Original Article

Mechanical property evaluation of the right ventricular myocardium in cancer patients with chemotherapy by echocardiography: a systematic review and meta-analysis

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Background: Cancer therapy-related cardiotoxicity has recently become an area of intense research. As the prognostic role of the right ventricle (RV) in a variety of cardiovascular diseases has been confirmed, and several studies have paid increased attention to RV function in cancer patients who have underwent chemotherapy, we provide a meta-analysis to objectively evaluate the mechanical properties of the right ventricular myocardium by echocardiography in this population.

Methods: We systematically searched Embase, PubMed, and Cochrane databases were applied to search for studies (published before August 11, 2021) comparing RV contraction measured by echocardiography at baseline to follow-up in cancer patients who underwent chemotherapy or radiotherapy. The mechanical properties of the right ventricular myocardium were pulmonary artery systolic pressure (PASP), tricuspid annular plane systolic excursion (TAPSE), systolic velocity of tricuspid annulus (S'), right ventricular free wall longitudinal strain (RVFWLS), right ventricular global longitudinal strain (RVGLS), and right ventricular fractional area change (RVFAC). We analyzed pooled data using a random-effects model and assessed risk of bias in the included studies using the Newcastle-Ottawa Scale.

Results: Twenty-one trials were enrolled (N=1,355 participants). Cancer patients who underwent chemotherapy but not radiotherapy showed an increase in PASP [standardized mean difference (SMD) =0.161, 95% CI: 0.007 to 0.316) compared with the condition at baseline, as well as reductions in TAPSE (SMD =−0.543, 95% CI: −0.698 to −0.389), S' (SMD =−0.507, 95% CI: −0.748 to −0.266), RVFWLS (SMD =0.833, 95% CI: 0.549 to 1.118) and RVGLS (SMD =1.017, 95% CI: 0.751 to 1.283). There was no significant difference in RVFAC (SMD =−0.097, 95% CI: −0.213 to 0.018). Furthermore, these indicators pointed to a deterioration of right ventricular contraction function in cancer patients who underwent chemotherapy and radiotherapy. The risk of bias of the included studies evaluated by the Newcastle-Ottawa Scale was medium to high.

Discussion: Right ventricular contraction function would deteriorate in cancer patients who underwent chemotherapy and radiotherapy, especially with the prolongation of chemotherapy duration and accumulation of chemotherapeutic drugs. Further studies are needed to establish the definition of right ventricular systolic dysfunction in clinical practice.

Keywords: Right ventricle (RV); echocardiography; cancer patients; chemotherapy

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Introduction

With the development of modern cancer treatment, the mortality rate of cancer patients has significantly decreased (1,2). However, cancer therapy-related cardiotoxicity remains as the leading cause of morbidity and mortality in cancer survivors (3,4), and cardiovascular complications caused by cancer therapy have become the second largest threat to the long-term survival of patients (5). As a result, for patients with cancer, contemporary management should focus on the identification of potential cardiotoxicity during anticancer therapy for early detection and intervention.

Cardiovascular side effects caused by chemotherapy or radiotherapy mainly include myocardial dysfunction, heart failure, myocardial ischemia, arrhythmia, arterial hypertension, and pulmonary hypertension, among which myocardial dysfunction and heart failure are the most common cardiotoxicities (6). According to the type and the intensity of the anticancer regimen, the risk and the degree of cardiotoxicity are different. Common chemotherapeutic drugs that cause cardiotoxicity include anthracycline and fluorouracil, as well as, targeted agents such as human epidermal growth factor 2 (HER-2) inhibitors and angiogenesis inhibitors. Most cardiotoxicity caused by anthracyclines is type I, which involves myocyte death, as well as, irreversible and permanent myocardial injury in a dose-dependent manner (7), while trastuzumab, an HER-2 inhibitor, mostly leads to type II treatment-related cardiac damage, whose effects are reversible in a dose-independent manner and without the induction of significant ultrastructural changes (7).

Position papers and recommendations on the prevention and treatment of cancer therapy-related cardiotoxicity refer mainly to the left ventricle. The guidelines recommend measuring the left ventricular ejection fraction (LVEF) to monitor the occurrence of cardiotoxicity, defining cancer therapy-related cardiotoxicity by the left ventricular index, and using the left ventricular global longitudinal strain (LVGLS) to monitor myocardial function (8-10). The importance of right ventricular structure and function in a variety of cardiovascular diseases, such as heart failure, coronary artery disease, valvular disease, pulmonary hypertension, and hypertrophic cardiomyopathy, has been confirmed (11-15), and greater attention has been paid to the inclusion of right ventricular assessment in cancer patients who have underwent chemotherapy and radiotherapy.

An increasing number of studies have begun to evaluate changes of the right ventricle (RV). Some studies have reported that RV function decreases early, even before the derangement of LV function, while other studies have not identified significant statistical changes in RV contraction. Furthermore, several indexes can evaluate right ventricular contraction, and different studies have reported changes in different parameters at variable degrees. Thus, a meta-analysis of these studies was performed to objectively evaluate the mechanical properties of the right ventricular myocardium by echocardiography in cancer patients who have underwent chemotherapy. We present the following analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2324/rc).

Methods

Searching strategies and selection criteria

This systematic review and meta-analysis was reported in accordance with the PRISMA Statement (16) and was registered at the International Prospective Register of Systematic Reviews (No. CRD42021284129). Selected studies were published before August 11, 2021 by application of Embase, PubMed, and CENTRAL (Cochrane Central of Controlled Trials) databases. A manual search was adopted as well. The combined texts and MeSH terms were used during the searches as follows: "right ventricle" "cardiotoxicity" "chemotherapy", and "deformation". The complete search terms used for PubMed were: (chemotherapy[MeSH Terms] OR chemotherap* OR trastuzumab OR pertuzumab OR trastuzumab emtansine OR lapatinib OR neratinib OR anthracycline OR doxorubicin OR adriamycin OR idarubicin OR epirubicin OR daunorubicin OR mitoxantrone OR 5-fluorouracil OR paclitaxel OR cyclophosphamide) AND (cardiotoxicity[MeSH Terms] OR heart failure[MeSH Terms] OR ventricular dysfunction[MeSH Terms] OR cardiotox* OR heart failure OR ventricular dysfunction) AND (right ventricle OR heart right ventricle wall) AND (deformation OR strain OR global longitudinal strain). All potentially eligible studies were selected for reviewing irrespective of primary outcomes or languages.

Study selection and evaluated outcomes

Studies were regarded as eligible for enrollment if they were performed in cancer patients who underwent chemotherapy and reported right ventricular global longitudinal strain (RVGLS), right ventricular free wall longitudinal strain (RVFWLS), tricuspid annular plane systolic excursion (TAPSE), systolic velocity of tricuspid annulus (S'), right ventricular fractional area change (RVFAC), and pulmonary artery systolic pressure (PASP) by echocardiography at baseline and follow-up. Studies were excluded if they did not adhere to the aforementioned criteria. Ethical approval was not required as this was a systematic review and meta-analysis.

