Original Article

Association between global longitudinal strain and occurrence of cardiovascular events among pediatric patients following high-dose cyclophosphamide chemotherapy: a prospective cohort study

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Background: The fatal cyclophosphamide cardiotoxicity is associated with high mortality in the adult population, and the study of its effects on children represents a gap in the field. This study aimed to evaluate the potential of global longitudinal strain (GLS) as a predictor of cardiovascular events among children with high-dose cyclophosphamide chemotherapy.

Methods: This was a prospective cohort study of patients aged 14 years or younger who received high-dose (>120 mg/kg) cyclophosphamide chemotherapy recruited consecutively. Blood collection and echocardiography were performed 1 day before and after cyclophosphamide chemotherapy, and patients were followed up for 30 days with echocardiography. GLS and other echocardiography indicators were calculated accordingly. The primary outcome was the occurrence of cardiovascular events within 30 days after cyclophosphamide chemotherapy. The association between GLS and outcome was analyzed by using univariate and multivariable-adjusted Poisson regression.

Results: A total of 29 subjects were included. Among them, 10 patients (34.48%) developed cardiovascular events during a median follow-up of 10 (interquartile range, 5–13) days. Although similar before cyclophosphamide chemotherapy, GLS 1 day after cyclophosphamide chemotherapy was significantly lower in the cardiac injury group than in the noncardiac injury group (–18.33%±1.81% *vs.* –20.03%±1.49%, P=0.01). In the multivariable analysis adjusted for total cyclophosphamide dose (160 *vs.* 120–159 mg/kg) and global circumferential strain, GLS remained an independent predictor for cardiovascular events [incidence rate ratio: 1.46, 95% confidence interval: 1.02–2.09, P=0.04].

Conclusions: GLS after cyclophosphamide chemotherapy may be a reliable indicator to predict cardiovascular events in patients receiving cyclophosphamide chemotherapy, which might be essential in optimizing treatment strategies for this high-risk patient group.

Keywords: Cyclophosphamide-induced cardiac injury; cardio-oncology; global longitudinal strain (GLS)

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Introduction

Cyclophosphamide is a type of alkylating chemotherapeutic drug that is utilized predominantly in stem cell transplantation for managing rheumatic autoimmune disorders and treating a range of tumors. However, the clinical application of cyclophosphamide is limited by the cardiovascular events induced by high doses (>120 mg/kg) of this drug. Notably, the incidence of cardiovascular events ranges from 7% to 28% in adult patients, depending on chemotherapy dosage (1). These cardiovascular events, which typically occur within 2–10 days, are dose-dependent (2) and are associated with manifestations of congestive heart failure, pericarditis, pericardial effusion and cardiac tamponade (3,4). Moreover, cardiovascular events associated with high doses of 170–180 mg/kg have a secondary mortality rate ranging from 11% to 43% (5). Ishida reported 11 of 12 patients who died from progressive acute cardiac failure on day 7 (range, 5–30 days) after the first administration of cyclophosphamide, and a short time to the first symptom after the administration of cyclophosphamide tended to be associated with early death (6). In summary, fatal cyclophosphamide cardiotoxicity is associated with high mortality in the adult population (6). Kusumoto (7) reported a case of heart failure induced by high-dose cyclophosphamide, which occurred 2 months after the administration of high-dose cyclophosphamide (254 mg/kg) with impaired contractile function [left ventricular ejection fraction (LVEF), 47%] accompanied by pericardial effusion.

High-dose cyclophosphamide is a necessary medication for myeloablative pretreatment in patients. Regular monitoring is crucial in improving the quality of patients receiving cyclophosphamide chemotherapy. Although various factors, including enzyme markers in blood samples, measurements from echocardiography (including measurements from the myocardial strain) and electrocardiography (ECG) readings, have been considered predictive of cardiac damage associated with chemotherapy drugs (8,9), there is a notable absence of the factors for predicting cardiovascular events induced by high doses of cyclophosphamide in pediatric patients. The GLS plays a crucial role in detecting left ventricular (LV) dysfunction. Notably, a meta-analysis highlighted that GLS is more effective at suggesting cardiac damage earlier than the LVEF in adult patients post-chemotherapy (10). This finding underscores the importance of GLS as a sensitive indicator of cardiovascular events after receiving high-dose cyclophosphamide chemotherapy. Our study evaluated the potential of GLS as a predictor of cardiovascular events among patients receiving high-dose cyclophosphamide chemotherapy. This model leverages new biomarkers for the identification and ongoing monitoring of cardiovascular events. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-119/rc).

