Original Article

Global Longitudinal Strain as Predictor of Chemotherapy-Induced Cardiotoxicity

Strain Longitudinal Global como Preditor de Cardiotoxicidade Induzida por Quimioterapia

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Abstract

Background: Chemotherapy-induced cardiotoxicity (ChC) is an important complication among patients receiving anthracyclines. Biomarkers and imaging parameters have been studied for their ability to identify patients at risk of developing ChC. Left ventricular global longitudinal strain (LV-GLS) is a sensitive parameter for detecting systolic dysfunction despite the presence of preserved left ventricular ejection fraction (LVEF).

Objective: To evaluate the role of the LV-GLS as a predictor of ChC.

Methods: This was a post-hoc analysis of the Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity trial, which evaluated the primary prevention of cardiotoxicity with carvedilol during doxorubicin chemotherapy in a population of patients with breast cancer. Cardiotoxicity was defined as a reduction ≥10% in LVEF. LV-GLS was determined before chemotherapy in patients with no prior cardiovascular disease or echocardiogram abnormalities.

Results: Thirty-one patients for whom a complete echocardiography study including measurement of LV-GLS was performed before chemotherapy were included in this analysis. An absolute LV-GLS<16.9% before chemotherapy showed 100% sensitivity and 73% specificity for predicting cardiotoxicity (area under the curve [AUC], 0.85; 95% confidence interval [CI], 0.680–0.959; p<0.001). In this population, LVEF values before chemotherapy did not predict ChC (95% CI, 0.478 to -0.842; p=0.17). The association of low LV-GLS (<17%) and brain-type natriuretic peptide serum levels (>17 pg/mL) at 2 months after chemotherapy increased the accuracy for detecting early-onset ChC (100% sensitivity, 88% specificity; AUC, 0.94; 95% CI, 0.781–0.995; p<0.0001).

Conclusions: Our data suggest that LV-GLS is a potential predictor of ChC. Larger studies are needed to confirm its clinical relevance in this clinical setting.

Keywords: Cardiotoxicity; Chemotherapy; Prevention; β-blockers; Echocardiogram; *Strain*.

Resumo

Fundamento: *A cardiotoxicidade induzida por quimioterapia (CiC) é uma complicação importante entre os pacientes que recebem antraciclinas. Biomarcadores e parâmetros de imagem têm sido estudados por sua capacidade de identificar pacientes com risco de desenvolver essa complicação. O strain longitudinal global do ventrículo esquerdo (SLG-VE) tem sido descrito como um parâmetro sensível para detectar disfunção sistólica, mesmo na presença de fração de ejeção do ventrículo esquerdo (FEVE) preservada.*

Objetivo: avaliar o papel do SLG-VE como preditor de CiC.

Métodos: *O presente estudo consiste em uma análise post-hoc do estudo CECCY (Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity [Carvedilol para Prevenção da Cardiotoxicidade Relacionada à Quimioterapia]), que avaliou a prevenção primária de cardiotoxicidade com carvedilol durante quimioterapia com doxorrubicina em uma população com câncer de mama. Definiu-se cardiotoxicidade como uma redução ≥10% na FEVE. O SLG-VE foi obtido antes da quimioterapia em pacientes sem doença cardiovascular prévia ou anormalidades no ecocardiograma.*

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Resultados: *Trinta e um pacientes submetidos a estudo ecocardiográfico completo incluindo avaliação de SLG-VE antes da quimioterapia foram incluídos nesta análise. Um SLG-VE absoluto <16,9% antes da quimioterapia mostrou 100% de sensibilidade e 73% de especificidade para predizer cardiotoxicidade (AUC=0,85; IC 95% 0,680–0,959, p<0,001). Nesta população, os valores de FEVE antes da quimioterapia não foram preditores de CiC (IC 95% 0,478 a -0,842, p=0,17). A associação de baixos níveis séricos de SLG-VE (<17%) e BNP (>17 pg/mL) dois meses após a quimioterapia aumentou a precisão para detectar CiC de início precoce (100% de sensibilidade, 88% de especificidade, AUC=0,94; IC 95% 0,781–0,995, p<0,0001).*

