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Serum TP53 Protein Level as a Sensitive Biomarker for the Diagnosis of Myocardial Damage in Children

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: High levels of TP53 protein can lead to apoptosis of myocardial cells. However, TP53 protein influence of myocardial damage remains unclear. This prospective study investigated the involvement of TP53 protein in secondary myocardial damage in children up to 18 years of age.

Material/Methods: Serum TP53 protein, N-terminal prohormone B-type natriuretic peptide (NT-ProBNP), cardiac troponin-I (cTnI), and creatine kinase isoenzyme MB (CK-MB) concentrations were measured in 50 hospitalized patients with secondary myocardial damage, 50 hospitalized patients without myocardial damage, and 50 healthy individuals (control). Cardiac damage was diagnosed based on cTnI, NT-ProBNP, and CK-MB levels, with electrocardiographic evidence as the reference. The appropriate cut-off value of TP53 protein for secondary myocardial damage was analyzed by receiver operating characteristic (ROC) curves.

Results: The serum TP53 protein, NT-ProBNP, cTnI, and CK-MB concentrations of the patients with and without myocardial damage were 10.20±1.20 and 0.30±0.10 ng/L, 505.30 and 107.8 ng/L, 0.23±0.13 and 0.02±0.01 μg/L, and 28.30±5.13 and 12.24±4.29 IU/L, respectively. For the 50 patients with myocardial damage, the area under the ROC curve for serum TP53 protein, NT-ProBNP, cTnI, and CK-MB concentrations were 0.89 (95% CI: 0.81-0.95), 0.83 (95% CI: 0.77-0.91), 0.92 (95% CI: 0.84-0.97), and 0.85 (95% CI: 0.78-0.93), respectively, and the diagnostic cut-off values were 12.00 ng/L, 500.00 ng/L, 0.16 μg/L, and 27.00 IU/L, respectively, with positive likelihood ratios of 20.8, 13.2, 24.6, and 15.6.

Conclusions: TP53 protein is a valid biomarker of secondary myocardial damage in pediatric patients and can be diagnostic.

Keywords: Biomarkers • Pediatrics • TP53 Protein, Human

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Background

Secondary myocardial damage is not an independent disease but a complication of others. However, there are no confirmed diagnostic criteria for myocardial damage in this condition. Currently, the diagnosis of myocardial damage is mainly based on cardiac troponin I (cTnI), N-terminal prohormone B-type natriuretic peptide (NT-ProBNP), and creatine kinase isoenzyme MB (CK-MB) release, with or possibly without an abnormal electrocardiogram [1]. However, many factors can affect cTnI, CK-MB, and NT-proBNP release, and the positive expression rate of cTnI and CKMB is not 100% [1,2]. Moreover, cTnI is not stable enough, which may affect the determination [3], and the specificity of NT-probNP and CK-MB is low [1,2] and, therefore, they are not optimal biomarkers. Hence, the diagnosis of secondary myocardial damage is difficult. From this perspective, multiple indicators are better than a single indicator in the judgment of myocardial damage. Therefore, it is necessary to find new markers.

The human tumor protein 53 (TP53) is considered the "guardian of the genome" owing to its powerful function as a tumor suppressor [4-6]. However, mutated TP53 has been associated with inflammation and immune dysfunction [7] and cell damage and apoptosis [8,9]. Deng et al [10] demonstrated that the upregulated expression of TP53 protein was associated with the damage and apoptosis of coronary artery smooth muscle cells.

The present study aimed to investigate whether serum TP53 protein levels are associated with secondary myocardial damage in children aged up to 18 years, determine whether TP53 protein is a valid biomarker of secondary myocardial damage in pediatrics, and determine a cut-off value that can be used to confirm the diagnosis.

Material and Methods

This prospective study was approved by the Ethics Committee of Shunde Women's and Children's Hospital of Guangdong Medical University (protocol code: sdfy2017028; date of approval: March 6, 2017). All participants provided their written informed consent before the start of the study. We also obtained the written informed consent from the parents or guardians on behalf of the children enrolled in our study.