Highlight box

Key findings

- Global longitudinal strain (GLS) after cyclophosphamide chemotherapy may be a reliable indicator to predict cardiovascular events in patients receiving cyclophosphamide chemotherapy.

What is known and what is new?

- GLS can predict cardiac injury after chemotherapy in adults.
- In pediatric patients treated with high-dose cyclophosphamide chemotherapy, GLS could be a promising predictor for cardiovascular events.

What is the implication, and what should change now?

- GLS may become an indicator for monitoring cardiovascular events after high-dose cyclophosphamide chemotherapy in pediatric patients.

Methods

Subjects

The participants in this study were patients aged 14 years or younger who were treated in the pediatric hematology department from July 2021 to February 2022. Eligible patients who received high-dose cyclophosphamide (>120 mg/kg) with no other cardiotoxic drugs during the study (such as anthracyclines) reported in the European Society of Cardiology (ESC) (1) had an Eastern Cooperative Oncology Group (ECOG) score of 2 or less and provided informed consent (signed by guardians for patients under 10 years; signed by both the child and guardian for those 10 years or older). The exclusion criteria included a history of congenital heart disease, severe arrhythmia, myocarditis, valvular or rheumatic heart disease, previous thoracic radiotherapy or cardiac surgery. Withdrawal from the study was permitted under the following circumstances: family's voluntary decision, violation of the clinical trial protocol, unsuitability for continuation, or the occurrence of serious adverse effects during the trial. The chemotherapy protocols were based on myeloablative approaches (for patients with

benign disease) and modified BUCY (for patients with malignant disease). No patient received other cardiotoxic agents, radiation therapy, or cardiac protective protocols during this study. The infusion time for cyclophosphamide exceeded 2 hours, and an infusion pump was used. MESNA at a dosage of 400 mg/m^2 was administered at 0, 4, and 8 hours after cyclophosphamide injection to safeguard the mucous membranes of the urinary system, while patients were ensured proper hydration (total fluid volume over 2,000 mL/kg) and diuresis.

After providing informed consent, we gathered each subject's demographic data and clinical manifestations.

All patients were measured for GLS 1 day before cyclophosphamide chemotherapy (i.e., before medication) and were followed from the day of receipt of the cyclophosphamide chemistry until the date of incident cardiovascular injury or 30 days after the completion of the chemotherapy. Blood biomarkers, including troponin T and coagulated D-dimer, were also assessed 1 day prior to cyclophosphamide chemotherapy and 1 day post-chemotherapy.

Echocardiographic imaging

Echocardiography was evaluated before treatment and 1 day after chemotherapy and when there were signs of heart failure within 30 days after the completion of chemotherapy. Images were obtained in the left lateral decubitus position with a commercially available system (CX50, Phillips Medical Systems, Amsterdam, the Netherlands) with two probes: an 8-3 probe (probe frequency, 1.0–3.0 MHz) and an S5-1 probe (probe frequency, 1.0–5.0 MHz). All the images were acquired according to recommendations of the American Society of Echocardiography (11). Cardiac ultrasound images were acquired over four cardiac cycles using two-dimensional (2D) echocardiography. The left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) were then automatically calculated. The LVEF was calculated according to the recommendation of the American Society of Echocardiography with the Simpson biplane method (11). Speckle-tracking parameter values were obtained via on-machine analysis using QLAB software version 9.0 (Philips Medical Systems, Andover, MA, USA). All the measured values were averaged over six cardiac cycles. Regional strain values were averaged to determine global longitudinal/circumferential strain (GLS/GCS). For assessing GLS/GCS, standard 2D grayscale images of the LV were acquired from conventional, apical 2-, 3-, and 4-chamber views. The peak strain of each segment in the LV was defined as the peak negative value observed on the strain curve. This value is identified from the time of end-diastole, characterized by the largest LV chamber volume, to the end-systole, marked by the smallest LV chamber volume, across 16 LV segments. The GLS/GCS was then calculated by averaging the peak strain values from these 16 segments using the generated strain curve. According to guidelines from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, it is currently recommended that a GLS $\leq$–20% be considered the normal reference value limit (12). Echocardiographic imaging and analysis for all subjects were performed by the same operator to avoid the interoperator variability. The researcher conducting the analysis was blinded to the treatment.