Conclusões: *Nossos dados sugerem que o SLG-VE é um possível preditor de cardiotoxicidade induzida por quimioterapia. São necessários estudos maiores para confirmar a relevância clínica desse parâmetro ecocardiográfico nesse cenário clínico.*

Palavras-chave: *Cardiotoxicidade; Quimioterapia; Prevenção; Betabloqueadores; Ecocardiograma; Strain.*

Introduction

The cardiovascular effects of chemotherapeutic agents are responsible for a significant proportion of severe complications, particularly among female patients with breast cancer.[1] There is evidence of increasing cardiovascular disease among hospitalized patients with cancer.[2] One of the most widely used agents,[3,4] anthracyclines (ANT), is responsible for early and late dose-related cardiotoxicity, particularly heart failure (HF).[5-7]

The detection of cardiotoxicity is routinely performed by left ventricular ejection fraction (LVEF). Although LVEF predicts the occurrence of HF, it has limited sensitivity.[8] Failure to detect subtle changes in LV systolic function occurs for many reasons: the need for geometrical assumptions for calculations, possible inadequate visualization of the LV apex, impossibility of identifying marginal regional wall motion abnormalities, and intrinsic measurement variability.[9] A decreased LVEF after chemotherapy is often a sign of already extensive myocardial damage and HF.[10]

Due to increased morbidity and mortality among patients with chemotherapy-related HF, higher-sensitivity markers of subclinical cardiac dysfunction and myocardial injury have been investigated to detect chemotherapy-induced cardiotoxicity (ChC). For this purpose, the evaluation of two-dimensional speckle-tracking imaging has emerged. This technique allows for the study of global and regional myocardial deformation. Several studies have already emphasized the role of LV global longitudinal strain (LV-GLS) to detect subtle alterations in systolic function particularly related to ANT chemotherapy.[11] The evaluation of GLS for the detection of subclinical LV dysfunction induced by chemotherapy is recommended by expert consensus.[12]

Considering this new field assessing ANT-induced cardiotoxicity using LV-GLS, we conducted a *post-hoc* analysis of the randomized double-blind placebo-controlled Carvedilol Effect in Preventing Chemotherapy Induced CardiotoxicitY (CECCY) trial, which aimed to evaluate the LV-GLS before ANT chemotherapy as a predictor of cardiotoxicity.

Methods

Study design

This *post-hoc* analysis of the CECCY trial evaluated the primary prevention of cardiotoxicity with carvedilol during doxorubicin chemotherapy in women with breast cancer. Cardiotoxicity was defined as a ≥10% reduction in LVEF. Patients were recruited and followed up at two different institutions, the Heart Institute and the Cancer Institute from the University of Sao Paulo, Sao Paulo, Brazil. The Ethics Committee of the Heart Institute and Cancer Institute from the University of Sao Paulo, Sao Paulo, Brazil, review board of both institutions approved the trial protocol. All methods were performed in accordance with the relevant guidelines and regulations. All participants were informed of the research objectives, research protocol, and treatment alternatives, and all participants provided written informed consent to participate. The trial was registered at ClinicalTrials.gov (NCT01724450) before study initiation.

Study patients

The CECCY trial included patients with *HER2*-negative breast cancer tumor status and therapy that included ANT, cyclophosphamide, and taxane from April 2013 to January 2017. The standard chemotherapy protocol comprised four cycles of cyclophosphamide 600 mg/m^2 and doxorubicin 60 mg/m^2 every 21 days (with a total cumulative dose of 240 mg/m^2), followed by paclitaxel 80 mg/m^2 weekly for 8 weeks. The trial design and results were described elsewhere.[13]

Study procedures

The present *post-hoc* analysis included only patients who underwent echocardiography studies and accomplished follow-up at the Heart Institute from the University of Sao Paulo, where the institutional protocol included speckle tracking echocardiography. Eligible patients underwent comprehensive transthoracic echocardiography before starting chemotherapy including proper imaging acquired to perform the strain analysis. Patients with an unsatisfactory acoustic window for the speckle tracking analysis due to artifacts caused by breast reconstruction techniques were excluded from the study. Echocardiographic studies were performed using a commercially available system (Vivid E9; General Electric, GE Vingmad Ultrasound AS, Norway) equipped with a 2–5-MHz transducer. All measurements were performed and reported according to American Society of Echocardiography recommendations (Lang 2015, Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging). LVEF was measured by Simpson's rule.

