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# The primary study on cardiac troponin T in normal, IUGR, and preterm neonates.

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**ORIGINAL ARTICLE**

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# The primary study on cardiac troponin T in normal, IUGR, and preterm neonates

**Running title:** Joanna Kłaczewska et al., Cardiac troponin in neonates

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## ABSTRACT

**Introduction:** The study hypothesis was that serum analysis of high-sensitivity troponin T in newborns could be a diagnostic tool to predict the health risks caused by intrauterine growth restriction and preterm birth.

**Material and methods:** A total of n = 107 newborns were stratified into three groups: 52 healthy (26 male and 26 female), that is, newborns with body weight ≥ $10^{th}$ percentile, born in good condition [Apgar score (APG) 8–10 pts] of pregnancy not complicated by diabetes, 21 (10 male and 11 female) with intrauterine growth restriction, that is, weight < $10^{th}$ centile in centile grids for sex and gestational age of the newborn, and 34 (19 male and 15 female) preterm infants, that is, children born between 22 and 36 weeks from gestation counted from the first day of the last menstrual period. The lowest minimum troponin levels of 0.004 ng/mL defined the preterm group.

**Results:** The healthy group was defined by the highest maximal troponin levels (0.895 ng/mL), while the intrauterine growth restriction group had the lowest maximal troponin level of 0.539 ng/mL. A significant difference was observed between the IUGR and premature groups, p = 0.00413.

**Conclusions:** cTnT levels between IUGR and preterm newborns reflect developmental differences between these two groups that can influence future child development.

**Keywords:** troponin T, neonates, intrauterine growth restriction, preterm, diagnostics

## Introduction

The fetal growth rate below the 10$^{th}$ percentile according to gestational age, sex, and race is defined as an intrauterine growth restriction (IUGR) that can be classified into asymmetric, symmetric, and mixed IUGR [1]. It can be caused by genetic, placental, fetal, and maternal factors or a combination [2]. The postnatal diagnosis of babies with IUGR includes, among others, clinical examination, anthropometry, and the ponderal index [3]. As a result of delayed brain development, cognitive and neurodevelopmental abnormalities can appear among IUGR infants [4]. Growth retardation can also be observed in babies with IUGR [5]. IUGR may also affect cardiovascular development during infancy, resulting in abnormalities in the myocardium [6] caused by a reduced number of cardiomyocytes at birth [7, 8].

The troponin complex consists of three subunits: troponin I, troponin T, and troponin C [9]. Troponin T contains a binding site for tropomyosin and is probably responsible for binding the troponin complex to tropomyosin. It is found mainly in the cardiac muscles. Troponin I (TnI) prevents muscle contraction in the absence of calcium. It is a cardiac-specific protein marker [10]. Troponin C is present in the cardiac and skeletal muscles [11].

During fetal development, the skeletal isoforms of troponin present in the heart are replaced by cardiac troponin I (cTnI) and cardiac troponin T (cTnT) [12]. cTnI is unlikely to be reexpressed in muscle-damaged tissues [13]. However, cTnT expression occurs in cardiac tissue and damaged skeletal muscles [14]. cTnT is a highly sensitive marker of myocardial damage [15] and is a valuable evaluator of the severity of cardiac failure [16].

In recent years, the diagnostic utility of cTnT has been confirmed [17]. Its potential applicability for the assessment of myocardial damage in newborns has also been tested [18]. cTnT has been shown to be a diagnostic tool for posthypoxic heart damage in neonates [19] and a tool for the detection of myocardial injury in pediatric age [20]. It has also been shown to be a useful marker of neonatal and cardiorespiratory morbidity [21]. However, some show that high-sensitivity cTnT

levels (hs-cTnT) should be treated with caution regarding cardiac health in newborns [22].

To verify the current knowledge of the relation between hs-cTnT levels of hs-cTnT as a function of the cardiological postpartum status of a newborn, an observational retrospective study on hs-cTnT levels was performed in healthy, preterm, and healthy neonates.