We compared the mechanical properties of the right ventricular myocardium in cancer patients who underwent chemotherapy at baseline and follow-up, without restrictions on treatment history. The evaluated outcomes were as follows: RVGLS, RVFWLS, TAPSE, S', and PASP, which were measured by echocardiography at baseline, at the end of several cycles, or several months after the completion of the entire regimen. The RVFAC was calculated by measuring the end-diastolic and end-systolic area of the RV.

Data extraction and assessment

Titles and abstracts from different studies were reviewed by two independent investigators. Studies qualified for inclusion were retrieved, and the full text was reviewed. Trials selected for detailed analysis and data extraction were analyzed by two independent investigators, and disagreements were evaluated and resolved by a third investigator. The following data were extracted from the selected studies: basic characteristics of the study (author, published year, sample size, and ultrasound system), features of the included patients (average age, gender, weight, height, body mass index, body surface index, heart rate, blood pressure, malignancy history, comorbidities, cumulative dose of drugs, received radiotherapy or not), and the outcomes including RVGLS, RVFWLS, TAPSE, S', PASP and RVFAC at baseline and follow-up.

Two independent reviewers assessed risk of bias according to PRISMA recommendations. The quality of the included studies was assessed using the validated Newcastle-Ottawa Scale, which evaluates nonrandomized observational studies recommended by the nonrandomized research methodology group of Cochrane Collaboration. The Newcastle-Ottawa Scale evaluated the quality of the enrolled articles from three dimensions, including selection, comparability, and outcome, with a full score of nine stars.

Statistical analysis

The mechanical properties of the right ventricular myocardium in cancer patients who underwent chemotherapy were assessed based on six parameters as follows: RVGLS, RVFWLS, TAPSE, S', PASP, and RVFAC, which were measured by echocardiography. These indexes were regarded as continuous variables and reported absolute differences between arithmetic means before and after chemotherapy. Pooled estimates of the standardized mean differences of these indexes were calculated using a random-effects model. Meanwhile, pre-planned sensitivity analysis was performed before formal meta-analysis of TAPSE, S', RVFWLS and RVGLS. The possibility of publication biases of these parameters was also assessed utilizing the Egger test and the Begg test, and P values <0.05 were taken as significant publication bias. The Cochran Q test was performed to assess heterogeneity between studies, and P values <0.05 were taken as significant heterogeneity. The I^2 test was also adopted to assess the magnitude of the heterogeneity, and values greater than 50% were taken as moderate-to-high heterogeneity. In cases of obvious heterogeneity, Stata software was used for sensitivity analysis of the impact of a single study on the overall study. Stata version 16.0 software (StataCorp LP, College Station, TX, USA) was used for all statistical analysis.

Results

Characteristics of included trials

Two hundred and fifty-nine studies were identified from databases and manual search after excluding duplicated studies. Finally, twenty-one trials published between 2013 to 2021, including 1,355 participants, were adopted in our analysis (17-37). The detailed process of literature searching and the explanation for exclusion are described in *Figure 1*.

The characteristics of these studies included study information, and the demographic characteristics are summarized in *Tables 1,2*. Among the included studies, all patients received chemotherapy, and in five studies, patients received radiotherapy. Most studies provided percentages or numbers pertaining to the mean age (ranged from 11.85 to 60 years), male ratio (ranged from 0% to 65.6%), mean cumulative dose (Anthracycline ranged from 175 to 483.0 mg/m^2), mean body mass index (ranged from 25.1 to 27.9 kg/m^2), and ratio of smokers (ranged from 10% to 68.7%). Some patients presented comorbidities, such as hypertension (the ratio ranged from 11.8% to 77.14%),

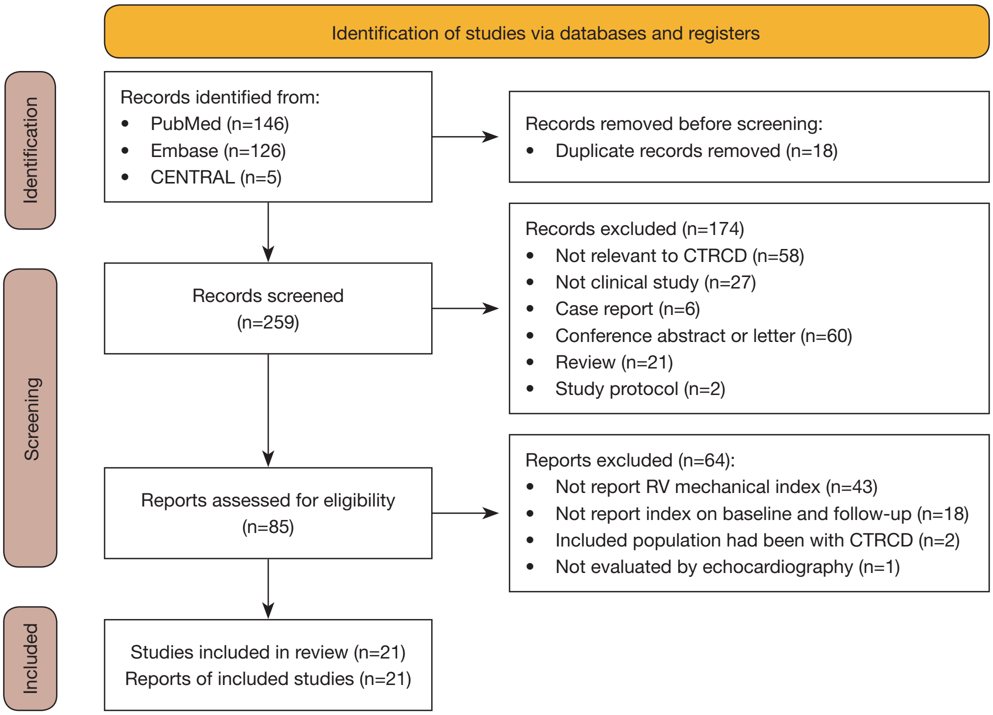
Identification of studies via databases and registers
Identification
Screening
Included
Records identified from:
• PubMed (n=146)
• Embase (n=126)
• CENTRAL (n=5)
Records removed before screening:
• Duplicate records removed (n=18)
Records screened (n=259)
Records excluded (n=174)
• Not relevant to CTRCD (n=58)
• Not clinical study (n=27)
• Case report (n=6)
• Conference abstract or letter (n=60)
• Review (n=21)
• Study protocol (n=2)
Reports assessed for eligibility (n=85)
Reports excluded (n=64):
• Not report RV mechanical index (n=43)
• Not report index on baseline and follow-up (n=18)
• Included population had been with CTRCD (n=2)
• Not evaluated by echocardiography (n=1)
Studies included in review (n=21)
Reports of included studies (n=21)

Figure 1 Detailed process of literature searching and exclusion. CENTRAL, Cochrane Central of Controlled Trials; CTRCD, cancer therapeutics related cardiac dysfunction.

diabetes mellitus (the ratio range from 1.6 % to 54.2%), and hyperlipidemia (the ratio ranged from 6.7% to 51.4%). The quality of the enrolled articles evaluated by the Newcastle-Ottawa Scale was medium to high, with a total score of 6–9 (*Table 3*). The main confounding factors included medications and heart disease history before chemotherapy, which may have affected the outcomes. These indexes were used to evaluate the mechanical properties of the right ventricular myocardium reported in most studies during the different stages of chemotherapy. Notably, strain of the right ventricular myocardium was reported in seventeen studies.