Patients

All the patients were hospitalized children who were seen between March 2017 and March 2020 at Shunde Women's and Children's Hospital of Guangdong Medical University. Included patients were children up to 18 years of age, with or without myocardial damage (cTnI >0.15 μg/L; and/or NT-ProBNP >300 ng/L; and/or CK-MB >24 IU/L). Patients treated for myocardial damage prior to hospital admission were excluded.

The patients with and without myocardial damage were being treated for the following: mycoplasma pneumoniae pneumonia (n=12, n=19), rotavirus enteritis (n=11, n=18), sepsis (n=5, n=2), myocarditis (n=5, n=0), suffocating (n=3, n=3), severe hand-foot and mouth disease (n=3, n=1), cardiomyopathy (n=2, n=0), congenital heart disease (n=3, n=4), poisoning (n=2, n=1), and Kawasaki disease (n=4, n=2).

For this analysis, the study population comprised 3 groups of 50 participants each, as follows: patients with diseases plus myocardial damage, patients with diseases but without myocardial damage, and healthy individuals who were not patients (control group).

Blood Specimen Collection

Blood samples of patients (5 mL venous) were obtained on admission to the hospital and were routinely processed. Serum TP53 protein, NT-ProBNP, cTnI, and CK-MB levels were measured and interpreted in a blinded manner.

Detection of TP53 Protein, NT-ProBNP, cTnI, and CK-MB

The serum TP53 protein concentration was analyzed with an enzyme-linked immunosorbent assay (ELISA) kit (Xinyu Biotechnology, Shanghai, China). The serum NT-ProBNP concentration was measured with a fluorescence quantitative analyzer (YZB/CAN 91001, Canada Response Biomedical, Burnaby, Canada). Serum cTnI and CK-MB levels were analyzed by using a chemiluminescence analyzer (Beckman Coulter, Brea, CA, USA).

Determining the Optimal Cut-Off Values of Serum TP53 Protein for Myocardial Damage in Patients

The receiver operating characteristic (ROC) curve, area under the ROC curve (AUC), 95% confidence interval (CI), sensitivity, specificity, diagnostic cut-off value, and positive likelihood ratio (LR+) were compared to determine the serum TP53, cTnI, CK-MB, and NT-proBNP concentrations indicative of secondary myocardial damage in pediatric patients.

Diagnosis of Myocardial Damage

Myocardial damage was diagnosed based on the cTnI, NT-ProBNP, and CK-MB results, with or possibly without an abnormal electrocardiogram [1,11]. Myocardial damage was indicated by the following values which could include all or 1 of these items [1,11]: cTnI >0.15 μg/L; and/or NT-ProBNP >300 ng/L; and/or CK-MB >24 IU/L.

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Table 1. Characteristics of the patient population at admission.

	All patients	Myocardial damage	Non-myocardial damage	*P*
Number of subjects	100	50	50	–
Age, y	7.86±1.6	8.23±3.12	8.05±1.4	0.26
Male %	53.7	56.0	51.4	0.74
Heart rate, beats/min	110±26	126±28	95±25	<0.05
Systolic blood pressure, mmHg	102±14.3	98±15.7	105±12.8	0.44
Arterial oxygen saturation, %	84±12	78±15	90±9	<0.05
TP53, ng/L	5.25±0.65	10.20±1.20	0.30±0.10	<0.001
NT-proBNP, ng/L(M)	306.6	505.3	107.8	<0.001
cTnI, μg/L	0.13±0.04	0.23±0.13	0.02±0.01	<0.001
CK-MB,IU/L	20.27±4.71	28.30±5.13	12.24±4.29	<0.001
Plasma glucose, mmol/L	6.5±1.2	6.8±1.6	6.2±0.8	0.57
Alanine transaminase, U/L	57±15	66±13	48±17	<0.05
C reaction protein, mg/L	28±6.9	31±6.5	25±7.3	<0.05
Procalcitonin, mg/L	5±2.9	6±3.5	4±2.3	<0.05
Blood lactic acid, mmol/L	3±1.3	3±1.5	3±1.1	0.67
Ejection fraction, %	55±3.1	45±3.8	65±2.4	<0.05
E peak/A peak	1.4±0.	1.5±0.2	1.3±0.2	0.26