## Materials and methods

The study was carried out according to the Declaration of Helsinki of the World Medical Association (WMA). The bioethics committee approved the study, waiver no: KB/154/2009. Parents of the children examined provided a signed form of informed consent to participate in the study.

### Study participants

The study used data from blood examinations of newborns whose mothers were hospitalized in the Department of Neonatology, Department of Obstetrics, Feminine Diseases and Gynecology Oncology, Regional Hospital Bródnowski, Warsaw, Poland. A total of n = 107 newborns were studied and stratified into three groups: 52 healthy groups (26 men and 26 female); newborns with body weight ≥ $10^{th}$ percentile, born in good condition [Apgar score (APG) 8–10 pt] from pregnancy not complicated by diabetes. The intrauterine growth restriction group (IUGR) comprised 21 children (10 men and 11 women) defined by body mass < $10^{th}$ centile on centile grids for sex and gestational age of the newborn. The preterm group comprised 34 children (19 men and 15 female); children born between 22 and 36 weeks of gestation were counted from the first day of the last menstrual period.

### Experimental methods

Blood was collected by venepuncture in a tube with lithium heparin. The samples were chilled to 4°C. The clotted blood was centrifuged at 1500 rpm for 60 min, and blood serum was collected. The serum collected was stored at –20°C until laboratory tests were performed.

High-sensitive cardiac troponin T was measured using the Cobas Elecsys assay in neonatal blood serum on a Cobas 8000 analyzer. The assay consisted of three steps: in Step 1, a complex was incubated, for which a biotinylated antigen was used with a specific cardiac troponin T monoclonal antibody and a cardiac troponin T specific monoclonal antibody, which was labeled with a ruthenium complex. Step 2 incubation with particles coated with streptavidin. In this step, the complex was bound to the solid phase as a result of the affinity of biotin and streptavidin.

The mixing mixture was then transferred to a measuring chamber, where the tropomyosin T concentration was measured by the electrochemiluminescence level. The troponin concentration was expressed in ng/mL.

### Statistical analysis

All statistical analyses were performed using the R package. The normality of a sample distribution was assessed using the Shapiro-Wilk normality test. Then, statistical inferences between samples were derived using the Kruskal-Wallis test. Finally, post hoc analysis was performed using the Wilcoxon signed-rank test.

## Results

There are no statistical differences between the sexes. The graphic representation of the distribution of the studied samples and the statistical differences is shown in Figure 1.

The general characteristics of the samples studied are summarized in Table 1. Table 2 includes a statistical description of the results obtained. The analysis of Table 2 reveals similar minimal troponin levels in healthy and IUGR groups: 0.028 ng/mL and 0.021 ng/mL, respectively. The lowest troponin levels of 0.004 ng/mL define the preterm group. The healthy group is defined by the highest troponin levels: 0.895 ng/mL. The IUGR group is defined by the lowest maximal troponin level: 0.539 ng/mL.

The upper reference levels for the IUGR and preterm groups equal 0.350 ng/mL and 0.547 ng/mL, respectively. There is a statistically significant difference between the IUGR and preterm groups, $p = 0.00413$.

## Discussion

Under the hypothesis that the size of troponin molecules prevents them from crossing the placenta and cannot influence neonatal troponin levels, the analysis of neonates' serum troponin levels might carry a potential clinical value supported by the following study [23–25]. However, there is a dearth of data on the relationships between cTnT levels and health status in neonates [22].

In addition, there is a significant disparity between the reported results. For example, in healthy infants, Clark et. al., [21] reported median cTnT levels of 0.025 ng/mL, while this study reports the value of 0.12 ng/mL. Karlen et al. [22] reported median hs-cTnT levels in cord blood of 92 ng/mL, whereas Tarkowska et. al., [26] reported cTnT values in the range of 0.052–0.069 ng/mL. A comparison of the results of this study with those of Trevisanuto et al. [27] revealed analogous levels of cTnT.

The results of this report confirmed the previous study indicating that cTnT levels are sex independent [26] and disprove the results of the study carried out by Baum et al. [28] who reported statistically significant differences in cTnT levels between men and women. Furthermore, this study reports a significantly higher upper reference limit in healthy newborns than that reported by Baum et. al., [28]: 0.546 ng/mL vs. 0.097 ng/mL, respectively. Therefore, an amalgam of reports on physiological cTnT levels in healthy newborns does not allow the established unified reference range.