Changes of mechanical properties in patients without radiotherapy

Sixteen articles reported changes in the mechanical properties of the RV during the different stages of chemotherapy. This cohort comprised of 975 cancer patients who underwent chemotherapy but not radiotherapy.

PASP increased [standardized mean difference (SMD) =0.161, 95% CI: 0.007 to 0.316, P=0.040, *Figure 2*] compared to the condition at baseline. An analysis of this outcome showed a prominent heterogeneity between the studies (P value of Q test =0.005, I^2=58.8%). The Egger or Begg test demonstrated that there was no evident publication bias (P value of Egger test =0.295, P value of Begg test =0.193).

The results of TAPSE assessed in a pooled analysis indicated there was a reduction in patients who underwent chemotherapy (SMD =–0.543, 95% CI: –0.698 to –0.389, P=0.000, *Figure 3*) compared to the condition before chemotherapy, and there was significant heterogeneity between each study (P value of Q test =0.000, I^2=81.4%). The Egger or Begg test demonstrated evident publication bias in this study (P value of Egger test =0.000, P value of Begg test =0.004). Moreover, all subgroups showed a significant reduction with no publication bias, except the subgroup of “1–2 Cycles”, and TAPSE showed a reduction at the stage of “6–8 Cycles” without heterogeneity between studies (*Table 4*).

Combined data from these studies implied that the mechanical property of the RV evaluated by S' exhibited a reduction after chemotherapy (SMD =–0.507, 95% CI: –0.748 to –0.266, P=0.000, *Figure 4*), and a statistically significant heterogeneity was observed (P value of Q test =0.000, I^2=89.5%). We found that the data from Lange’s

Table 1 Characteristics of included studies

Study	Region	Sample	Mean age, y	Male, n [%]	Cumulative dose (mg/m^2)	Malignancy history, n [%]	Radiotherapy, n [%]	Ultrasonic system
Zhao 2020	Shanghai, China	74	48.9±11.8	41 [55]	Anthracycline 358.20±69.04	DLBCL	Without	iE33, Philips Medical Systems (Andover Massachusetts)
Wang 2018	Nanjing, China	36	34±7	0 [0]	Anthracycline –	Breast cancer	Without	Toshiba Artida SSH-880CV (Japan)
Wang 2021	Cangzhou, China	61	50.8±12.1	29 [47.5]	Anthracycline 311.2±99.8	DLBCL	Without	iE33, Philips Medical Systems (Bothell, WA, USA)
Song 2017	Shanghai, China	89	49.3±12.5	60 [59]	Anthracycline 358.20±69.03	DLBCL	Without	iE33, Philips Medical Systems (Andover WA, USA)
Planek 2020	USA	35	50.6±13.2	21 [60]	Anthracycline 239±104	Lymphoma	Without	Vivid 7, GE Vingmed Ultrasound AS (Horten, Norway)
Paraskevaidis 2017	Greece	80	45±11	44 [55]	–	NHL 40 [50]; AML 32 [40]; CML 8 [10]	Without	Vivid 7, GE Vingmed Ultrasound (Horten, Norway)
Moustafa 2016	USA	50	60±13	0 [0]	Anthracycline ≤240	Breast cancer	31 [62]	VVI system, Siemens Medical Solutions USA (Malvern, PA, USA)
Keramida 2019	USA	101	54.3±11.4	0 [0]	Anthracycline 483.0±145.1	Breast cancer	55 [54.4]	Vivid E9, GE Vingmed Ultrasound; iE33, Philips Medical Systems
Boczar 2016	Canada	49	53.4±3.3	1 [2]	Doxorubicin 232±30.99; Epirubicin 294.12±23.90	Breast cancer	Without	TomTec Imaging Systems (Unterschleissheim, Germany)
Cherata 2019	Romania	68	55±14	35 [51]	–	HL 9 [13.2]; NHL 20 [29.4]; MM 17 [25]; AML 10 [14.7]; ALL 7 [10.3]; others 5 [7.4]	Without	Vivid E9 GE Healthcare (Horten, Norway); iE33, Philips Ultrasound
Chen 2019	Shanghai, China	128	60±19	84 [65.6]	–	NSCLC: squamous 34 [26.6]; non-squamous 4 [73.4]	128 [100]	Vivid 7 or E9, GE Vingmed Ultrasound (Horten, Norway)
Chang 2016	Taiwan, China	35	45.33±8.48	0 [0]	Anthracycline 354.19±336.08	Breast cancer	2 [5.71]	Vivid E9, GE Vingmed Ultrasound AS (Horten, Norway)
Arciniegas Calle 2018	USA	66	52±9	0 [0]	Anthracycline 252±45; trastuzumab 5.4±2.7 g	Breast cancer	50 [76]	GE Vivid 7 system (General Electric Company)
Anqi 2019	China	36	47.27±9.90	0 [0]	Anthracycline 363.90±107.77	Breast cancer	Without	EPIQ7C, Philips Medical Systems

Table 1 (*continued*)

Table 1 (*continued*)

Study	Region	Sample	Mean age, y	Male, n [%]	Cumulative dose (mg/m^2)	Malignancy history, n [%]	Radiotherapy, n [%]	Ultrasonic system
Mornoş 2014	Romania	59	51±10	24 [40.7]	Anthracycline 175±62	NHL 12 [20.3]; HL 10 [16.9]; ALL 8 [13.6]; AML 2 [3.4]; breast cancer 26 [44.1]; osteosarcoma 1 [1.7]	Without	Vivid 9 General Electric (Milwaukee, WI); version 6.0, GE Healthcare (UK)
Lange 2016	Germany	27	56 [38–75]	0	–	Breast cancer	Without	–
Xu 2019	Shanghai, China	60	52±14	35 [58.3]	Anthracycline 238±21.8	DLBCL	Without	iE33，Philips Medical Systems (Andover, WA, USA)
Wang 2020	Nanjing, China	32	33.2±8.3	0	–	Breast cancer	Without	Artida SSH-880CV (Toshiba, Japan)
Mornos 2013	Romania	74	51±11	31 [41.9]	Anthracycline 259±52	NHL 15 [20.3]; HL 13 [17.6]; ALL 9 [12.1]; AML 2 [2.7]; breast cancer 33 [44.6]; osteosarcoma 2 [2.7]	Without	Vivid 7 GE, Milwaukee (Wisconsin, USA); version 6.0, GE Healthcare (UK)
Khairat 2019	Egypt	100	11.85±2.09	50 [50.0]	Anthracycline 450	Osteosarcoma	Without	Vivid 7 or E9 GE Vingmed Ultrasound (Horten, Norway)
Xu 2021	Nanjing, China	95	53.2±8.7	0	Anthracycline 360	Breast cancer	Without	GE Vivid E9 ultrasound machine (Horten, Norway)

DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; ALL, acute lymphoblastic leukemia; MM, multiple myeloma; NSCLC, non-small cell lung cancer.

study had an impact on the overall result, namely, in the sensitivity analysis of TAPSE and S'. We speculate that the small sample size of this trial may have affected the accuracy of the results. The Begg test illustrated that no evident publication bias was found in this study (P value of Begg test =0.369). Furthermore, this significant reduction of S' was observed in a late stage of treatment without publication bias (*Table 4*).