For the speckle tracking analysis, images were acquired

with an adjusted device to record three cardiac cycles within a period of 100 msec before and after the cycle. The second harmonic image, in grayscale, with a frame rate of 40–80 frames/s was used. To measure LV-GLS, cardiac images were obtained through the apical windows (APLAX, A4C and A2C). After the acquisition, the studies were stored for offline analysis with the EchoPAC software (v30 12; GE Vingmad Ultrasound AS). The analysis was performed of the sixteen LV segments, and the quantitative peak systolic longitudinal strain was quantified for each segment as well as the whole LV during a cycle cardiac. All scans were read by experienced board certified echocardiographers who were blinded to the patients' clinical information.

Statistical analysis

The data are expressed as median and 95% confidence interval. We tested the normality of a variable distribution using the D'Agostino-Pearson test. For comparisons between two independent samples, an unpaired *t*-test was used for variables with Gaussian distribution, while the Mann-Whitney rank sum test was applied for variables with non-Gaussian distributions. For comparison between paired samples with Gaussian distribution, the paired t-test was used, while the Wilcoxon matched pairs ranked test was used for pairs with a non-Gaussian distribution. We used receiver operating characteristic (ROC) curve analysis to determine the accuracy and optimal cutoff. The best cutoff for each variable was chosen through the shortest distance from the upper left angle to the curve obtained in the graph of the ROC curve by the method of DeLong et al.[14] P values <0.05 were considered significant.

Results

In this *post-hoc* analysis of the randomized double-blind placebo-controlled CECCY trial, we evaluated 53 patients who underwent echocardiography with the speckle tracking technique at the Heart Institute. Of these, six (11%) had an unsatisfactory acoustic window and were excluded from the analysis. Another 16 patients were excluded for attending subsequent echocardiographic follow-up at another institution. The population included in the analysis was at low risk of cardiovascular. The baseline characteristics of the remaining 31 patients are described in Table 1. Our population had low prevalence of cardiovascular comorbidities and risk factors for cardiotoxicity. In this group, 3 (9.7%) developed cardiotoxicity (LVEF decrease ≥10% from baseline). Considering the alternative and most accepted definition of cardiotoxicity as a decrease of 10 percentage points to a value below the low normal value of 50%,[15] only 1 patient fulfilled the criteria for cardiotoxicity and had a decrease of LVEF to 35% and a GLS of 13%. The 3 patients with cardiotoxicity were aged 51–63 years, only one had a diagnosis of arterial hypertension, and none had other risk factors for cardiovascular disease such as diabetes mellitus, hypercholesterolemia under statin treatment, or current/past smoking status.

LV-GLS predicted the development of cardiotoxicity (cutoff value, ≤16.9%), with 100% sensitivity and 73.1% specificity (area under the curve [AUC], 0.859; p<0.001). A serum brain-type natriuretic peptide (BNP) level >16 pg/mL measured 2 weeks after starting chemotherapy was also associated with cardiotoxicity with 100% sensitivity and 69.2% specificity (AUC, 0.878; p<0.001) (Figure 1, Central Illustration). On the other hand, baseline LVEF (AUC, 0.680; p=0.17) and serum troponin (AUC, 0.577; p=0.69) were not associated with the incidence of cardiotoxicity.

Table 2 shows the median and 95% CI values for serum LVEF, BNP, and troponin before and 2, 4, and 24 weeks after starting chemotherapy stratified according to baseline LV-GLS. Baseline LVEF was not significantly different in patients with an LV-GLS ≤16.9% versus >16.9%. Similarly, there was no intergroup difference in baseline BNP or troponin

Table 1 - Baseline characteristics of the study population.