The observed disparities may be due to the nonparametric distribution of cTnT in newborns that was established in this and previous studies [29]. Furthermore, the report of this study confirms previous observations that indicate higher levels of cTnT in preterm newborns [30].

Analysis of the current literature reveals a cross-correlation between intrauterine growth restriction and cardiovascular system development [31].

Consequently, following the study's results on cross-correlations between heart defects and cTnT levels in newborns [32], one should expect higher levels of cTnT than those observed in healthy newborns. This study does not confirm this hypothesis and reveals lower median levels of cTnT in IUGR than in healthy newborns: 0.08 ng/mL vs. 0.12 ng/mL, respectively. However, the observed increase in mean hs-cTnT levels in the preterm group may reflect disturbances in the ‘developmental programming’ of the cardiovascular system [33] and cardiovascular pathologies such as low ventricular output, low systemic arterial pressure, and cardiac instability [34].

## Article information

**Authors Contributions:** *Conceptualization, J.K. and R.T.; methodology, R.T.; software, formal analysis, R.T., and M.W.; writing — original draft preparation, R.T., and M.W.; writing — review and editing, R.T., M.W., and J.K.; All authors have read and agreed to the published version of the manuscript.*

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**Conflicts of Interest:** *The authors declare no conflict of interest.*

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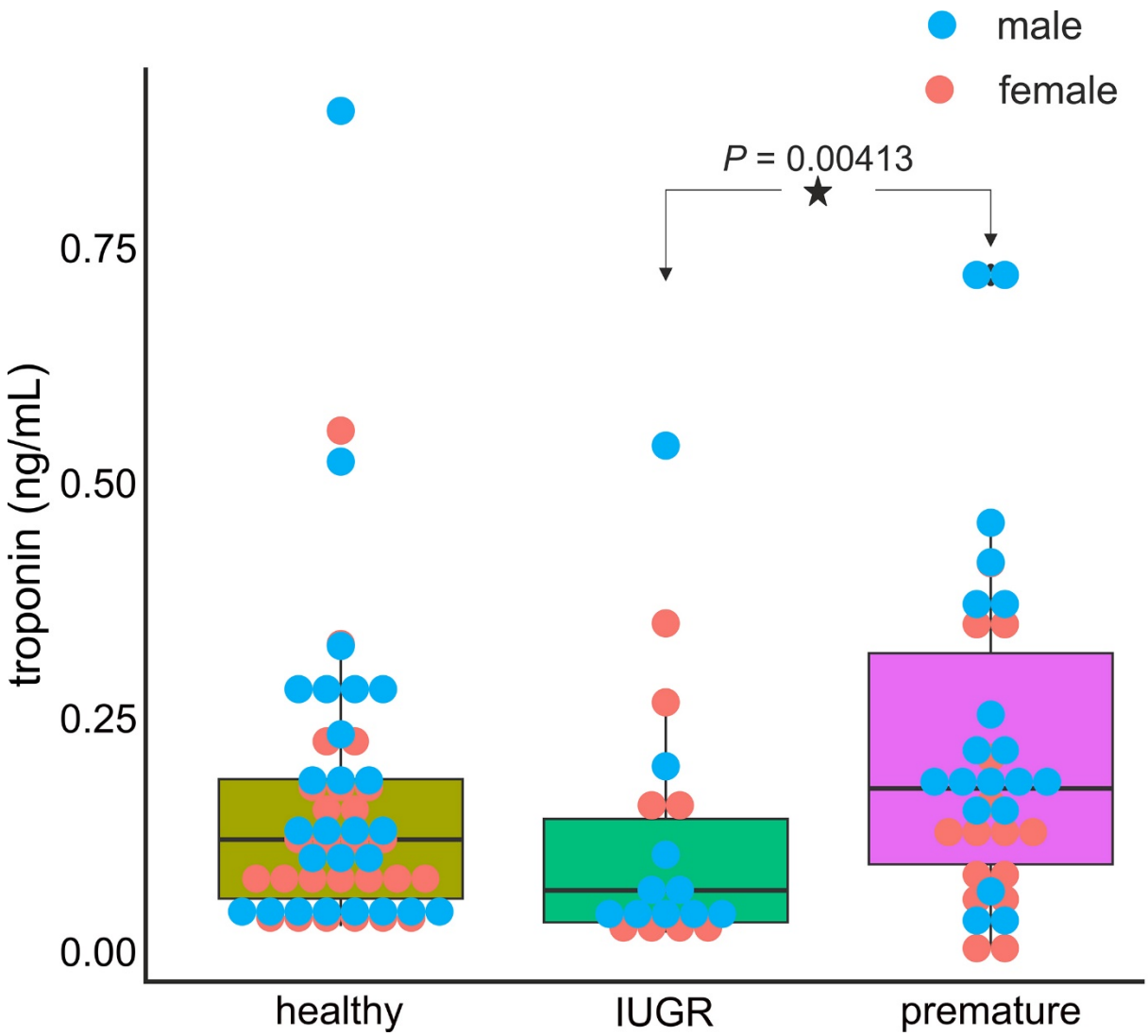
**Table 1.** Characteristics of the samples studied: healthy — newborns with bodyweight ≥ 10$^{th}$ percentile, born in good condition [Apgar score (APG) 8–10 pts] from pregnancy not complicated by diabetes, IUGR — weight < 10$^{th}$ centile on centile grids for sex and gestational age of the newborn, and preterm — children born between 22 and 36 weeks from gestation counted from the first day of the last menstrual period

