IMPACT OF CANCER TREATMENT ON PULSE WAVE VELOCITY IN CANCER SURVIVORS: A META-ANALYSIS

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ABSTRACT

Cancer survivors are at an increased risk of morbidities such as cardiovascular diseases (CVD). Cancer treatments such as chemotherapy and radiation have been correlated with cardiotoxicity. However, the magnitude of these effects is unclear. The gold-standard methodology to non-invasively measure arterial stiffness, a measure of CVD risk, is pulse wave velocity (PWV). Therefore, the objective of this meta-analysis was to measure the PWV response to cancer treatment in cancer survivors. Electronic databases were searched from inception through April 2023. Eligible studies included adult cancer survivors and PWV measurements (before and after treatment). One hundred thirty-seven articles were identified and 20 articles (24 trials) met inclusion criteria. Compared to baseline (pre-treatment), cancer treatment resulted in a moderate-large significant increase (worsening) in PWV (SMD=0.634 m/s, 95% CI: 0.348, 0.920, df=20, p=0.002). Sub-group analysis did not reveal any significant effects of PWV device (df=7, p=0.150) or PWV site (df=4, p=0.360). However, a significant effect was seen based on cancer type (df=9, p=0.045) with breast cancer survivors (SMD=-0.939 m/s, 95% CI: -1.839, -0.039, df=6, p=0.041) and acute lymphoblastic leukemia survivors (SMD=1.000 m/s, 95% CI: 0.164, 1.836, df=1, p=0.019) having large significant changes in PWV. Additionally, a significant effect was seen based on time between baseline and post-treatment visits (df=1,p=0.045). Trials with a short visit timeline (less than 12 weeks) resulted in a moderate increase in PWV (SMD=0.569 m/s, 95% CI: 0.012, 1.126, df=5, p=0.045) whereas, trials with a long visit timeline (greater than 13 weeks) resulted in a small-moderate increase in PWV (SMD=0.317 m/s, 95% CI: -0.013, 0.647, df=13, p=0.060). In conclusion, cancer treatment does significantly affect PWV indicating an increased CVD risk. Further research is needed to identify effective interventions to mitigate these effects.

CHAPTER 1: INTRODUCTION

Due to advances in medical treatments and an aging U.S. population, the prevalence of cancer survivors has increased significantly and continues to (Bluethmann et al., 2016; Solomou et al., 2019). The number of cancer survivors in the United States is projected to increase from 15.5 million survivors in 2016 to 26.1 million survivors in 2040 (Bluethmann et al., 2016). Following treatment, cancer survivors are at an increased risk of morbidities such as cardiovascular disease (CVD) when compared to the general population (Okwuosa et al., 2017; Armenian et al., 2016).

The long-term cardiovascular issues in the cancer survivor population include cardiomyopathy/heart failure, hypertension, dysrhythmias, autonomic dysfunction, valvular heart disease, coronary artery disease, pericardial diseases, and increased arterial stiffness (Okwuosa et al., 2017; Solomou et al., 2019). In this population, these cardiovascular issues can be linked to cancer treatment, physical inactivity, and sedentary behavior (SB) (Okwuosa et al., 2017; Solomou et al., 2019, Irwin, 2008). A variety of anti-cancer medications are used in cancer populations with the most common cancer treatments being chemotherapy and radiation. These treatments have increased survival in cancer patients however, they have deleterious side effects and have been established as cardiotoxic whose manifestation varies based on the treatment (Rosa et al., 2016).

The cardiotoxic effects of cancer treatment and the corresponding changes in CVD risk can be assessed through arterial stiffness. Arterial stiffness is a fundamental mechanical behavior or rigidity of the material properties of the artery wall (Stoner et al., 2021). Arterial stiffness is dependent on the structural and functional components of blood vessels and is considered an index of vascular aging and CVD risk (Stoner et al., 2021; Boutouyrie et al., 2021). One way to

sub-clinically measure arterial stiffness is pulse wave velocity (PWV) (Stoner et al., 2021; Milan et al., 2019). Cancer survivors often have increased arterial stiffness due to anti-cancer therapies (Solomou et al., 2019). However, the magnitude of these effects is not well understood.