We used free wall longitudinal strain (FWLS) and global longitudinal strain (GLS), whose values were negative, to evaluate the change of strain of the RV. Our study demonstrated a significant decrease of RVFWLS (SMD =0.833, 95% CI: 0.549 to 1.118, P=0.000, *Figure 5*) and RVGLS (SMD =1.017, 95% CI: 0.751 to 1.283, P=0.000, *Figure 6*) with heterogeneity between studies (P value of Q test =0.000, I^2=91.3%). The sensitivity analysis of right ventricular strain showed that the results reported by Wang had an effect on the overall study. The subjects of this study were mainly young patients, and the observation period was relatively short, which might have contributed to the limitations of the test results. The Begg test showed that there was no evident publication bias in this analysis (P value of Begg test =0.055). All subgroups showed an evident reduction of strain without publication bias (*Table 4*).

There was no significant difference in RVFAC (SMD =–0.097, 95% CI: –0.213 to 0.018, P=0.099) with significant heterogeneity between these studies (P value of Q test =0.000, I^2=68.8%).

Changes in the mechanical properties in all patients who underwent chemotherapy

We further explored the changes in the mechanical properties of the RV in cancer patients who underwent

Table 2 Demographic characteristics of included studies

Study	Height (cm)	Weight (kg)	BMI (kg/m^2)	BSA (m^2)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	Smoker, n [%]	Hyper-tension, n [%]	Diabetes mellitus, n [%]	Hyper-lipidemia, n [%]
Zhao 2020	166.9±6.1	65.6±11.6	–	–	78.6±11.9	117.4±9.6	75.2±7.4	20 [27]	–	5 [7]	–
Wang 2018	–	–	–	–	–	–	–	–	–	–	–
Wang 2021	–	–	26.6±5.5	1.73±0.17	65.9±10.1	125.1±15.7	77.2±8.6	18 [29.5]	20 [32.8]	9 [14.8]	–
Song 2017	166.9±6.1	65.6±11.6	–	1.7±0.1	78.6±11.9	117.4±9.6	75.2±7.4	–	–	–	–
Planek 2020	–	–	27.9±5.6	–	89.1±14.2	–	–	13 [37.1]	27 [77.14]	19 [54.2]	18 [51.4]
Paraskevaidis 2017	–	–	–	–	77±12	125±6	76±6	16 [20]	12 [15]	–	8 [10]
Moustafa 2016	–	–	26.5±5.2	–	71±11	–	–	5 [10]	14 [28]	8 [16]	10 [20]
Keramida 2019	–	–	–	1.8±0.2	–	–	–	–	15 [14.8]	–	–
Boczar 2016	–	–	25.9±1.3	–	83.0±31.3	–	–	21 [42.9]	12 [24.5]	7 [14.3]	7 [14.3]
Cherata 2019	–	–	–	1.84±2.14	79±13	127±17	75±12	9 [13]	11 [16]	3 [4.4]	–
Chen 2019	–	–	–	–	–	–	–	88 [68.7]	–	–	–
Chang 2016	157.57±5.74	56.88±6.86	–	1.63±0.21	73.5±8.24	129.66±14.01	82.66±7.37		–	–	–
Arciniegas Calle 2018	–	–	–	–	71±12	–	–	13 [20]	13 [20]	3 [5]	12 [18]
Anqi 2019	1.60±0.43	65.41±9.15	25.45±3.44	1.66±0.13	83.92±9.86	131.42±16.75	76.65±9.85	–	10 [27.78]	–	–
Mornoş 2014	–	–	25.1±3.8	–	73±10	121±17	76±9	10 [16.9]	7 [11.8]	1 [1.6]	4 [6.7]
Lange 2016	–	–	26.26±3.74	–	–	–	–	–	–	–	–
Xu 2019	–	63±14	–	–	80.6±11.6	–	–	–	–	–	–
Wang 2020	–	–	–	–	–	–	–	–	–	–	–
Mornos 2013	–	–	25.3±3.7	–	72±10	120±16	75±9	15 [20.2]	11 [14.8]	3 [4.0]	8 [10.8]
Khairat 2019	–	–	–	1.39±0.07	–	–	–	–	–	–	–
Xu 2021	–	–	25.5±3.4	1.6±0.1	70.8±8.0	113.2±9.9	71.4±6.2	–	–	–	–

BMI, body mass index; BSA, body surface index; HR, heart rate; bpm, beat per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3 Quality of the enrolled articles evaluated by Newcastle-Ottawa Scale

	Selection				Comparability	Outcome			
Study	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total score
Zhao 2020	*	*	*	*	**	*		*	8
Wang 2018	*	*	*	*		*		*	6
Wang 2021	*	*	*	*	**	*	*	*	9
Song 2017	*	*	*	*	*	*		*	7
Planek 2020	*	*	*	*	**	*	*	*	9
Paraskevaidis 2017	*	*	*	*	**	*	*	*	9
Moustafa 2016	*	*	*	*	*	*	*	*	8
Keramida 2019	*	*	*	*	*	*	*	*	8
Boczar 2016	*	*	*	*	**	*	*	*	9
Cherata 2019	*	*	*	*	*	*	*	*	8
Chen 2019	*	*	*	*	*	*		*	7
Chang 2016	*	*	*	*	*	*	*	*	8
Arciniegas Calle 2018	*	*	*	*	*	*	*	*	8
Anqi 2019	*	*	*	*	**	*		*	8
Mornoş 2014	*	*	*	*	**	*	*	*	9
Lange 2016	*	*	*	*		*	*	*	7
Xu 2019	*	*	*	*		*		*	6
Wang 2020	*	*	*	*		*		*	6
Mornos 2013	*	*	*	*	**	*		*	8
Khairat 2019	*	*	*	*		*	*	*	7
Xu 2021	*	*	*	*	*	*	*	*	8

*, give asterisks according to the description of the Newcastle-Ottawa Scale, a higher total score indicates that the quality of the study is better. (Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability).