Characteristic	Population (N=31)	LV-GLS ≤16,9% (N=10)	LV-GLS >16,9% (N=21)	P value
Age, years	51±9.69	54.9±6.7	49±10.4	NS
Menopause, no. of patients (%)				
Pre-menopause	14 (45)	4 (40)	10 (47)	NS
Post-menopause	17 (55)	6 (60)	11 (53)	
Therapy, no. of patients (%)				
Neoadjuvant	17 (55)	6 (60)	11 (47)	NS
Adjuvant	14 (45)	4 (40)	10 (53)	
Drug carvedilol, no. of patients (%)	18 (48)	6 (60)	12 (57)	
Body mass index (kg/m2)	27.1±7.45	30.3± 6.9	25.6±7.3	0.09
Cardiovascular risk factors, no of patients (%)				
Hypertension	1 (3.2)	1 (10%)	0	NS
Diabetes mellitus	1 (3.2)	0	1 (4)	NS
Hypercholesterolemia	1 (3.2)	1 (10%)	0	NS
Current/past smoker	11 (35.4)	4 (40)	7 (33)	NS
Systolic blood pressure (mmHg)	121±12.46	121±10.9	121±13.8	NS
Diastolic blood pressure (mmHg)	79±8.1	81±7.2	77±8.5	NS
Heart rate, beats/min	79±11.5	85±12.2	77±10.2	0.06

Data are expressed as mean ± SD or number. LV-GLS: left ventricular global longitudinal strain; NS: not significant.

values. However, LVEF evaluated by echocardiography was significantly lower after 4 weeks of chemotherapy in the group with a baseline LV-GLS ≤16.9% (p=0.003). Furthermore, serum BNP measured after 4 weeks of chemotherapy treatment was higher in the group with an LV-GLS ≤16.9% (p=0.004). There was no significant intergroup difference for troponin values at any time point.

Figure 2 shows median and 95% CI values for LVEF and LV-GLS before and after 12 months after chemotherapy. We observed that LV-GLS decreased significantly from baseline values (p=0.005), whereas LVEF did not. In the follow-up period after chemotherapy, LV-GLS decreased more than 5%, 10%, and 15% from baseline in 77%, 66%, and 42% of patients, respectively, whereas LVEF decreased more than 10% in only 9.7% of patients.

Discussion

In this *post-hoc* analysis of the randomized double-blind placebo-controlled CECCY trial that evaluated the role of the speckle tracking echocardiography in ANT-induced cardiotoxicity, LV-GLS was a potential predictor of ChC in patients with a low prevalence of cardiovascular comorbidities and risk factors for cardiovascular disease. In this scenario, LV-GLS was a better predictor of cardiotoxicity than LVEF. In addition, the combination of LV-GLS and BNP during follow-up could be a predictor of cardiotoxicity.

There has been great interest in the early detection of cardiotoxicity to reverse and prevent associated cardiomyopathy.[16] LVEF is a strong predictor of cardiac events, but it lacks sensitivity for the detection of subclinical changes in cardiac function.[17] Strain is defined as change in the length of the myocardium divided by the original length of the myocardium and peak systolic deformation between systole and diastole.[18] LV-GLS has emerged as the main measurement of subclinical myocardial dysfunction and demonstrated utility in predicting subsequent reductions in LVEF in patients after cancer treatment.[8,19,20] Ali et al.[8] demonstrated that an absolute LV-GLS value of less than -17.5% was associated with an increase in HF among patients with hematologic cancer undergoing ANT chemotherapy. Charbonnel et al.[11] showed that an LV-GLS value of greater than -17.45% obtained after ANT 150 mg/m^2 is an independent predictor of future cardiotoxicity.

Our study findings are in concordance with other studies that showed that the strain measure before chemotherapy predicts the development of cardiotoxicity.[19]

The SOCCOUR trial recently compared cardioprotection guided by changes in LV-GLS versus LVEF among patients undergoing ANT chemotherapy. In the trial, 331 patients were randomized to receive angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers guided by a ≥12% relative reduction in LV-GLS (GLS-guided arm) or 10% absolute reduction in LVEF (EF-guided arm). Patients were followed for LVEF and cancer

Table 2 - Evolution of LVEF, serum troponin, and BNP after 2, 4, and 24 weeks of chemotherapy divided by LV-GLS value before chemotherapy.