Objective

The objective of this meta-analysis is to consolidate the literature investigating the effect of cancer treatment on PWV, the primary outcome, in adult cancer survivors. We anticipate that the findings of this meta-analysis will identify a significant effect of cancer treatment on PWV when pre-treatment values are compared to post-treatment values. Due to the known cardiotoxicity of cancer treatments, we anticipate that cancer treatment will lead to an increase in PWV. The findings could lead to a better understanding of the increased CVD risk seen in cancer survivors. The results of this analysis could also identify gaps in the literature that need to be addressed by further research.

CHAPTER II: LITERATURE REVIEW

This review is divided into three sections: 1) Overview of Cardiovascular Disease in Cancer Survivors; 2) Overview of Arterial Stiffness, PWV, and CVD Risk; 3) Physical Activity and Benefits for Cancer Survivors; and 4) Overview of A Previously Published Meta-Analysis.

Section 1: Overview of Cardiovascular Disease in Cancer Survivors

The two international leading causes of morbidity and mortality are cardiovascular disease (CVD) and cancer (Karlstaedt et al., 2022). A strong relationship between cancer and CVD has been identified due to their shared risk factors (Karlstaedt et al., 2022). These risk factors include smoking tobacco, diet, obesity, sedentary lifestyle, hypertension, alcohol consumption, and hyperlipidemia (Rothe et al., 2017). Following treatment, cancer survivors are at an increased risk of morbidities such as cardiovascular disease (CVD) in comparison to the general population (Okwuosa et al., 2017; Armenian et al., 2016). The long-term cardiovascular issues in the cancer survivor population include cardiomyopathy/heart failure, hypertension, dysrhythmias, autonomic dysfunction, valvular heart disease, coronary artery disease, pericardial diseases, and increased arterial stiffness (Okwuosa et al., 2017; Solomou et al., 2019). As the number of cancer survivors increases due to advances in medical treatments and an aging U.S. population, there is a growing need to better understand how to identify, prevent, and mitigate CVD in cancer survivors to further increase cancer survivor lifespan (Bluethmann et al., 2016; Solomou et al., 2019).

Cancer therapies were first recognized as agents of cardiac dysfunction in the 1960s (Rosa et al., 2016). Anti-cancer medications have been correlated with cardiotoxicity in the form congestive heart failure, hypertension, arrhythmias, myocardial ischemia, and other cardiovascular diseases (Rosa et al., 2016). A variety of anti-cancer medications are used in

cancer patients and the manifestation of cardiotoxicity varies based on the treatment (Rosa et al., 2016). Anthracyclines are commonly used to treat hematological and solid tumors as they bind to the DNA of replicating cells (Rosa et al., 2016). Cancer patients treated with anthracyclines are 5 times more likely to chronic heart failure than those treated with nonanthracycline treatments (Rosa et al., 2016). Alkylating agents also prevent cell replication by attacking the DNA (Rosa et al., 2016). Alkylating agents have been associated with a variety of clinical diagnoses such as asymptomatic pericardial effusion and myopericarditis (Rosa et al., 2016). Another type of cancer treatment are taxanes which are commonly used to treat breast cancer and ovarian cancer (Rosa et al., 2016). Taxanes such as Paclitaxel and Docetaxel are related to arrhythmias and cardiac ischemia (Rosa et al., 2016). The cardiac damage correlated with anti-cancer therapies may be reversible depending on the treatment used. However, a better understanding on these effects and their magnitude is needed in order to develop efficient interventions to mitigate this damage.

In addition to anticancer therapies being associated with cardiotoxicity that manifests in different clinical forms, other aspects of a cancer diagnosis play a role in the increased CVD risk experienced by cancer patients and survivors. Half of cancer patients display cachexia which is characterized by loss of adipose tissue and skeletal muscle mass (Suzuki et al., 2013). Cachexia can impact a patient's quality of life, display of symptoms, and ability to partake in physical activity and therefore indirectly leads to an increase in CVD risk (Suzuki et al., 2013). Fatigue is one of the most common side effects of cancer and similar to cachexia, decreases one's ability to be physical active (Bower, 2014). Physical inactivity and sedentary behavior have been shown to increase arterial stiffness and the risk of CVD (Elagizi et al., 2020). These aspects of a cancer

diagnosis, in conjunction to the cardiotoxic effects of cancer treatment lead to cancer survivors having an increased arterial stiffness and CVD risk.