Statistical Analyses

Statistical analyses were performed using SPSS version 20.0 statistical software (IBM Corp, Armonk, NY, USA). Continuous data are shown as mean±standard deviation. Only the distribution of plasma NT-proBNP levels were not normal (Z=2.516, *P*<0.001), and they are presented as medians. One-way ANOVA and Newman-Keuls test were applied to compare the differences in mean age and serum TP53 protein, cTnI, and CK-MB levels among the groups. The Kruskal-Wallis test was used to compare the serum NT-proBNP levels among the groups. Pearson's test was used for the correlation analyses between serum TP53 protein and NT-proBNP, cTnI, or CK-MB levels in each patient with myocardial damage.

ROC curves were applied to determine the appropriate cut-off values of serum TP53 protein to indicate myocardial damage. The cut-off values were based on the area under the AUC with 95% CI, sensitivity, specificity, and LR^+. *P*<0.05 was considered significant.

Results

A comparison of the respective clinical characteristics (**Table 1**) showed that, compared with the patients without myocardial damage, the patients with myocardial damage had significantly higher heart rate, alanine transaminase, C-reactive protein, and procalcitonin, while arterial oxygen saturation and ejection fraction were lower (all *P*<0.05). The most significant differences were in the serum levels of TP53 protein, NT-proBNP, cTnI, and CK-MB (all *P*<0.001), which were all higher in the patients with myocardial damage. These differences in serum levels of TP53 protein, NT-proBNP, cTnI, and CK-MB were also significant between the 2 patient groups and the control group (all *P*<0.001; **Table 2**).

In pediatric patients with and without myocardial damage and in healthy children, serum TP53 levels were 10.20±1.20 ng/L, 0.30±0.10 ng/L, and 0.21±0.10 ng/L, respectively; median serum NT-proBNP levels were 505.3 ng/L, 107.8 ng/L, and 59.7 ng/L, respectively; serum cTnI levels were 0.23±0.13 μg/L, 0.02±0.01 μg/L, and 0.01±0.01 μg/L, respectively; and serum CK-MB levels were 28.30±5.13 IU/L, 12.24±4.29 IU/L, and 6.31±3.11 IU/L, respectively. These differences in serum TP53 protein, NT-proBNP, cTnI, and CK-MB levels were also significant among the 2 patient groups and the control group (all *P*<0.001; **Table 2**).

Among the patients with myocardial damage, there were positive associations between TP53 protein and NT-proBNP, cTnI, and CK-MB (*r*=0.637, 0.815, 0.697, respectively; all *P*<0.001; **Figure 1**).

We used ROC curve analysis to determine the serum TP53 protein, NT-proBNP, cTnI, and CK-MB diagnostic cut-off values for myocardial damage in patients (**Figure 2, Table 3**).

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Table 2. Comparison of TP53, NT-proBNP, cTnI, and CK-MB levels in patients with secondary myocardial damage, patients without myocardial damage, and healthy children.

Subjects	n	TP53 (ng/L)	NT-proBNP (ng/L,M)	cTnI (μg/L)	CK-MB (IU/L)
Myocardia damage	50	10.20±1.20	505.3	0.23±0.13	28.30±5.13
Non-myocardia damage	50	0.30±0.10	107.8	0.02±0.01	12.24±4.29
Healthy children		0.21±0.10	59.7	0.01±0.01	6.31±3.11
χ^2		63.25	40.35	45.21	35.27
P		0.000	0.000	0.000	0.000