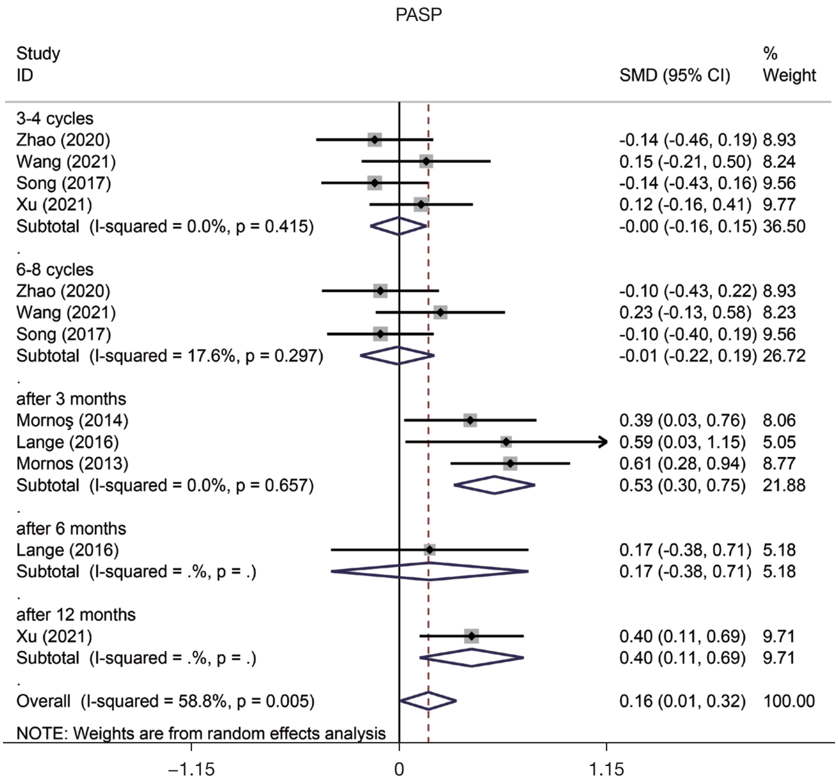

Figure 2 Forest plot of the change of PASP. PASP, pulmonary artery systolic pressure; SMD, standardized mean difference.

chemotherapy and radiotherapy. This analysis included PASP, TAPSE, S', RVFWLS, and RVGLS (*Table 5*). The results of PASP assessed in this analysis indicated there was an increase in cancer patients who underwent chemotherapy or radiotherapy (SMD =0.175, 95% CI: 0.027 to 0.324, P=0.020). The pooled analysis of TAPSE showed a significant reduction in the mechanical properties of the RV after chemotherapy (SMD =−0.475, 95% CI: −0.606 to −0.345, P=0.000) compared with the baseline, and this phenomenon was observed in every stage of treatment. Our study also demonstrated a reduction of S' (SMD =−0.401, 95% CI: −0.580 to −0.222, P=0.000) and RVFWLS (SMD =0.702, 95% CI: 0.482 to 0.923, P=0.000). Notably, almost in every subgroup, we found an evident reduction of right ventricular strain, especially GLS (SMD =0.853, 95% CI: 0.655 to 1.052, P=0.000).

Discussion

Cancer therapeutics related cardiac dysfunction (CTRCD)

With improvements in cancer diagnosis and treatment, the incidence of anticancer therapy-related cardiotoxicity and complications of cancer survivors has increased. Modern oncological treatment regimens often incorporate chemotherapy, radiotherapy, and immune checkpoint inhibitors, whose deleterious cardiac effects might be additive or synergistic. Anthracyclines are the most extensively studied chemotherapeutic agents associated with myocardial injury. The complex of anthracycline-Top (topoisomerase) IIβ-DNA is a leading mechanism of irreversible DNA damage and mitochondrial dysfunction in cardiomyocytes, which contributes to myocardial energetic depletion, oxidative stress, and apoptotic cell death (38). Trastuzumab was the first monoclonal antibody to inhibit the receptor tyrosine-protein kinase erbB-2 pathway that was studied in detail for the treatment of cancer. While erbB-2 is present in cardiac myocytes, it is also involved in some pathways which promote cardioprotection that regulate apoptosis, hypertrophic growth, mitotic growth, cell elongation, intercellular adhesion, angiogenesis, and sensitivity to adrenergic signaling. Therefore, an interruption of these cellular pathways may be potentially harmful to the heart (39). Radiation to the chest can damage the heart in a dose-dependent manner. Radiotherapy

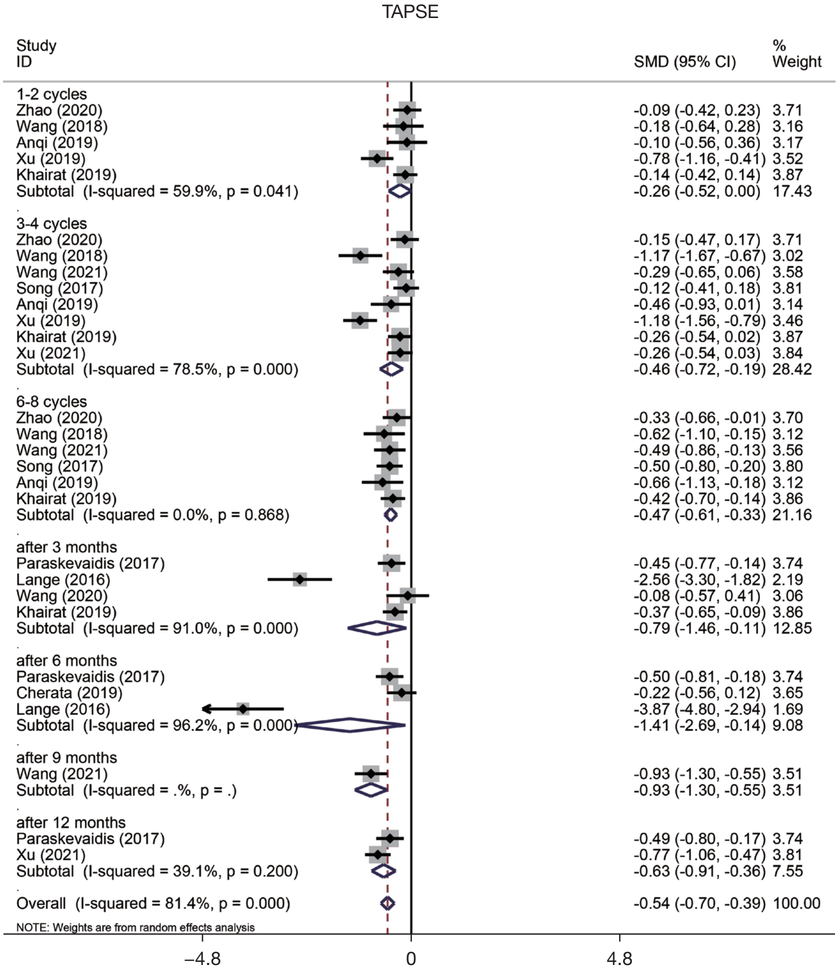

Figure 3 Forest plot of the change of TAPSE. TAPSE, tricuspid annular plane systolic excursion; SMD, standardized mean difference.

can cause ischemic damage, heart failure, pericarditis, valvular dysfunction, and arrhythmias, which are a result of radiation-induced activation of acute inflammatory pathways that cause a chronic pathogenic cascade (40). Although the mechanism of myocardial injury caused by radiotherapy and chemotherapy is different, radiotherapy combined with anthracycline can enhance the cardiotoxicity of the agent (6).

Assessment of right ventricular function

In the emerging field of cardio-oncology, experts usually focus on the evaluation of left ventricular function. The guidelines recommend measuring LVEF at baseline, during, and post-therapy to monitor the occurrence of cardiotoxicity, with long-term follow-up of different frequencies based on the clinical predictors of cardiotoxicity risk (8,9). The consensus document of cardiac oncology experts of the American Echocardiography Society (ASE) and the European Association of Cardiovascular Imaging (EACVI) define CTRCD using LVEF and recommend the routine use of LVGLS to monitor myocardial function during treatment (10). The prognostic role of the RV in cardiac diseases has recently emerged (41,42). Presently, right ventricle dysfunction (RVD) has been an area of intense research of cardio-oncology.