Section 2: Overview of Arterial Stiffness, PWV, and CVD Risk

Arterial stiffness has been established as a strong predictive measure of cardiovascular disease (CVD). Vascular aging is biological aging occurring in the vasculature risk (Kucharska-Newton et al., 2019). As vascular aging occurs, there is a reduction in vascular elasticity, an increase in stiffness, and impairments in endothelial function which increases CVD risk (Kucharska-Newton et al., 2019).

The gold standard for arterial stiffness measurement is pulse wave velocity (PWV) (Jannasz et al., 2019; Milan et al., 2019; Stoner et al., 2021). PWV is the speed at which the forward pressure wave is transmitted between two arterial segments and is measured in meters/second (m/s) (Stoner et al., 2021). Increased arterial stiffness is indicated by faster PWV (Stoner et al., 2021).

PWV can be obtained through obtained through a variety of methods including applanation tonometry and cuff-based oscillometry (Milan et al., 2019). Additionally, there are various types of PWV that vary based on the arterial segments being analyzed. Common PWV measurements include carotid-femoral PWV (cfPWV), brachial-ankle PWV (ba-PWV), and carotid-radial PWV (cr-PWV) (Solomou et al., 2019). Carotid-femoral PWV (cfPWV) is the most widely used and has been established as the most useful indicator of CVD risk (Solomou et al., 2019; Stoner et al., 2021; Kucharska-Newton et al., 2019).

Obtaining PWV measurements is a noninvasive way to assess CVD risk in general populations as well as cancer survivors (Parr et al., 2021). A 1 m/s increase in cfPWV was shown to be associated with a 14% increased risk of a cardiovascular event (cardiovascular death

and non-fatal events), 15% increased risk of cardiovascular mortality, and 15% increased risk for all-cause mortality (Vlachopoulos et al., 2010; Kucharska-Newton et al., 2019). Cancer survivors often display increased PWV as a result of anti-cancer therapies and physical inactivity. Anthracycline treatment in breast cancer patients is associated with increased PWV (Novo et al., 2021). Colorectal cancer patients have also been shown to display an increase in PWV after chemotherapy (Visvikis et al., 2019). The increases in PWV in these cancer survivors are consistent with the decreased cardiovascular health of cancer survivors (Okwuosa et al., 2017; Armenian et al., 2016).

Section 3: Physical Activity and Benefits for Cancer Survivors

Throughout the development of this thesis, the focus and research question of this meta-analysis have changed. The information below is indirectly relevant to the meta-analysis as this section offers background information on potential interventions that could mitigate the effects explored in the meta-analysis. Further research is needed to directly apply this information to the results of the meta-analysis.

In cancer survivor populations, physical activity has been shown to improve quality of life, psychological health, bone health, and muscular strength (Kim et al., 2019; Dieli-Conwright et al., 2018). In general, postdiagnosis physical activity has been shown to reduce the risk of all-cause mortality for cancer survivors (Rock et al., 2022). Significant risk reduction in all-cause mortality of 40%, 42%, and 33% were found in studies respectively analyzing kidney cancer survivors, breast cancer survivors, and female reproductive cancer survivors with varying physical activity levels (Rock et al., 2022). Cancer patients and cancer survivors are encouraged to be physical activity throughout their lifetime to reduce the risk of all-cause mortality and recurrence (Rock et al., 2022).

In cancer survivors, physical activity interventions have shown to positively impact cardiovascular variables such as resting heart rate and systolic blood pressure. After a 26-week combined aerobic and resistance intervention, 62% of cancer survivors experienced a decrease in resting heart rate when compared to baseline (Grote et al, 2020). In the same study, there were no significant differences in heart rate variability (HRV), a measure of vagal tone and parasympathetic nervous system activity, from baseline to post-intervention (Grote et al., 2020). The researchers suggests that anti-cancer therapies do not affect vagal tone and that another aspect of the cancer experience is responsible for the decreased vagal tone that is often seen in cancer survivors however further research is needed to identify the responsible mechanism (Grote et al., 2020). At the completion of a 12-week tai chi chih intervention, breast cancer survivors showed a decrease in systolic blood pressure compared to the health education control group that did not participate in the PA intervention (Campo et al., 2015). However, no significant decreases were found in diastolic blood pressure (Campo et al., 2015). These studies suggest that physical activity interventions may be beneficial to the cardiovascular health of cancer survivors however, the mechanisms are not well understood (Campo et al., 2015; Grote et al., 2020).