ECG

The bedside ECG machine (ECG18U-DB15, Nalong Health Co., Ltd., Xiamen, China) was performed to detect cyclophosphamide-induced ECG changes. The ECG was recorded at a sampling rate of 1 kHz, allowing millisecond precision for the measurement of ECG intervals. ECG parameters (PR interval, QRS interval, and QT interval) were measured. It is measured by the variation in the PR intervals (from the start of the P wave to the start of QRS). The QRS interval was measured from the beginning of a Q wave to the termination of an S wave. The QT interval was measured from QRS onset to T-wave offset. All the ECG analyses were performed by the same ECG specialist.

Outcome

All subjects were followed for 30 days after the conclusion of cyclophosphamide chemotherapy. Our interesting outcome was the occurrence of cardiovascular events between 2 and 30 days after cyclophosphamide chemotherapy. Definition of cyclophosphamide-induced cardiac dysfunction: characterized by one or more of the following manifestations: (I) cardiomyopathy characterized by a decreased LVEF, presenting as reduced overall function or markedly decreased interventricular septal movement; (II) symptoms associated with congestive heart failure (such as a third heart sound gallop or tachycardia) or meeting the New York Heart Association (NYHA) classification. To evaluate cardiac dysfunction, the lower limit of LVEF was

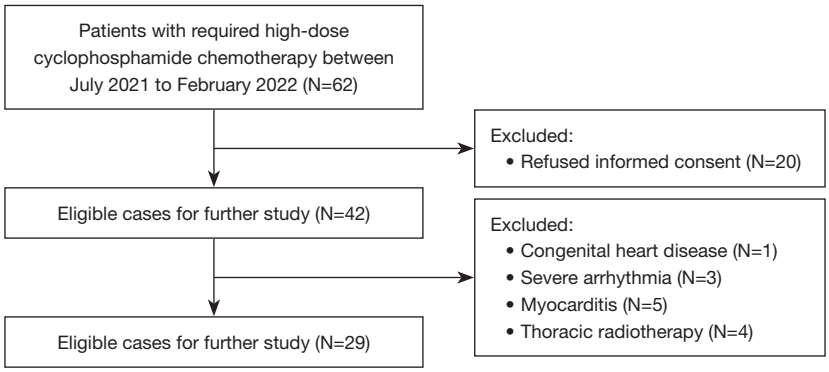

Figure 1 Flow diagram of patient selection.

taken as the 5th percentile for children with different body surface areas [according to the normal reference values of pediatric echocardiography from Pediatric Ultrasound Diagnostics (13); Table S1]. The patients were categorized into a cardiac injury group and a noncardiac injury group based on cyclophosphamide-induced cardiovascular events within 30 days following high-dose cyclophosphamide chemotherapy. The main outcome was a LVEF below the 5th percentile among children with different body surface areas. The secondary outcome was the incidence of arrhythmias.

Ethical considerations

This study was reviewed and approved by the Ethics Committee of the First Hospital Affiliated with Shandong First Medical University [No. (2020)250]. This study was registered at the American Clinical Trials Center (registration number: NCT05150080). Informed consent for participation was obtained from the parents or legal guardians of the patients in this study. This study was conducted in accordance with the Declaration of Helsinki (revised in 2013).

Statistical analysis

Statistical analyses were performed using STATA-MP 17.0 (StataCorp, College Station, TX, USA) and R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). The missing values were imputed by applying an imputation method based on random forests. Three pediatric patients showed no clinical symptoms of heart failure after medication until the end of our observation period, so no measurements of LVEF after medication were performed. These three patients were classified into the non-cardiac injury group. Normally distributed data are expressed as the mean ± standard deviation and were compared between groups using the *t*-test. Nonnormally distributed data are expressed as medians with interquartile ranges and were compared using the rank-sum test. Due to the exploratory nature of this study, sample size calculations were not performed. The cohort size was determined by the selection criteria among the consecutively recruited patients during the study period. Possible predictors of cardiovascular events (such as age, sex, body surface area, dosage of drugs, primary disease diagnosis, history of exposure to anthracyclines, GLS/GCS, PR interval, QRS interval, QT interval, troponin T, and coagulated D-dimer) were determined by univariate Poisson regression. Variables significantly associated with the outcome ($P<0.05$) and of clinical relevance were included in the multivariable-adjusted Poisson regression model. A P value <0.05 was considered to indicate statistical significance.

