children**[17].**

No statistically significant differences in anthropometric measurements of children with congestive heart failure stratified according to modified ROSS classification.

Heuschmade the assumption that individuals with heart failure (HF) had higher resting heart rates (HR), which is consistent with our findings. A decrease in death is correlated with the degree of HR drop in HF patients' treatment trials **[18]**.

Using the modified ROSS classification as a stratification tool, we discovered statistically significant differences in the proportions of liver function findings among children with congestive heart failure. The results for kidney and liver function did not differ significantly among children with congestive heart failure who were categorized using the modified ROSS classification.

**Drăghici et al. [19]** believed that elevated levels of serum cholestasis indicators, such as bilirubin, alkaline phosphatase (AP), and gamma-glutamyl transferase (GGT), represent the main alterations in laboratory tests for heart failure. The levels of the liver cytolysis enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), are very slightly elevated roughly two to three times higher than normal.

Against our results, **Saner et al. [20]** discovered that about 25% of patients have a modest rise in prothrombin time and a minor drop in blood albumin. Cardiac function is more negatively impacted by more noticeable changes in laboratory results, leading to severe tricuspid regurgitation, increased filling pressures, and a lower cardiac index.

In our studySerum melatonin level was significantly higher in children with severe CHF compared with children with mild CHF. While other groups differences were not significant.

Emerging studies as the study of **Dzida et al., [21]** discovered that melatonin levels are lowered in HF patients and that melatonin levels in the blood can be a helpful indicator of HF. Melatonin therapy is thought to be a possible treatment for heart failure.

In our study a significant negative correlation between age and serum melatonin level was noted. While significant positive correlations between heart rate, respiratory rate, AST enzyme activity, and serum melatonin levels was found. While no significant correlations between other

parameters and serum melatonin levels in children with congestive heart failure stratified according to modified ROSS classification was seen.

**Lahiri et al., [22]** undertook a study to evaluate the effects of dietary melatonin on the levels of the hormone in various tissues as well as age-related variations in melatonin levels. According to a sensitive and quantitative enzyme-labeled immunosorbent test (ELISA), the liver, kidney, cerebral cortex, and heart had the highest levels of melatonin, followed by the serum. They also refuted the theory that aging causes a drop in serum melatonin levels. Different tissues' levels of 6-hydroxymelatonin sulfate were measured separately. In every tissue examined, the amounts of 6-hydroxymelatonin sulfate, a metabolite of melatonin, were considerably greater than those of free melatonin.

Receiver operating characteristic (ROC) curve analysis **in our study** demonstrated that serum melatonin has a fair discriminating power, with an area under the curve (AUC) of 0.765 for serum melatonin, able to distinguish between children with mild to moderate CHF and children with severe CHF. At a cutoff expression value of greater than 574, the ideal sensitivity and specificity were 80% and 85%, respectively. The predictive values for positive and negative outcomes were 72.7% and 89.5%, respectively. Serum melatonin may be a useful predictive biomarker in children with congestive heart failure (CHF), as it can predict the severity of the condition in these patients. There were two categories in the modified ROSS classification: severe and mild or moderate.

In agreement with us, the results of the study of **Dominguez et al.[23]** suggested the serum melatonin levels as a useful marker for heart failure.

## *CONCLUSION*

In kids with severe heart failure, serum melatonin levels are protective. Elevating melatonin levels in juvenile patients with congenital heart failure is probably a compensatory strategy. Additionally, we found that serum melatonin in children with CHF is a good diagnostic biomarker and possible prognostic indicator.

## CONFLICTS OF INTEREST

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

## FUNDING

None declared.

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