Physical activity has been shown to decrease PWV in populations with co-morbidities such as diabetic or elderly individuals. In non-diabetic, prediabetic, and type 2 diabetic elderly subjects, increments of 1000 steps per day were associated with a 0.05 m/s decrease in cfPWV (Metsämarttila et al., 2018). Another study found a significant decline in cfPWV in hypertensive subjects (Fantin et al., 2012). Older obese adults showed a significant decrease in ba-PWV after a combined aerobic- and resistance-exercise intervention. However, the effectiveness of healthy lifestyle interventions and arterial stiffness in cancer survivors are not well understood.

Section 4: Overview of A Previously Published Meta-Analysis

In 2020, Parr et al. published a systematic review and meta-analysis titled "Anticancer Therapy-Related Increases in Arterial Stiffness." This article provided an overview of the current evidence for increases in arterial stiffness after cancer treatment of studies published before 2019. Two separate meta-analyses were conducted with one including longitudinal studies (pre-treatment vs. post-treatment) and the other including cross-sectional studies (cancer survivors vs. control subjects). The first meta-analysis revealed a significant overall increase of 0.890 m/s from pre-treatment to post-treatment arterial stiffness measurements (SMD=0.890 m/s; 95% CI, 0.448–1.332; z=3.95; P≤0.0001; Parr et al., 2020). The second meta-analysis revealed that cancer survivors had an higher overall arterial stiffness than control subjects (SMD=0.860 m/s; 95% CI, 0.402–1.318; z=3.68; P=0.0002; Parr et al., 2020). Subgroup analysis were performed based on follow-up time and treatment type.

However, several limitations should be borne in mind when considering this article and its findings. Parr et al. did not limit the article selection by age meaning that 3 studies with pediatric populations were included. Arterial stiffness and PWV may be useful indicator of CVD risk in adolescents and young adults however, normative data and reference values are still being established for this population (Agbaje, 2022). Normal PWV values for adults range from 6.2 m/s for those less than 30 years old to 10.9 m/s for those 70 years old and older (Reference Values for Arterial Stiffness' Collaboration, 2010). However, 50th percentile values for children range from 4.348 m/s at 7 year old to 4.742 m/s at 12 years old (Reusz et al., 2010). The difference in magnitude of normative values between children and adults makes the comparison between the two groups inappropriate. Therefore, the inclusion of pediatric population by Parr et al. is viewed as a limitation of the article. Additionally, multiple measures of arterial stiffness

were analyzed including PWV, aortic distensibility, and β-stiffness index. With PWV being the established gold standard for arterial stiffness measurement, the inclusion of aortic distensibility and β-stiffness index is also viewed as a limitation (Jannasz et al., 2019; Milan et al., 2019; Stoner et al., 2021). Parr et al., 2020 included studies published between inception and January 2019 meaning articles published between then and April 2023 were not included. This thesis strove to build upon the work of Parr et al. and provide an updated consolidation of the literature by including recently published studies, excluding pediatric populations, and utilizing PWV as the sole measure of arterial stiffness.

CHAPTER III: METHODOLOGY

This meta-analysis was carried out in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Barendregt and Doi, 2015).

Data Sources and Searches

Electronic databases (PubMed) were searched by two authors (JL and LBF) utilizing the following search terms: (cancer OR tumor) AND (chemotherapy OR radiation OR drug therapy or treatment) AND (pulse wave velocity OR PWV).

The reference lists of all identified trials and relevant reviews or editorials were also examined. The search was limited to titles and abstracts written in English language with human adult (18 years of age and older) populations published between database inception and April 2023.

Article Selection

Two researchers (JL and LBF) completed the study selection independently. For the purpose of this meta-analysis, the term “article” is used synonymously with “study” and “trial” is the unit included in the meta-analysis. A given article may have resulted in more than one eligible “trial” if the article included more than one cancer group. Initially, article titles and abstracts were screened for relevance by two reviewers (JL and LBF). The full-text versions of potentially eligible articles were obtained to evaluate for eligibility, also by two reviewers (JL and LBF). The following criteria were used to select trials for inclusion in this review: (i) English language, (ii) human studies, (iii) adults (18 years of age and older), (iv) cancer patients/survivors (any type), (v) inclusion of cancer treatment (vi) inclusion of at least two PWV measurements (pre-treatment and post-treatment). Repeated publications from the same studies were excluded.