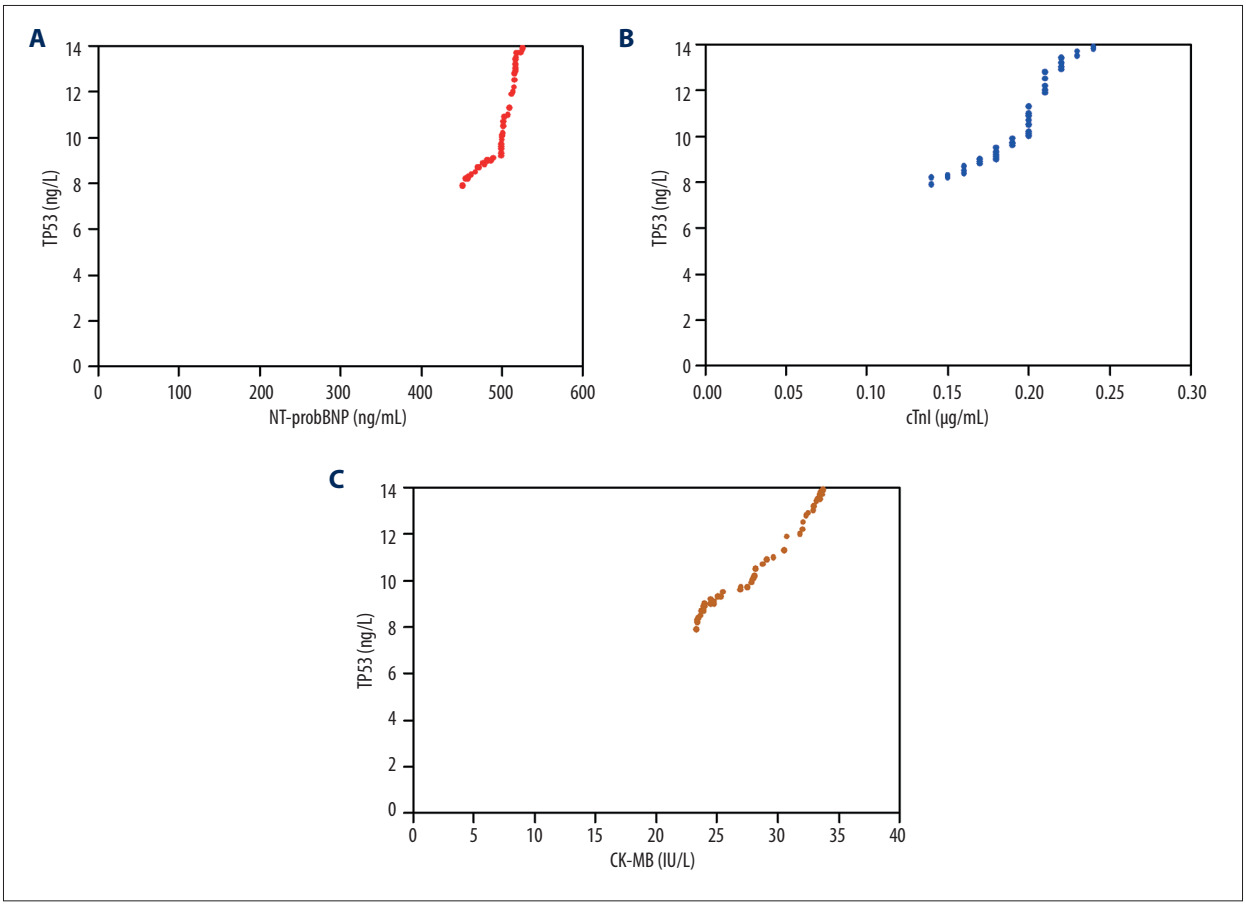

Figure 1. (**A-C**) Association between TP53 levels and NT-proBNP, cTnI, and CK-MB levels in patients younger than 18 years and with secondary myocardial damage (r=0.637, r=0.815 and r=0.697; P<0.001 for all). Figures were generated using GraphPad software (GraphPad Software, La Jolla, CA, USA).

The diagnostic cut-off value of serum TP53 protein levels for myocardial damage in patients was 12.00 ng/L (LR^+=20.8; **Table 3**). The AUC was 0.89 (95% CI 0.81-0.95), sensitivity 0.93 (95% CI 0.88-0.98), and specificity 0.91 (95% CI 0.88-0.94).

The diagnostic cut-off value of serum NT-proBNP levels for myocardial damage in patients was 500.00 ng/L (LR^+=13.2; **Table 3**). The AUC was 0.83 (95% CI 0.77-0.91), sensitivity 0.91 (95% CI 0.88-0.94), and specificity 0.81 (95% CI 0.61-0.88).