Results

Patient characteristics

Among 62 pediatric patients who required high-dose cyclophosphamide chemotherapy, 20 refused and requested to maintain their original conservative treatment. One patient with congenital heart disease, three with severe arrhythmia, five with myocarditis, and four with a history of thoracic radiotherapy were excluded. A total of 29 children, comprising 17 males and 12 females (median age of 8 years; range, 1–14 years), were enrolled in the study (*Figure 1*). The median follow-up time was 33 days, ranging from 32

to 34 days. The primary diagnoses of the patients included acute lymphoblastic leukemia in seven patients, acute myeloid leukemia in seven patients, very severe aplastic anemia in 14 patients, and pyruvate kinase deficiency in one patient (Table S2). These patients can be categorized into 14 patients with malignant disease and 15 patients with benign disease. All 14 patients with malignant diseases had a history of exposure to anthracycline drugs. Prior to enrollment in the study, 7 patients with acute lymphoblastic leukemia had cumulative doses of anthracyclines (132.86±24.30 mg/m^2) and cyclophosphamide (1.61±0.58 g/m^2). Seven patients with acute myeloid leukemia received a cumulative dose of anthracyclines (180.00±28.28 mg/m^2) before high-dose cyclophosphamide chemotherapy. Other patients had no exposure to anthracyclines or cyclophosphamide before being included in this study. The cardiac injury group included 10 patients (34.48%), and the non-cardiac injury group included 19 patients (65.52%). Comparative analysis revealed no significant differences between the two groups in terms of sex, age, height, weight, body surface area, primary diagnoses, or history of exposure to anthracycline drugs (*Table 1*). The differences between the two groups in GLS, GCS and ECG measurements before chemotherapy were not statistically significant (*Table 1*). The PR interval, QRS interval, and QT interval from ECG measurements (before medication) were missing in one case respectively. Troponin T (before medication) and coagulated D-dimer (before medication) levels were missing in seven cases respectively. The missing values of all variables were filled out using multiple imputation (*Table 1*).

One day after cyclophosphamide chemotherapy, changes in T-wave morphology were observed in two patients (6.90%), a prolonged QT interval in one patient (3.45%), and sinus tachycardia in three patients (10.34%). At 10 days after cyclophosphamide chemotherapy, incomplete right bundle branch block was observed in two patients (6.90%), changes in T-wave morphology in four patients (13.79%), prolonged QT interval in one patient (3.45%), sinus tachycardia in five patients (17.24%). A patient (3.45%) with pathological Q waves was diagnosed 30 days after cyclophosphamide chemotherapy. Cardiomyopathy, myocarditis, hypertension, pericardial, and valvular heart diseases were not observed during our study period.

Univariate and multivariable analyses of cardiovascular events

Change of GLS between baseline and 1 day after cyclophosphamide chemotherapy is shown in Figure S1. Before medication, GLS was similar between the two groups (–19.35%±0.63% *vs.* –20.74%±0.58%, P=0.15), whereas 1 day after cyclophosphamide chemotherapy, the GLS was significantly lower in the cardiac injury group than in the noncardiac injury group (–18.33%±1.81% *vs.* –20.03%±1.49%, P=0.01). According to the univariate analysis, GLS 1 day after cyclophosphamide chemotherapy was significantly associated with cardiovascular events. Among the factors reported to be related to cardiovascular events, including echocardiography, ECG and myocardial enzyme measurement indicators, only the total cyclophosphamide dose (160 *vs.* 120–159 mg/kg), GLS and GCS were found to be significant (P=0.04, 0.003 and 0.01, respectively; *Table 2*). According to the Poisson regression model adjusted for these three variables, considering the occurrence time of cardiovascular events as the exposure variable, GLS remained an independent predictor of cardiovascular events (incidence rate ratio: 1.46, 95% confidence interval: 1.02–2.09, P=0.04) (*Table 3*).

