

Peer Review File

Article information: <http://dx.doi.org/10.21037/tcr-21-2324>

Reviewer comments:

Comment 1: *English language of this paper needs professional editing after extensive revisions.*

Reply 1: Thank you for your nice advice. The wordings of the main text of our manuscript were checked and polished by a native English-speaking expert after revised. We resubmit the language-edited version of our manuscript now.

Comment 2: *In the background of abstract, it remains unclear why the author performed this meta-analysis and whether meta-analysis is appropriate for addressing the research question; the sentence “Since individual studies are focus on the function of left ventricle” is unclear. The method part is unclear, which should define the inclusion of studies by using the PICOS criteria. The literature search strategies should be provided in detail. Risk of bias assessment of included studies should be reported here. In the part of results, the authors should report the results of risk of bias assessment. The conclusion should be made with cautions given the methodology limitations of included studies.*

Reply 2: We gratefully thanks for the precious time the reviewer spent making constructive remarks. We modified the background part of abstract as reviewer’ s suggestion to make the expression clearer. Meanwhile, we have rewritten the text to describe the method part in more detail. Since the limitation of the number of words in abstract, we described the method of literature search in detail in *Methods* part of main text. We feel sorry for the inconvenience brought to the reviewer. In the part of results, we have added the results of risk of bias assessment. Given the methodology limitations of included studies, we reorganized the text to make the conclusion more rigorous.

Changes in the text: We have modified our text as advised (see Page 1-2, line 7-40).

Background[↵]

Cancer therapy-related cardiotoxicity has recently become an area of intense research. [↵]

As the prognostic role of the right ventricle in a variety of cardiovascular diseases has been confirmed, and several studies have paid increased attention to RV function in cancer patients who have undergone 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. [↵]

who underwent chemotherapy and radiotherapy. The risk of bias of the included studies evaluated by the Newcastle-Ottawa Scale was medium to high. [↵]

Conclusions[↵]

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.[↵]

Comment 3: *In the introduction part, the authors should explain why a focus on mechanical properties of right ventricular myocardium as the early signs of cardiotoxicity. In general, meta-analysis is not used to generate knowledge, rather it is used to address inconsistent findings on the same research topic. The authors should provide such evidence to support the need for this meta-analysis and explain why meta-analysis is appropriate to address this issue.*

Reply 3: Thank you for your rigorous consideration. Mentioned the reason that we write this article, there were two reasons. First, some studies found right ventricular function decreases early even before the derangement of LV function, while some studies have not found significant statistical changes, our analysis was used to address the inconsistent findings. Second, indexes evaluating right ventricular contraction includes PASP, TAPSE, S', RVFWLS, RVGLS, and RVFAC, we tried to find out the changes of these different indexes. We have added some texts in order to express our purpose of this analysis clearer.

Changes in the text: We have modified our text as advised (see Page 4, line 83-87).

An increasing number of studies have begun to evaluate changes of the right ventricle. 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

Comment 4: *In the literature search part, the authors said no language restrictions but they only performed the search in English-language databases. Please define the inclusion of studies to be included according to the PICOS criteria, for example, outcomes and research design of studies to be included remain unclear. The authors should use a separated paragraph to describe the assessment of risk of bias of included studies. Please explain why NOS is suitable. It is not used for non-RCT, in fact, it is used for case-control and cohort studies only.*

Reply 4: Thank you so much for your careful check. The words “without language restrictions” is indeed ambiguous, we have deleted this sentence for the sake of rigor. Besides, Embase, PubMed, and CENTRAL database were recommended as the most important sources to search for reports of trials in Cochrane Handbook. Because there are very few randomized controlled trials on this topic, in order to expand the scope of retrieval and ensure the size of the samples, we did not strictly limit the type of research. We revised the complete search term to make it clearer. According to the PICOS criteria, we describe the inclusion of studies in detail in *Study selection and evaluated outcome* part, the inclusion criterion is studies which performing in cancer patients with chemotherapy (*P* and *I*), and reporting right ventricular contraction measured by echocardiography (*O*) at the baseline and follow-up (*C*). The included studies in our analysis were observational study, literature quality evaluation tools commonly used in observational research are the Newcastle-Ottawa Scale (NOS), critical appraisal skill program (CASP) and Agency for Healthcare Research and

Quality (AHRQ). Among them, the NOS extends from the evaluation methods of randomized controlled trials, and can be well applied to the systematic evaluation of nonrandomized controlled trials. It was recommended by the non-randomized research methodology group of Cochrane Collaboration, so we chose NOS to evaluate the risk of bias of included studies. We have used a separated paragraph in *Data extraction and assessment* part to describe the assessment of risk of bias of included studies in detail.

Changes in the text: We have modified our text as advised (see Page 5, line 102-109; Page 7, line 145-148).

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

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.←

Comment 5: *In the statistics part, please describe the examination of sources of heterogeneity. Please explain why random effects model was used.*

Reply 5: We totally understand the reviewer' s concern. In our analysis, we chose random effects because of founding high statistical heterogeneity between studies.

Given the heterogeneity between studies, we added a sensitivity analysis to further study the source of heterogeneity. We have also discussed the possible reasons in *Discussion* part.

Changes in the text: We have modified our text as advised (see Page 8, line 164-165; Page 10, line 217-220; Page 11, line 229-232).

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

was observed (P-value of Q test = 0.000, $I^2 = 89.5\%$). We found that the data from Lange's 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

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

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.