The diagnostic cut-off value of serum cTnI levels for myocardial damage in patients was 0.16 μg/L (LR^+=24.6; **Table 3**). The AUC was 0.92 (95% CI 0.84-0.97), sensitivity 0.95 (95% CI 0.92-0.98), and specificity 0.97 (95% CI 0.95-0.99).

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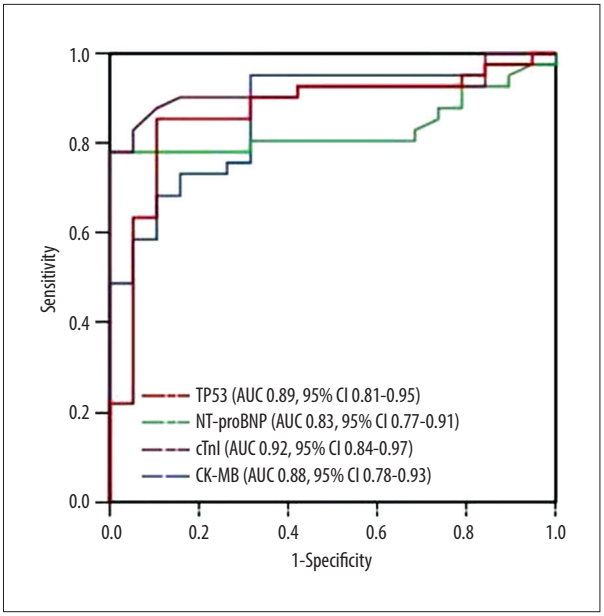

Figure 2. Receiver operating characteristic (ROC) curves for TP53, NT-proBNP, cTnI, and CK-MB in patients with secondary myocardial damage. ROC curves of TP53, NT-proBNP, cTnI, and CK-MB for determining myocardial damage. The area under the ROC curve and positive likelihood ratio (LR^{+}) of TP53 were larger than that of NT-proBNP and CK-MB ($P<0.05$). Figures were generated using GraphPad software (GraphPad Software, La Jolla, CA, USA).

The diagnostic cut-off value of serum CK-MB protein levels for myocardial damage in patients was 27.00 IU/L ($LR^{+}=15.6$; **Table 3**). The AUC was 0.85 (95% CI 0.78-0.93), sensitivity 0.94 (95% CI 0.91-0.97), and specificity 0.88 (95% CI 0.85-0.91).

The ROC curve showed that the AUC and LR+ of TP53 were greater than those of CK-MB and NT-proBNP, and the differences between them was significant (all $P<0.05$; **Table 3**).

These data suggest that analysis of serum TP53 levels in children provides new parameters for the diagnosis of myocardial damage.

Discussion

The influence of myocardial damage on TP53 protein remains unclear. We investigated the involvement of TP53 protein in myocardial damage in children aged up to 18 years. The appropriate cut-off value of TP53 protein for myocardial damage was analyzed by ROC curves. We found that the cut-off value of TP53 protein can aid the diagnosis of pediatric myocardial damage.

Studies have shown that myocardial injury is related to changes in immune function through inflammatory mediators [12-14]. The TP53 protein is a typical tumor suppressor and is considered a guardian of immunity [4,6]. However, TP53 can mutate to sabotage immunity [7], and the mutated TP53 protein becomes an active substance that promotes cell damage and apoptosis [8,9,15]. Agupitan et al [7] confirmed that mutant TP53 is associated with inflammation. Most of the patients recruited for this study had an inflammatory disease, and the TP53 protein expression in patients with myocardial damage was significantly higher than that of patients without myocardial injury. We speculate that the TP53 protein detected may have been mutated. Further studies are needed to confirm this.

The cTnI, CK-MB, and NT-probNP are the most common biomarkers used to identify myocardial damage in clinical diagnosis [1,7,12,16,17]. The positivity rates (higher than normal) of CK-MB and cTnI in patients with myocardial damage are 35% to 68% and 25% to 42%, respectively [17]. However, many factors can affect cTnI, CK-MB, and NT-probNP levels, and as biomarkers they are not perfect [1,3,18-21]. For example, CK-MB is found in the myocardium but also in brain tissues and skeletal muscle. The specificity of cTnI is relatively higher than

Table 3. Receiver operating characteristic analysis determining viability of plasma TP53 levels for differentiating patients with myocardial damage*.