Data Extraction and Quality Assessment

Data extraction, quality assessment and investigation of the pulse wave velocity measurement were completed by two reviewers (JL and LBF). Data extracted for each eligible trial included bibliographic information (author, publication year), baseline participant characteristics (age, BMI, cancer type), details of pulse wave velocity measurement (device, measurement site) and reported outcomes.

Study quality was assessed using the Study quality was assessed using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies (range 1-3), which includes items related to selection bias, study design, confounders, blinding, data collection methods, withdrawal and drop-outs, intervention integrity, and analyses.

Data Synthesis

Aggregation (LBF) and calculation of final results (CP) were each conducted by one author. For each outcome of interest, the pre- and post-treatment values (mean and standard deviation) were extracted. For studies reporting multiple time points, only the final time point was used in analyses. Primary study outcome was PWV (m/s).

Data Analysis

A single author (CP) conducted all statistical analysis using the MetaXL software (Doi et al., 2015b), and ancillary analysis using the metafor-package (Cohen, 1988) for the R statistical environment (RKWard version 0.7.1). PWV parameter estimates were reported as standardized mean differences (SMD) (Cohen, 1998). Data were pooled using the inverse variance heterogeneity (IVhet) model of meta-analysis to account for potential heterogeneity within and between studies (Sterne et al., 2011). This method has been shown to be a preferred alternative to the more traditional random-effects model which has been suggested to underestimate statistical

error and produce overconfident estimates when using heterogenous data. Additionally, the IVhet models were adjusted according to the adjudicated quality of each included study (Duval and Tweedie, 2000). The SMD was used to assess the magnitude of effect, where <0.2, 0.2, 0.5, and 0.8 was defined as trivial, small, moderate, and large, respectively (Furuya-Kanamori et al., 2018).

Subsequent to running the IVhet and Quality Effects models, we examined the robustness of the pooled results and the potential for publication bias. Potential outliers were identified by analyzing Cook's distance and studentized residuals. Sensitivity analyses were conducted by removing one potential outlier at a time at a time. Measures of publication bias included visual inspection of Begg's funnel plots (Higgins et al., 2003). Statistical heterogeneity will be assessed using the I^2 statistic, where <25, 25–75, and >75% represent low, moderate, and considerable heterogeneity, respectively (Peddie et al., 2013). Heterogeneity >25% was assumed to indicate that effect sizes could not be treated as estimates of one common effect size, justifying *a priori* determined sub-group analysis based on cancer type, PWV device, PWV site, and time between baseline and post-treatment visits.

The metafor-package for R statistical software was used to conduct ancillary analyses (Crespo et al., 2016). Meta-analysis statistical models typically assume independent effect sizes (Crespo et al., 2016). To more robustly account for effect size dependency, a 3-level model was conducted with restricted maximum likelihood estimation (Cohen, 1988; Crespo et al., 2016). The 3 sources of variance taken into account included: variance at the level of the subject (Level 1), variance between effect sizes extracted from the same study (Level 2), and variance between studies (Level 3). To determine the significance of the level 2 and level 3 variance, the full model was compared to a model excluding one of these variance parameters in two separate log-

likelihood ratio tests. In the event of significant level-2 and/or level-3 variance, the distribution of effect sizes was considered heterogeneous.

CHAPTER IV: RESULTS

Literature Search and Trial Selection

Figure 1 outlines the literature search strategy. A total of 137 potentially eligible articles were identified. Following screening of titles and abstracts, 94 articles were excluded because they did not meet selection criteria. Of these, 43 articles underwent full text screening and 23 were excluded (Budinskaya et al., 2017; Daskalaki et al., 2014; Dockery et al; 2000; Dockery et al., 2002; Frye et al., 2018; Herceg-Cavrak et al., 2011; Iannaccone et al., 2018; Jenei et al., 2013; Jordan et al., 2018; Koelwyn et al., 2016; Krystal et al., 2015; Laugensen et al., 2016; Novo et al., 2020; Sekijima et al., 2011; Smith et al., 2001; Stamatelopoulos et al., 2003; Steeghs et al., 2009; Stelwagen et al., 2020; Vallerio et al., 2016; van Leeuwen-Segarceanu et al., 2013; Willemse et al., 2013; Yersal et al., 2018; Zhang et al., 2017). The final analysis included 20 articles (24 trials) (Alivon et al., 2015; Burt et al., 2021; Catino et al., 2018; Chaosuwannakit et al., 2009; Dockery et al., 2003; Dockery et al., (a&b) 2009; Drafts et al., 2013; Grover et al., 2015; Kertmen et al., 2022; Lin et al., (a&b) 2021; Militaru et al., 2018; Militaru et al., 2019; Mizia-Stec et al., 2013; Moreo et al., 2016; Ng et al., 2020; Novo et al., 2021; Res et al., (a,b, & c) 2018; Souza et al., 2018; Steeghs et al., 2008; Visvikis et al., 2020).