	LV-GLS ≤16,9% (N=10)	LV-GLS >16,9% (N=21)	P value
LVEF before ChT, %	61.5 (59.9–64.0)	63.5 (60.9–64.4)	NS
LVEF 2 weeks, %	61.0 (58.2–66.0)	65.0 (62.8–67.0)	NS
LVEF 4 weeks, %	58.0 (56.1–62.9)	61.2 (62.5–65.5)	0.003
LVEF 24 weeks, %	63.0 (53.0–68.9)	63.0 (61.0–64.9)	NS
BNP before ChT, pg/mL	18.0 (7.42–46.9)	12.0 (9.2–19.2)	NS
BNP 2 weeks, pg/mL	19.0 (1.24–46.9)	9.0 (6.2–16.5)	NS
BNP 4 weeks, pg/mL	16.0 (-11.2–88.3)	13.0 (8.8–21.8)	NS
BNP 24 weeks, pg/mL	18.5 (-39.9–167.7)	8.0 (5.7–10.7)	0.004
Troponin before ChT, mg/mL	0.005 (0.003–0.011)	0.005 (0.004–0.006)	NS
Troponin 2 weeks, mg/mL	0.008 (0.005–0.016)	0.005 (0.006–0.011)	NS
Troponin 4 weeks, mg/mL	0.029 (0.014–0.077)	0.028 (0.025–0.054)	NS
Troponin 24 weeks, mg/mL	0.024 (0.015–0.048)	0.016 (0.009–0.037)	NS

BNP: brain-type natriuretic peptide; ChT: chemotherapy; LVEF: left ventricular ejection fraction; LV-GLS: left ventricular global longitudinal strain; NS: not significant.

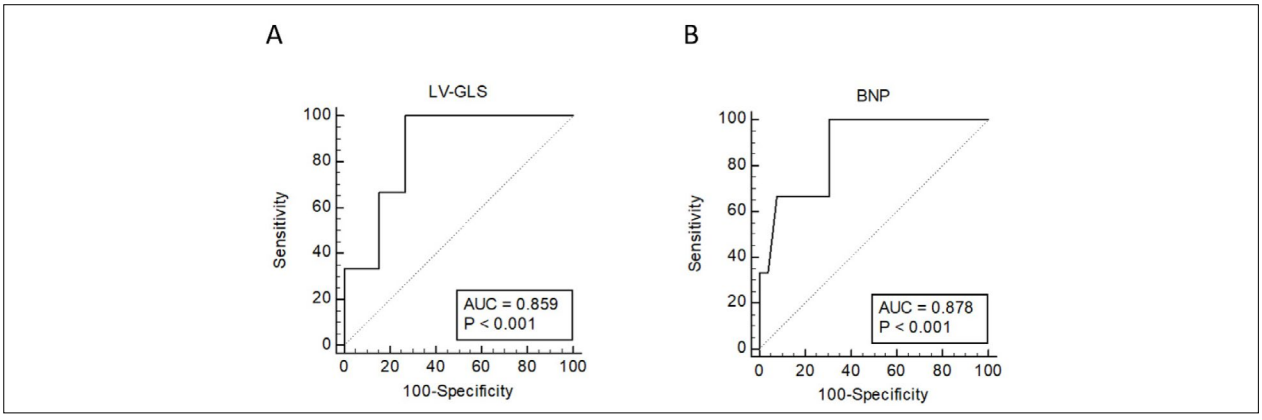

Figure 1 – *Receiver operating characteristic curve analyses of LV-GLS measured before the onset of chemotherapy (A) and BNP after 2 weeks of chemotherapy (B) and their association with cardiotoxicity. AUC: area under the curve; BNP: brain-type natriuretic peptide; LV-GLS: left ventricular global longitudinal strain (Central Illustration).*