| Group | n | Variable | min | max | Median | Mean | SD |
|---|---|---|---|---|---|---|---|
| Healthy | 52 | Nonate age (hr) | 1 | 120 | 72 | 64.154 | 24.104 |
| | | Mother age | 20 | 39 | 30.5 | 29.962 | 4.593 |
| | | Pregnancy | 1 | 4 | 2 | 1.846 | 0.916 |
| IUGR | 21 | Nonate age (hr) | 24 | 120 | 48 | 66.286 | 26.186 |
| | | Mother age | 20 | 39 | 26 | 27.6 | 5.225 |
| | | Pregnancy | 1 | 5 | 2 | 2 | 1.183 |
| Preterm | 34 | Nonate age (hr) | 24 | 144 | 48 | 62.118 | 29.016 |
| | | Mother age | 19 | 43 | 31 | 30.121 | 5.894 |
| | | Pregnancy | 1 | 6 | 2 | 2.147 | 1.374 |

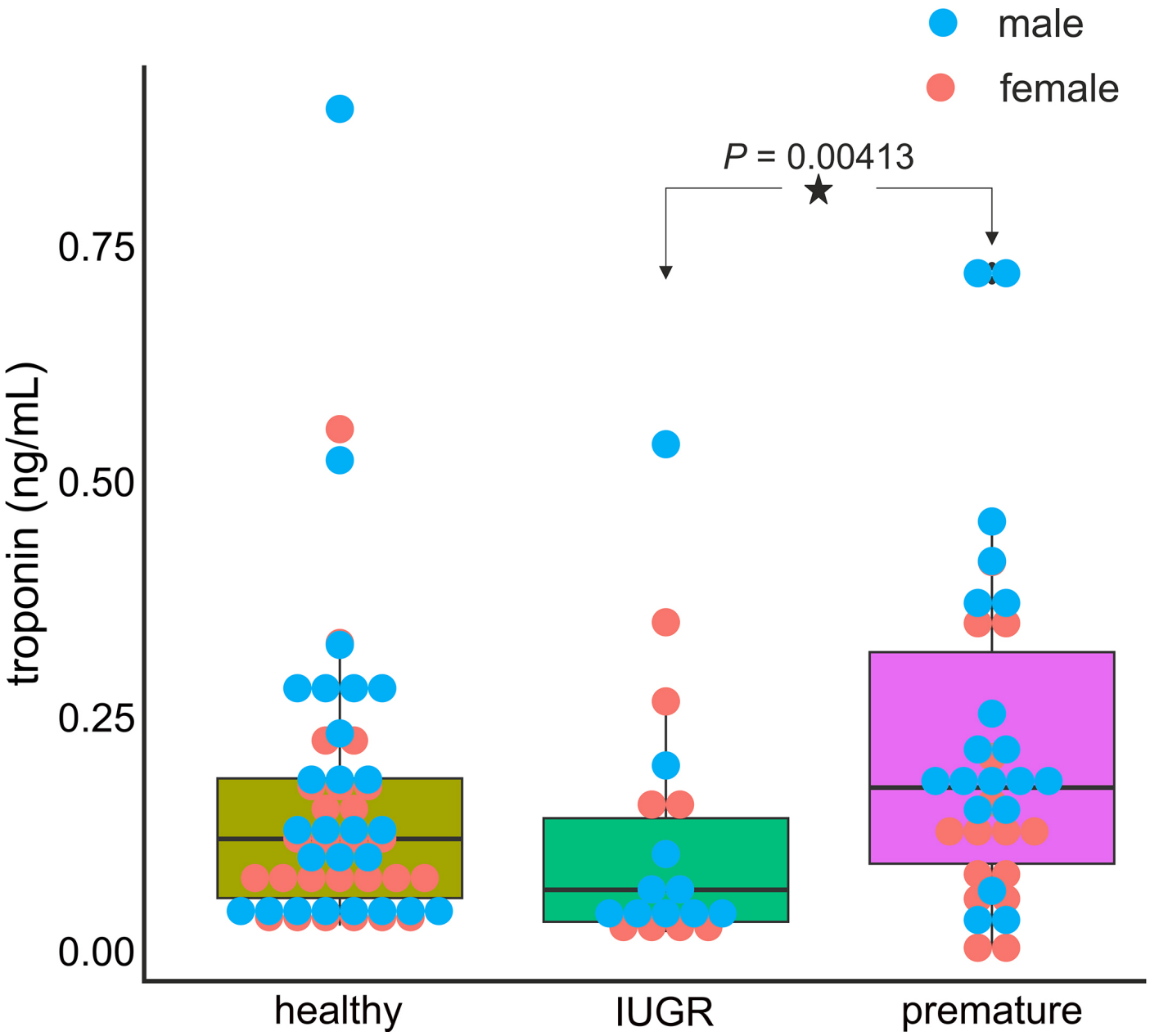
**Table 2.** The statistical description of serum blood troponin levels in healthy — newborns with bodyweight ≥ 10$^{th}$ percentile, born in good condition [Apgar score (APG) 8–10 pts] from pregnancy not complicated by diabetes, IUGR — weight < 10$^{th}$ centile in centile grids for sex and gestational age of the newborn, and preterm — children born between 22 and 36 weeks from gestation counted from the first day of the last menstrual period

| Group | Variable | n | Min [ng/mL] | Max [ng/mL] | Median [ng/mL] | Mean [ng/mL] | SD [ng/mL] | 97.5$^{th}$ percentiles [ng/mL] |
|---|---|---|---|---|---|---|---|---|
| 1 | Healthy | 52 | 0.028 | 0.895 | 0.120 | 0.158 | 0.155 | 0.546 |
| 2 | IUGR | 21 | 0.021 | 0.539 | 0.080 | 0.117 | 0.130 | 0.444 |
| 3 | Preterm | 34 | 0.004 | 0.728 | 0.174 | 0.216 | 0.178 | 0.547 |

**Figure 1.** Box plot representation of troponin levels stratified by study group. Healthy — newborns with bodyweight ≥ 10$^{th}$ percentile, born in good condition [Apgar score (APG) 8–10 pts] from pregnancy not complicated by diabetes, IUGR — weight < 10$^{th}$ centile on centile grids for sex and gestational age of the newborn, and preterm — children born between 22 and 36




weeks from gestation counted from the first day of the last menstrual period.


male
female
P = 0.00413
0.75
0.50
0.25
0.00
troponin (ng/mL)
healthy
IUGR
premature