In this study, we analyzed the changes in the mechanical properties of the right ventricular myocardium in cancer patients with chemotherapy by echocardiography. Indeed, right ventricular ejection fraction (RVEF), as measured by echocardiography was found to be poorly reliable and not recommended for clinical use or standard reference in

Table 4 The changes of mechanical properties in patients without radiotherapy

Variables	SMD	95% CI	I^2 (%)	Cochran Q (P)	Z	P	Model	Begg test	Egger test
PASP									
Overall	0.161	(0.007, 0.316)	58.8	0.005	2.05	0.040	Random	0.193	0.295
3–4 Cycles	–0.004	(–0.160, 0.151)	0.0	0.415	0.06	0.955	Random	1.000	0.835
6–8 Cycles	–0.011	(–0.215, 0.194)	17.6	0.297	0.10	0.920	Random	0.296	0.322
After 3 months	0.526	(0.302, 0.750)	0.0	0.657	4.61	0.000	Random	1.000	0.954
TAPSE									
Overall	–0.543	(–0.698, –0.389)	81.4	0.000	6.90	0.000	Random	0.004	0.000
1–2 Cycles	–0.258	(–0.519, 0.002)	59.9	0.041	1.94	0.052	Random	0.462	0.798
3–4 Cycles	–0.455	(–0.720, –0.191)	78.5	0.000	3.37	0.001	Random	0.063	0.045
6–8 Cycles	–0.472	(–0.613, –0.331)	0.0	0.868	6.54	0.000	Random	0.133	0.084
After 3 months	–0.787	(–1.463, –0.111)	91.0	0.000	2.28	0.022	Random	0.734	0.305
After 6 months	–1.414	(–2.692, –0.136)	96.2	0.000	2.17	0.030	Random	1.000	0.153
S'									
Overall	–0.507	(–0.748, –0.266)	89.5	0.000	4.13	0.000	Random	0.369	0.035
1–2 Cycles	0.050	(–0.180, 0.279)	0.0	0.789	0.43	0.670	Random	1.000	0.846
3–4 Cycles	–0.219	(–0.399, –0.039)	36.2	0.166	2.38	0.017	Random	0.452	0.291
6–8 Cycles	–0.362	(–0.669, –0.056)	70.1	0.010	2.32	0.020	Random	0.806	0.737
After 3 months	–1.514	(–2.865, –0.162)	97.1	0.000	2.19	0.028	Random	0.308	0.360
RVGLS									
Overall	1.017	(0.751, 1.283)	91.3	0.000	7.49	0.000	Random	0.055	0.002
1–2 Cycles	0.677	(0.266, 1.088)	67.0	0.048	3.23	0.001	Random	1.000	0.850
3–4 Cycles	1.124	(0.438, 1.809)	95.2	0.000	3.21	0.001	Random	0.707	0.074
6–8 Cycles	1.625	(0.696, 2.554)	96.2	0.000	3.43	0.001	Random	0.806	0.186
After 3 months	0.961	(0.498, 1.424)	78.5	0.009	4.07	0.000	Random	0.296	0.078

SMD, standardized mean difference; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion; S', systolic velocity of tricuspid annulus; RVGLS, right ventricular global longitudinal strain.

research. PASP indirectly reflects the function of the RV. This meta-analysis demonstrated that there was an increase in PASP compared with the condition before chemotherapy and radiotherapy or chemotherapy alone.

The current 2015 recommendations for cardiac chamber quantification of ASE and EACVI (43) recommend that RV systolic function evaluation be performed using conventional parameters, including TAPSE, S', and RVFAC. TAPSE and S', to quantify the displacement and the longitudinal velocity of excursion of the tricuspid annulus, although they may not accurately reflect global RV function because they reflect the function of the basal segment of the RV free wall and assume they are representative of RV global function. Furthermore, they are angle and load-dependent. However, they also have the important advantage of being easily measurable, even in the case of poor image quality and being highly reproducible (44). The pooled analysis also indicated a reduction in TAPSE and S' after chemotherapy, and these results were also observed in patients who underwent chemotherapy and radiotherapy. On the other hand, RVFAC reflects both the longitudinal and the radial components of RV contraction

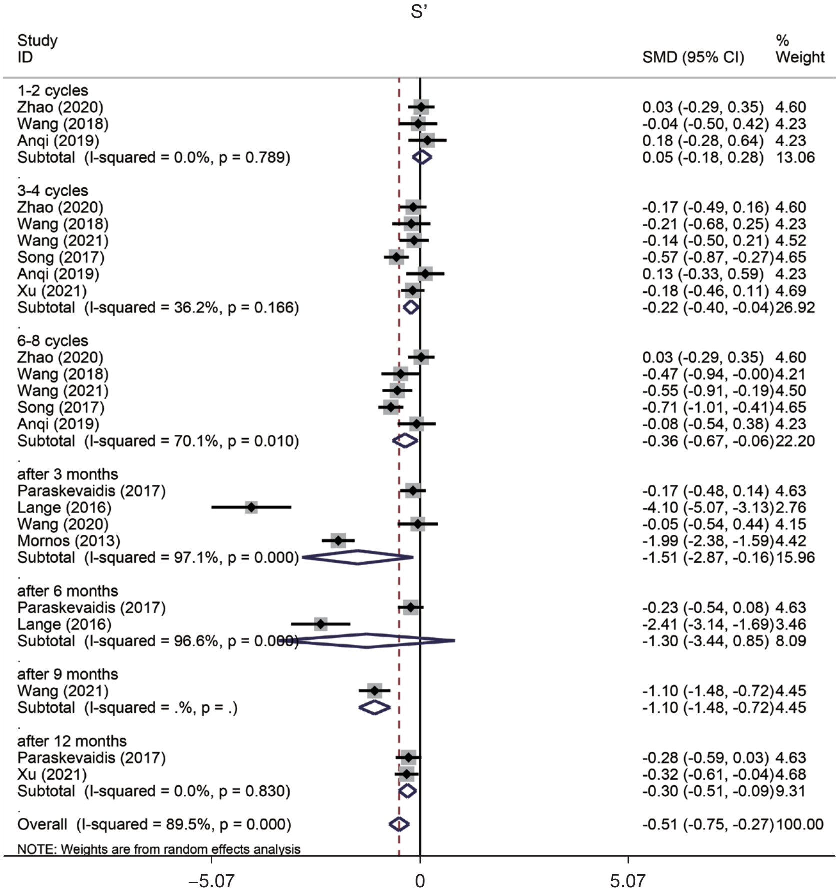

Figure 4 Forest plot of the change of S'. S', systolic velocity of tricuspid annulus; SMD, standardized mean difference.

and is angle independent. At the same time, it depends on image quality, requiring complete visualization of the entire RV structure. Furthermore, it was found to have high inter-observer and intra-observer variability when the definition of endocardial was unsatisfactory (44). However, there was no significant difference in RVFAC in this study. TAPSE is limited to longitudinal function and is the first to be altered in RVD. Preliminary evidence suggests that in the first stage of RVD, the systolic pattern of the RV may change, with reduced longitudinal but enhanced transverse contraction (45). Hence, the change of fractional area change (FAC) and TAPSE may be conflicting, with TAPSE being reduced and FAC being enhanced.