Description of the Included Trials

Characteristics of the included trials are summarized in Table 1. The number of participants in each trial ranged from 12 (Burt et al., 2021) to 133 (Novo et al., 2021). The mean age of the participants ranged from 41.4 ± 5.9 (Kertmen et al., 2022) to 74.67 ± 9.11 (Ng et al., 2020) years. Seven trials included clinical populations with breast cancer (Burt et al., 2021; Grover et al., 2015; Lin et al., (a&b) 2021; Mizia-Stec et al., 2013; Novo et al., 2021; Souza et al., 2018). Four trials included clinical populations with prostate cancer (Dockery et al., 2003;

Dockery et al.,(a&b) 2009; Ng et al., 2020). Five trials included clinical populations with a combination of cancers (Alivon et al., 2015; Chaosuwannakit et al., 2009; Drafts et al., 2013; Kertmen et al., 2022; Moreo et al., 2016) and 8 trials included clinical populations with miscellaneous cancers (Catino et al., 2018; Militaru et al., 2018; Militaru et al., 2019; Res et al., (a,b&c) 2018; Steeghs et al., 2008; Visvikis et al., 2020).

Of the 24 trials, 4 measured PWV using the AtCor Medical SphymoCor device (Alivon et al., 2015; Burt et al., 2021; Catino et al., 2018; Steeghs et al., 2008) and 8 trials utilized the COMPLIOR system (Dockery et al., 2003; Dockery et al.,(a&b) 2009; Moreo et al., 2016; Res et al., (a,b&c) 2018; Visvikis et al., 2020). Three trials utilized phase-contrast Cardiovascular Magnetic Resonance (PC-CMR) to measure PWV (Chaosuwannakit et al., 2009; Drafts et al., 2013; Grover et al., 2015). The remaining 9 trials utilized other devices to measure PWV including the Medexpert arteriograph, Mobil-O-Graph, Vascular Profiler-1000, dual-channel photoplethymysography, and cardiac ultrasound. Fifteen trials measured carotid-femoral PWV (Alivon et al., 2015; Burt et al., 2021; Catino et al., 2018; Dockery et al.,(a&b) 2009; Kertmen et al., 2022; Mizia-Stec et al., 2013; Moreo et al., 2016; Novo et al., 2021; Res et al., (a,b&c) 2018; Souza et al., 2018; Steeghs et al., 2008; Visvikis et al., 2020) and the remaining 9 trials measured PWV at other sites including the ascending to descending thoracic aorta PWV, carotid-radial PWV, aorto-radial PWV, femoralis-dorsalis pedis PWV, and brachial-ankle PWV.

The time between the collection of the pre-treatment values and the last post-treatment values varied from 5 weeks (Steeghs et al., 2008) to 96 weeks (Ng et al., 2020). Six of the trials had a visit timeline of less than 12 weeks (Alivon et al., 2015; Dockery et al., 2003; Kertmen et al., 2022; Militaru et al., 2019; Moreo et al., 2016; Steeghs et al., 2008). Four trials did not provide information about the average time between the baseline visit and the last visit (Res et

al., (a,b&c) 2018; Visvikis et al., 2020). The remaining 14 trials a visit timeline of great than 13 weeks.

Methodological Quality Assessment

As reported in Table 1, the quality of the studies ranged from 1 to 3 out 3. Overall, included studies had a median quality score of 2 indicating their moderate quality.