Discussion

Our study demonstrated that GLS 1 day after cyclophosphamide chemotherapy could be a promising predictor for cardiovascular events in patients receiving high-dose cyclophosphamide chemotherapy. This provides the possibility for early identification of cardiovascular events after high-dose cyclophosphamide chemotherapy. In this study, we determined that GLS could predict cardiovascular events after high-dose cyclophosphamide chemotherapy.

Adult patients receiving cyclophosphamide at a dose ≥170 mg/kg have a higher incidence of heart failure, with the incidence decreasing as the dose decreases (5). Patients with cyclophosphamide-induced heart failure have a higher mortality rate (14). Post-chemotherapy-related cardiovascular events were observed in 25% of patients who received intravenous cyclophosphamide at a dose of 200 mg/kg for 4 days (5) which is similar to our study. Katayama *et al.* reported the case of a 59-year-old man with diffuse large B-cell lymphoma who received high-dose cyclophosphamide (1.5 g/m^2 for 2 days) followed by autologous peripheral blood stem cell transplantation and developed congestive heart failure 5 days after cyclophosphamide administration. ECG revealed a very low voltage with ST-segment changes, and echocardiography revealed diffuse LV wall thickening, increased myocardial

Table 1 Characteristics of the study population

Characteristics	Total (n=29)	Cardiac injury group (n=10)	No-cardiac injury group (n=19)	P value
Age (years)	7.38±3.81	8.20±2.93	6.95±3.21	0.41
Gender (male)	17 (55.17)	6 (50.00)	11 (57.89)	0.91
Height (cm)	127.50±23.93	131.45±19.97	125.42±26.04	0.53
Weight (kg)	29.57±13.70	32.00±13.49	28.29±13.99	0.49
Body surface area unit (m^2)	1.01±0.32	1.07±0.31	0.98±0.34	0.49
Cyclophosphamide daily chemotherapy dose (mg/kg)	45.69±11.31	44.00±8.43	46.57±12.69	0.57
Cyclophosphamide chemotherapy duration (days)	3.21±0.82	3.00±0.67	3.32±0.89	0.33
Total cyclophosphamide chemotherapy dose (120–159 mg/kg)	19	12	7	0.050
Total cyclophosphamide chemotherapy dose (mg/kg)	140±20	146.32±18.92	128±16.87	0.16
Primary disease diagnosis (benign)	15	3	12	0.19
History of exposure to anthracyclines (have)	14	7	7	0.19
Prior anthracyclines dose (mg/m^2)	156.43±35.22	155.71±13.06	157.14±14.59	0.94
Prior cyclophosphamide dose (g/m^2)	1.61±0.58	1.33±0.33	1.83±0.28	0.31
GLS—before medication (%)	−20.26±0.45	−19.35±0.63	−20.74±0.58	0.15
GCS—before medication (%)	−21.86±0.51	−20.85±0.86	−22.42±0.63	0.15
GLS—1 day after cyclophosphamide chemotherapy (%)	−19.45±1.78	−18.33±1.81	−20.03±1.49	0.01
GCS—1 day after cyclophosphamide chemotherapy (%)	−21.83±3.56	−19.87±3.22	−22.86±3.35	0.03
PR interval—before medication (ms)	133.86±18.06	141.10±13.68	129.16±18.95	0.09
QRS interval—before medication (ms)	83.25±6.62	81.30±5.95	84.58±6.78	0.21
QT interval—before medication (ms)	345.46±43.83	360.10±36.87	341.58±48.57	0.30
PR interval—1 day after cyclophosphamide chemotherapy (ms)	135.68±14.43	139.80±11.17	132.58±13.86	0.17
QRS interval—1 day after cyclophosphamide chemotherapy (ms)	82.54±6.43	80.10±6.14	83.26±6.09	0.19
QT interval—1 day after cyclophosphamide chemotherapy (ms)	336.54±46.92	336.60±45.55	338.58±48.45	0.92
Troponin T—before medication (pg/mL)	6.65±4.08	6.08±4.39	6.96±4.00	0.59
Coagulated D-dimer—before medication (mg/L)	1.63±2.02	2.10±2.92	1.39±1.37	0.48
Troponin T—1 day after cyclophosphamide chemotherapy (pg/mL)	6.49±5.19	7.36±5.97	6.04±4.84	0.53
Coagulated D-dimer—1 day after cyclophosphamide chemotherapy (mg/L)	1.02±1.00	1.01±1.01	1.03±1.02	0.96