Strain is a useful parameter for estimating RV global and regional systolic function. RVGLS is also mainly a reflection of longitudinal contraction, and the term of RVGLS is not limited to analysis of the right ventricular free wall but also the septal segment, which contributes to RV systolic function through biventricular interactions. Sometimes, the term refers to the RV free wall segments only. RV longitudinal strain is less affected by overall cardiac motion (46,47), although it depends on loading conditions, size, and shape of the RV. It is well known that left ventricle positively contributes to right ventricular systolic performance through the shared ventricular septum (48). Therefore, subtle LV contractile dysfunction can reduce the direct contribution of LV contraction to RV function (49,50). This is the reason why RVGLS might be a better indicator of RV function and have a stronger prognostic value than RVFWLS or TAPSE. Furthermore, RVGLS was also superior to commonly used RV function parameters such as RVEF, FAC, TAPSE, and S' for predicting both the cardiovascular mortality and the overall mortality of patients with heart failure (51,52). Strain, as determined by Doppler tissue imaging (DTI), is angle-dependent, while RV speckle-tracking echocardiographic (STE) strain has the disadvantage of being influenced by the image quality, frame rate dependency, and intervendor variability. This

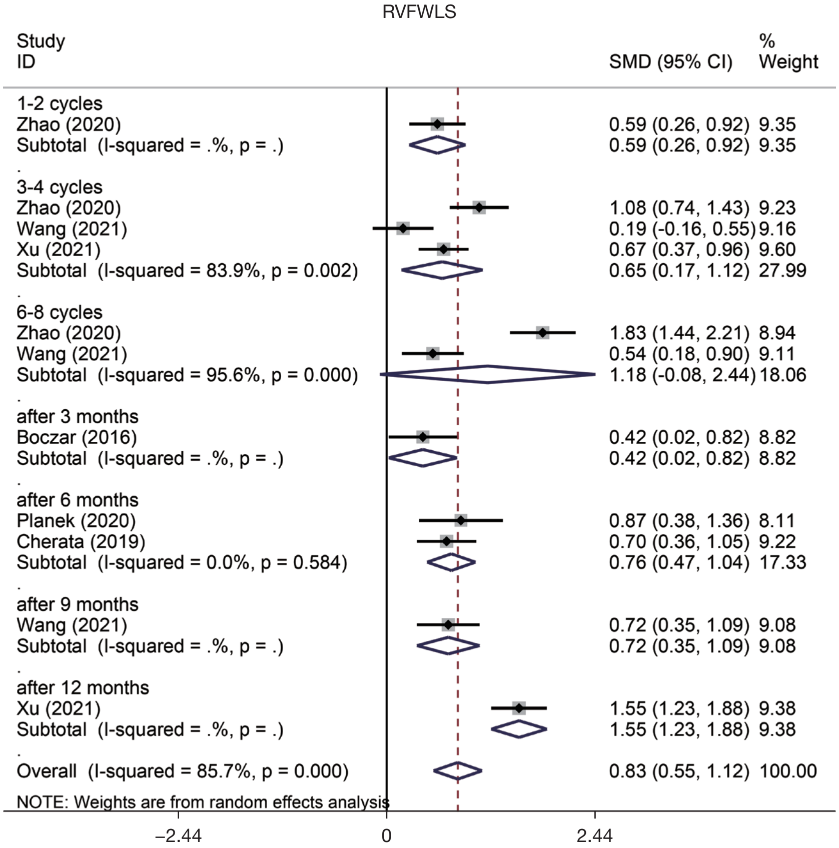

Figure 5 Forest plot of the change of RVFWLS. RVFWLS, right ventricular free wall longitudinal strain; SMD, standardized mean difference.

analysis demonstrated a reduction in TAPSE and S', such conventional indicators, as well as a significant depression of right ventricular strain, including RVFWLS and RVGLS. It is noteworthy that an evident reduction of strain, especially RVGLS, can be seen at every stage of treatment, while another indicator has not shown changes at the early stage.

All of the above indicators used to assess the mechanical properties of the RV pointed to a deterioration of RV contraction function after anticancer therapy. Chemotherapeutic regimens induced cardiotoxicity displays a regional pattern in which the subendocardial component of the ventricle is most susceptible to toxicity (53). The impaired contractility of the subendocardial layer could be compensated by the relatively normal epicardial layer at an early stage. However, if the toxic effects of chemotherapy persist, then cardiac decompensation and symptomatic heart failure will occur. This might be due to the thinner RV wall and less compensatory reserve, which might lead to the earlier decline in systolic function of RV. The structure of the right ventricular myocardium is composed of three layers, namely, the superficial layer, the middle layer, and the deep layer. In the longitudinal direction, the superficial and deep muscles spiral, so that cardiac contraction moves toward the direction of the ventricular outflow tract, causing the ventricle to move toward the bottom of the heart and the cardiac cavity to become shorter. In coordination with the ventricular septum, the blood is driven from the RV into the pulmonary artery. In the circular direction, the contraction of the middle muscle can narrow the cardiac cavity. Notably, the longitudinal myocardium (the superficial and deep layers) of the RV plays a crucial role in cardiac ejection function (54,55). Basic research has confirmed that the subendocardial longitudinal myocardial fibers are more vulnerable to many factors such as ischemia and poisoning. This may be because chemotherapeutic drugs first contact the subendocardial myocardium, which suffers a relatively large blood flow impact, and the drug concentration of microvessels on the endocardial side is high. The subendocardial myocardium is mainly composed of the longitudinal myocardium, so the longitudinal deformation appeared early and was further