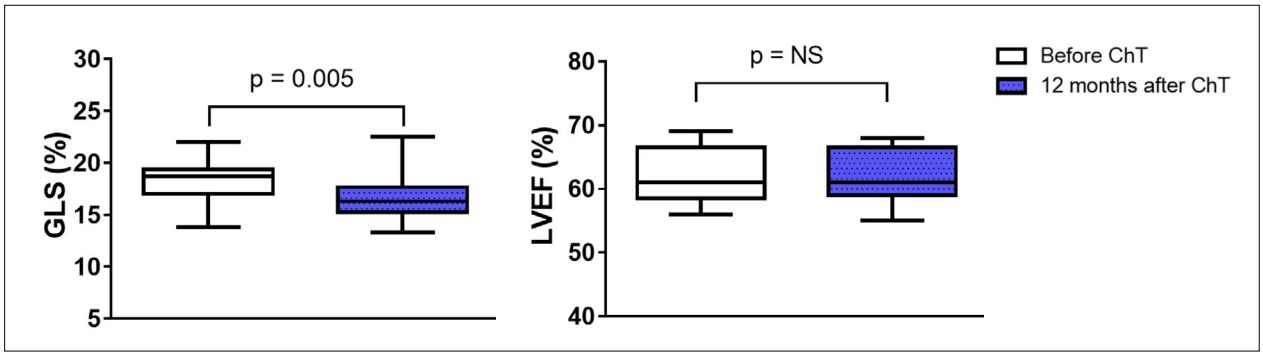

Figura 2 – *Mediana e IC de 95% para SLG-VE e FEVE antes e após 12 meses de quimioterapia. SLG-VE: strain longitudinal global do ventrículo esquerdo; FEVE: fração de ejeção do ventrículo esquerdo.*

therapy–related cardiac dysfunction (symptomatic drop of >5% or asymptomatic drop of >10% to <55%). At 1 year of follow-up, the LVEF did not change significantly in either group. However, in the GLS-guided arm, there was a greater use of cardioprotection and fewer patients met the cardiotoxicity criteria (5.8% vs. 13.7%; p=0.02). Patients who received cardioprotection in the EF-guided arm exhibited a greater reduction in LVEF at follow-up than those in the GLS-guided arm (9.1±10.9% *vs*. 2.9±7.4%; p=0.03) supporting the use of GLS for detecting cardiotoxicity.[21]

Oikonomou et al.[22] published a meta-analysis that evaluated the prognostic value of GLS for predicting cardiotoxicity and included 21 studies comprising 1782 patients with cancer treated with ANT with or without trastuzumab. The authors found an incidence of cardiotoxicity of 9.3–43.8%. Four studies evaluated the association of GLS before treatment initiation with subsequent cardiotoxicity: 2 found no association,[23,24] 1 reported a significant association (odds ratio per 1% decrease, 1.48; 95% CI, 1.15–1.89) and 1 reported an AUC of 0.76 (95% CI, 0.58–0.88), with an optimal cutoff value of -19.95% (sensitivity, 83%; specificity, 72%) for cardiotoxicity.[11]

Other biomarkers have been studied as a strategy for the early detection and monitoring of cardiotoxicity. The most studied biomarkers in cardiotoxicity include troponin and BNP. Regarding troponin, strong evidence favors its ability to predict cardiotoxicity and cardiac events.[15,25] However, the utility of BNP for chemotherapy-related cardiotoxicity remains controversial, with many studies reporting no prognostic value in this scenario.[26] Our study showed that the combination of the LV-GLS pre-chemotherapy with BNP during follow-up (until 24 weeks) could be a greater predictor of a >10% decrease in LVEF. However, the combination of LV-GLS with troponin showed no prognostic value regarding cardiotoxicity.

Limitations

This was a *post-hoc* analysis of the CECCY trial, so its findings were not pre-specified. We also included a small sample size due to difficulties obtaining speckle tracking images. We did not have a more robust modality for assessing EF such as planar equilibrium radionuclide angiocardiography or magnetic resonance imaging. Moreover, we noted a low incidence of cardiotoxicity that could have impaired the results.

Conclusion

LV-GLS is a potential predictor of ChC in patients with a low prevalence of cardiovascular comorbidities and risk factors for cardiovascular disease. LV-GLS was a better predictor of cardiotoxicity than LVEF, while the combination of LV-GLS and BNP during follow-up could be a predictor of cardiotoxicity. Overall, our findings confirm the ability of LV-GLS to detect subclinical cardiotoxicity and emphasize the need for early evaluations of LV-GLS to detect cardiotoxicity.

Authors' contributions

Plan Study, Conduct Study, Search Literature, Write Article: MS Avila, MSL Alves, and SMA Ferreira; Plan Study, Conduct Study, Search Literature, Review Article: MRB Wanderley: Conduct Study, Search Literature, Review Article: FD Cruz and SMG Brandão: Plan Study, Search Literature, Review Article: LA Hajjar and R Kalil Filho; Conduct Study, Review Article: CBBV Cruz, MC Abduch, and DB Moleta; Plan Study, Conduct Study, Search Literature, Review Article: EA Bocchi.

Conflict of interest

The authors have declared that they have no conflict of interest.

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