Data are presented as n, or n (%), or mean ± standard deviation. PR intervals: from the start of the P wave to the start of QRS; QRS interval: from the beginning of a Q wave to the termination of an S wave; QT interval: from QRS onset to T-wave offset. GLS, global longitudinal strain; GCS, global circumferential strain.

hypertrophy, strong echogenicity, pericardial effusion, and generally decreased systolic function. This case study demonstrated the rapid progression of congestive heart failure (15). Among the pediatric patients, however, we did not observe any cases of fatal heart failure in our study. Our study population was children under the age of 14 years, while previous studies were conducted in adult populations, some of whom had a history of heart disease and thoracic radiotherapy. Simultaneously, our study participants were all children without any history of cardiac disease who had

Table 2 Univariate analysis of predictors of cardiovascular events

Variables	IRR†	95% confidence interval		P value
		Lower limit	Upper limit	
Age (years)	1.07	0.91	1.25	0.41
Gender (female *vs.* male)	0.95	0.27	3.36	0.93
Height (cm)	1.01	0.98	1.03	0.55
Weight (kg)	1.01	0.97	1.06	0.52
Body surface area (m^2)	1.87	0.28	12.46	0.52
Cyclophosphamide chemotherapy single daily dose (mg/kg)	0.98	0.92	1.04	0.49
Cyclophosphamide chemotherapy duration (days)	0.73	0.36	1.46	0.37
Cyclophosphamide chemotherapy total dose (160 *vs.* 120–159 mg/kg)	0.19	0.04	0.89	0.04*
Primary disease diagnosis	0.32	0.08	1.22	0.09
History of exposure to anthracyclines	3.16	0.82	12.21	0.09
Prior anthracyclines dose (mg/m^2)	1.00	0.98	1.02	0.91
Prior cyclophosphamide dose (g/m^2)	0.34	0.04	3.25	0.35
GLS—before medication (%)	1.21	0.93	1.59	0.16
GLS—1 day after cyclophosphamide chemotherapy (%)	1.70	1.20	2.42	0.003*
GCS—before medication (%)	1.23	0.95	1.59	0.11
GCS—1 day after cyclophosphamide chemotherapy (%)	1.30	1.06	1.59	0.01*
PR interval—before medication (ms)	1.04	0.99	1.08	0.10
QRS interval—before medication (ms)	0.92	0.83	1.03	0.15
QT interval—before medication (ms)	1.01	0.99	1.02	0.31
PR interval—1 day after cyclophosphamide chemotherapy (ms)	1.04	0.99	1.08	0.13
QRS interval—1 day after cyclophosphamide chemotherapy (ms)	0.91	0.81	1.03	0.13
QT interval—1 day after cyclophosphamide chemotherapy (ms)	1.00	0.99	1.01	0.95
Troponin T—before medication (pg/mL)	0.94	0.77	1.13	0.49
Coagulated D-dimer—before medication (mg/L)	1.19	0.91	1.56	0.21
Troponin T—1 day after cyclophosphamide chemotherapy (pg/mL)	1.04	0.94	1.15	0.48
Coagulated D-dimer—1 day after cyclophosphamide chemotherapy (mg/L)	0.90	0.48	1.70	0.76

†, from a univariate Poisson regression; *, P<0.05. PR intervals: from the start of the P wave to the start of QRS; QRS interval: from the beginning of a Q wave to the termination of an S wave; QT interval: from QRS onset to T-wave offset. IRR, incidence rate ratio; GLS, global longitudinal strain; GCS, global circumferential strain.

not undergone thoracic radiotherapy.

Some chemotherapy drugs can lead to long-term heart damage, such as cyclophosphamide (16) and anthracyclines (17). Despite a relative decrease in fatal cardiotoxicity with modern dosing, both the short-term and long-term cardiac toxicities of cyclophosphamide still warrant attention. Studies have highlighted the cardiotoxic sequelae of cyclophosphamide, which can manifest chronically years after drug administration (18-20). One significant long-term study by Mäkinen *et al.* (16) reported persistent cardiotoxic effects over a follow-up period of 10.3–27.34 years. Patients exposed to cyclophosphamide in this study exhibited abnormalities such as altered QRS and PQ intervals, and depressed ST intervals, which contributed to heart failure.