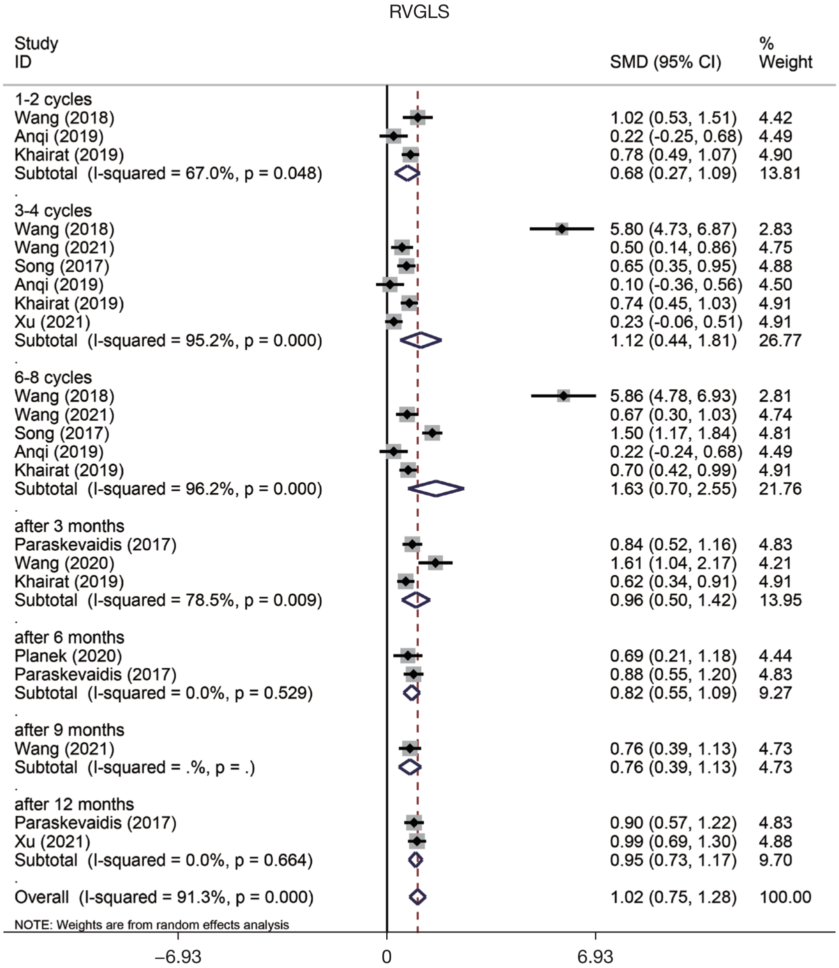

Figure 6 Forest plot of the change of RVGLS. RVGLS, right ventricular global longitudinal strain; SMD, standardized mean difference.

aggravated with the accumulation of dose (56).

Limitations

The present study has some limitations. Firstly, the technology of echocardiography associated with some disadvantages. Indeed, the echocardiographic imaging technique requires accurate acquisition of border tracing, while the complex geometry, thin walls, and localization behind the sternum of the RV may bring about considerable challenges in the positioning of the region. Additionally, the included studies are observational studies with comparatively small examples so that potential bias may still exist. The heterogeneity of the outcomes of the different studies can be attributed to several reasons, with differences in baseline cardiotoxicity risk, follow-up timepoints, and chemotherapeutic regimes with or without radiotherapy being the most important. Thirdly, the analysis of some outcomes showed a prominent heterogeneity between the studies, and a reasonable guess is the sample size of the included studies was insufficient. Therefore, the ability of RV functional indexes to predict the incidence of cardiotoxicity and the overall prognosis need to be confirmed in larger multicenter studies with different types of tumors. Meanwhile, a consensus on how to define RV systolic dysfunction ought to be made furtherly to adequately reflect the cancer therapeutics related cardiotoxicity to RV, when evaluating multiple echocardiography parameters together.

Conclusions

Our findings prove that right ventricular contraction function would deteriorate after anticancer therapy in

Table 5 The changes of mechanical properties in all patients with chemotherapy

Variables	SMD	95% CI	I^2 (%)	Cochran Q (P)	Z	P	Model	Begg test	Egger test
PASP									
Overall	0.175	(0.027, 0.324)	56.9	0.006	2.32	0.020	Random	0.161	0.202
3–4 Cycles	0.044	(−0.131, 0.219)	27.1	0.241	0.49	0.623	Random	0.462	0.216
6–8 Cycles	−0.011	(−0.215, 0.194)	17.6	0.297	0.10	0.920	Random	0.296	0.322
After 3 months	0.526	(0.302, 0.750)	0.0	0.657	4.61	0.000	Random	1.000	0.954
TAPSE									
Overall	−0.475	(−0.606, −0.345)	81.1	0.000	7.15	0.000	Random	0.000	0.000
1–2 Cycles	−0.317	(−0.567, −0.066)	60.9	0.026	2.48	0.013	Random	0.260	0.486
3–4 Cycles	−0.542	(−0.824, −0.259)	82.0	0.000	3.76	0.000	Random	0.029	0.011
6–8 Cycles	−0.472	(−0.613, −0.331)	0.0	0.868	6.54	0.000	Random	0.133	0.084
After 3 months	−0.602	(−1.133, −0.070)	90.5	0.000	2.22	0.026	Random	0.221	0.159
After 6 months	−0.642	(−1.137, −0.148)	91.9	0.000	2.55	0.011	Random	0.260	0.016
After 12 months	−0.378	(−0.747, −0.010)	81.7	0.001	2.01	0.044	Random	1.000	0.837
S'									
Overall	−0.401	(−0.580, −0.222)	87.5	0.000	4.39	0.000	Random	0.019	0.002
1–2 Cycles	−0.120	(−0.475, 0.234)	63.7	0.041	0.67	0.506	Random	0.734	0.573
3–4 Cycles	−0.235	(−0.395, −0.075)	25.9	0.231	2.89	0.004	Random	1.000	0.448
6–8 Cycles	−0.362	(−0.669, −0.056)	70.1	0.010	2.32	0.020	Random	0.806	0.737
After 3 months	−1.170	(−2.193, −0.147)	96.9	0.000	2.24	0.025	Random	0.221	0.174
After 6 months	−0.496	(−1.002, 0.011)	91.0	0.000	1.92	0.055	Random	0.086	0.019
After 9 months	−0.506	(−1.161, 0.149)	90.6	0.000	1.51	0.130	Random	1.000	0.403
After 12 months	−0.161	(−0.436, 0.114)	62.7	0.068	1.15	0.251	Random	1.000	0.542
RVFWLS									
Overall	0.702	(0.482, 0.923)	87.1	0.000	6.24	0.000	Random	0.049	0.181
3–4 Cycles	0.703	(0.322, 1.085)	77.4	0.004	3.62	0.000	Random	1.000	0.841
After 6 months	0.729	(0.382, 1.075)	77.4	0.004	4.12	0.000	Random	1.000	0.952
RVGLS									
Overall	0.853	(0.655, 1.052)	90.0	0.000	8.42	0.000	Random	0.038	0.001
1–2 Cycles	0.677	(0.266, 1.088)	67.0	0.048	3.23	0.001	Random	1.000	0.850
3–4 Cycles	1.124	(0.438, 1.809)	95.2	0.000	3.21	0.001	Random	0.707	0.074
6–8 Cycles	1.625	(0.696, 2.554)	96.2	0.000	3.43	0.001	Random	0.806	0.186
After 3 months	0.771	(0.376, 1.165)	85.1	0.000	3.82	0.000	Random	0.086	0.065
After 6 months	0.739	(0.459, 1.018)	75.6	0.001	5.18	0.000	Random	0.707	0.649
After 12 months	0.665	(0.311, 1.019)	79.4	0.002	3.68	0.000	Random	1.000	0.871

SMD, standardized mean difference; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion; S', systolic velocity of tricuspid annulus; RVGLS, right ventricular global longitudinal strain; RVFWLS, right ventricular free wall longitudinal strain.

patients, especially with the prolongation of chemotherapy duration and the accumulation of chemotherapeutic drugs. However, further larger multicenter studies are needed to establish the definition of right ventricular systolic dysfunction which can adequately reflect the cancer therapeutics related cardiotoxicity.

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2324/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 based on previously published studies, therefore, ethical approval and patient consent were not required.

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