	TP53	NT-proBNP	cTnI	CK-MB
Subjects, n	50	50	50	50
Optimal cut-off value	12.00 ng/L	500.00 ng/L	0.16 μg/L	27.00 IU/L
AUC	0.89 (0.81-0.95)	0.83 (0.77-0.91)	0.92 (0.84-0.97)	0.85 (0.78-0.93)
Sensitivity	0.93 (0.88-0.98)	0.91 (0.88-0.94)	0.95 (0.92-0.98)	0.94 (0.91-0.97)
Specificity	0.91 (0.88-0.94)	0.81 (0.61-0.88)	0.97 (0.95-0.99)	0.88 (0.85-0.91)
Positive likelihood ratio	20.8	13.2	24.6	15.6

* Reported as value (95% CI), unless otherwise noted.

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that of CK-MB, but its sensitivity is low, while the sensitivity of NT-proBNP is relatively higher, but its specificity is low [21]. Also, cTnI seemed to be a good biomarker; however, it is not stable enough, which may affect the determination [2]. From this perspective, multiple indicators are better than a single indicator in the judgment of myocardial damage. Additional effective biomarkers are needed to identify myocardial damage.

Currently, the main pathological mechanisms of TP53 expression in myocardial damage are not completely understood. Lopez-Candales et al [22] reported that the main pathological feature of an abdominal aortic aneurysm is cell damage and apoptosis, which is related to the overexpression of TP53; therefore, it was speculated that TP53 may be a marker of apoptosis. Ikeda et al [23] showed that TP53 is a key molecule and mediator of myocardial cell apoptosis during cardiac rupture. Deng et al [10] found that the high expression of TP53 promoted the increase of caspase-3 expression, leading to cell damage and apoptosis.

The present study found that in patients with myocardial damage, the TP53 concentration was elevated, as were NT-proBNP, cTnI, and CK-MB levels. AUC and LR+ values (0.89, 20.8) for TP53 were high for identifying myocardial damage, and were higher than the AUC values of NT-probNP (0.83,13.2) and CK-MB (0.85,15.6), while they were lower than those of cTnI (0.92, 24.6). The sensitivity (0.93) and specificity (0.91) of TP53 were also higher. A cut-off value of TP53 for identifying myocardial damage was 12.00 ng/mL, and the LR^+ value was high (20.8) and higher than the LR^+ values of NT-probNP (13.2) or CK-MB (15.6). These results strongly suggest that TP53 is an effective indicator for the diagnosis of myocardial damage, and TP53 protein may be important for the diagnosis of secondary myocardial damage in pediatric patients. TP53 may also be suitable for the diagnosis of secondary myocardial damage in adults, but this needs to be confirmed in future studies.

This study had some limitations. The single-center study with a small sample size may have introduced bias. Larger dedicated studies in patients from multiple regions, as well as analyses of new biomarkers in myocardial damage, are needed to confirm whether the TP53 protein cut-off values we determined are appropriate for use in all children, and even adults. Also, this study included a small number patients with primary heart diseases, which may have affected our judgment of whether the elevated serum TP53, NT-ProBNP, cTnI, and CK-MB levels were from the primary diseases themselves or from secondary myocardial injury. In future studies, we will investigate whether TP53 is more stable in serum than cTnI and CK-MB.

Conclusions

Our results showed that TP53 protein can be an important indicator to diagnose secondary myocardial damage in pediatric patients. Perhaps the inclusion of this biomarker will improve the identification of patients with secondary myocardial damage. Larger dedicated studies are warranted to confirm the TP53 cut-off values reported herein.

Institutional Review Board Statement

This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Shunde Women's and Children's Hospital of Guangdong Medical University (protocol code: sdfy2017028; date of approval: March 6, 2017).

Declaration of Figures' Authenticity

The authors confirm that the figures are original with no duplication and have not been previously published.

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