Table 3 Multivariable Poisson regression results

Variables	Incidence rate ratio[†]	95% confidence interval		P value
		Lower limit	Upper limit	
GLS—1 day after cyclophosphamide chemotherapy	1.46	1.02	2.09	0.04
GCS—1 day after cyclophosphamide chemotherapy	1.09	0.88	1.35	0.41
Cyclophosphamide chemotherapy total dose (160 *vs.* 120–159 mg/kg)	0.26	0.05	1.29	0.10

[†], incidence rate ratio and the 95% confidence interval was derived from a Poisson regression model adjusted for all the listed variables. GLS, global longitudinal strain; GCS, global circumferential strain.

Studies related to cyclophosphamide cardiovascular events in adults have focused mainly on the LV shortening fraction (SF) and ejection fraction (EF) and these topics are lacking because of the course of treatment and cardiac observations for children (21,22). Moreover, the sensitivity of EF indices for evaluating cardiac function is relatively weak (23). To date, this study is the first to investigate the cardiovascular event risk factors in children after high-dose cyclophosphamide chemotherapy.

Using ultrasound imaging parameters to improve risk stratification may be a more accurate and convenient assessment method (24). The American Society of Echocardiography, the European Association of Cardiovascular Imaging, and the ESC consensus documents suggest that the GLS of the LV measured by speckle-tracking echocardiography should be the best deformity index for early detection of subclinical LV dysfunction in patients after chemotherapy (25). A meta-analysis showed that GLS suggests cardiac damage earlier than LVEF in post-chemotherapy patients (26). Therefore, this study proposed that the GLS may be an indicator for predicting cardiovascular events. Our research indicated that GLS independently predicts cardiovascular events after high-dose cyclophosphamide chemotherapy, consistent with earlier studies on anthracycline chemotherapy-related cardiovascular events (9,27). Remy and colleagues' study, which included 23 patients receiving a conventional dose of cyclophosphamide chemotherapy, reported that cyclophosphamide was not associated with LVEF or GLS at the conventional dose of cyclophosphamide (8). Nonetheless, based on several studies, the cardiotoxic effects of cyclophosphamide are not prominent at routine doses, yet cardiac injury occurs at high doses (6,28), as observed in our study. Through regular echocardiographic measurements, for the first time, we highlighted the potential of GLS for predicting cardiovascular events within a 30-day follow-up period (characterized by increased mortality) due to high doses of cyclophosphamide chemotherapy. Early detection of cardiac injury through GLS may be important for early cardioprotective intervention or treatment.

Novelty and limitations

This study constructed GLS (1 day after cyclophosphamide chemotherapy) could predict cardiovascular events after high-dose cyclophosphamide chemotherapy. The limitation of this study lies in the small single-center sample size. The generalizability of our findings is limited by the fact that we focused only on early childhood patients aged 14 years and younger, although we see no reason why this finding would materially differ across the entire childhood. Nevertheless, multicenter studies with larger and more diverse populations are needed to validate our findings. Given that very few children receive high-dose (>120 mg/kg) cyclophosphamide chemotherapy in clinical practice, the sample size of this study was small. Therefore, the results may not be sufficiently robust, but considering the rarity of such patients, high clinical mortality, and interpretability of the results, they are still presented. As time progresses and sample sizes increase, we will obtain a more robust model and multicenter and large-sample studies can be conducted to further revise and improve the applicability of the model. Residual confounding cannot be ruled out and the generalizability of our findings to other settings needs to be validated.

Conclusions

Assessment of GLS based on 2D speckle tracking echocardiography might be a promising noninvasive predictor of the occurrence of cardiovascular events after high-dose cyclophosphamide chemotherapy, which might play an essential role in helping physicians enact better treatment strategies at the time of initial diagnosis.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-119/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-119/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-119/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (revised in 2013). This study was reviewed and approved by the Ethics Committee of First Hospital Affiliated with Shandong First Medical University [No. (2020) 250]. Informed consent for participation was obtained from the parents or legal guardians of the patients.

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