Synthesis of the Results

First Analysis Including All Trials

Cancer treatment resulted in a large, significant increase in PWV (SMD=1.096 m/s, 95% CI: 0.391, 1.800, df=23, p = 0.004) (Table 2). The heterogeneity of the three-level model was considerable (I^2 = 96.38%, p < 0.001). Cook's distance and studentized residuals identified 3 studies (Chaosuwannakit et al., 2009; Dockery et al., 2009, Drafts et al., 2013) as potential outliers or as being potentially influential. Sensitivity analysis indicated that 1 of these 3 trials (Chaosuwannakit et al., 2009) influenced the pooled estimate. Sub-group analysis did not reveal any effects of cancer type (df=9, p= 0.799). However, when grouped by device, there was a large significant effect of the trials that utilized PC-CMR to measure PWV (SMD=3.535 m/s, 95% CI: 1.912, 5.179, df=2, p < 0.001). Similarly, when grouped by PWV site, the ascending to descending thoracic aorta, the site used in PC-CMR, had a pooled estimate (SMD) of 3.235 m/s (95% CI: 0.885, 5.584, df=2, p = 0.007) which indicates a large significant effect of this site. Other subgroups cancer type and visit timeline) in these analyses did not have a significant effect. The results of this sub-group analysis warranted a second model excluding the studies that utilize PC-CMR.

Second Analysis Excluding PC-CMR Trials

Due to the result from the first analysis, the 3 studies that utilized PC-CMR (Chaosuwannakit et al., 2009; Drafts et al., 2013; Grover et al., 2015) were excluded for this second model. Cancer treatment resulted in a moderate-large significant increase (worsening) in PWV (SMD=0.634 m/s, 95% CI: 0.348, 0.920, df=20, p=0.002) (Table 3). The mean difference between pre-treatment and post-treatment was 0.6 m/s. For this analysis, a two-level model was justified as the three-level model did not improve the fit of the overall model. The heterogeneity of the two-level model was moderate (I^2 = 59.27%, p = 0.003). Cook's distance and studentized residuals identified 1 study (Burt et al., 2021) as a potential outlier or as being potentially influential. Sensitivity analysis indicated that none of the trials unduly influenced the pooled estimated. Visual inspection of the funnel plot did not reveal asymmetry (Figure 2).

Sub-group analysis did not reveal any significant effects of PWV device (df=7, p=0.150) or PWV site (df=4, p=0.360). However, a significant effect was seen based on cancer type (df=9, p=0.045) which may be explained by differences in the number of trials in each subgroup (range of 1 trial to 6 trials). In breast cancer survivors, a large significant decrease (improvement) in PWV was seen after treatment (SMD=-0.939 m/s, 95% CI: -1.839, -0.039, df=6, p=0.041). Additionally, in acute lymphoblastic leukemia survivors, a large significant increase in PWV was seen after treatment (SMD=1.000 m/s, 95% CI: 0.164, 1.836, df=1, p=0.019). A significant effect was seen based on time between baseline and post-treatment visits (df=1,p=0.045). Trials with a short visit timeline (less than 12 weeks) resulted in a moderate increase in PWV (SMD=0.569 m/s, 95% CI: 0.012, 1.126, df=5, p=0.045) whereas, trials with a long visit timeline (greater than 13 weeks) resulted in a small-moderate increase in PWV (SMD=0.317 m/s, 95%

CI: -0.013, 0.647, df=13, p=0.060). This may be due to the fact that 4 out of 24 trials did not provide this data and were therefore not included in this analysis.

CHAPTER V: DISCUSSION

The aim of this meta-analysis was to synthesize the existing literature investigating the effects of cancer treatment on pulse wave velocity. The main findings were that cancer treatment has a moderate-large, significant increase on PWV.

Limitations

Several limitations should be borne in mind when considering these findings. The trials included used different PWV assessment methodology and reported a variety of outcomes. In the included trials, PWV was sometimes a secondary outcome. The differences in methodologies was addressed by performing a sub-group analysis by device type and PWV measurement site in addition to conducting a multi-level analysis. Second, the amount of trials for each cancer type varied from 1 to 6 which limits the conclusions drawn from the sub-group analysis. Third, only 17 trials provided data on the time between baseline values and last post-treatment values which limits the conclusions drawn from the sub-group analysis. Fourth, some of the trials were mixed-sex and others included only males (prostate cancer) while others analyzed cancers that disproportionally affect females (breast cancer). It remains unclear whether both sexes respond similarly. Lastly, the quality of the included trials was generally suboptimal, and lacked information about participant withdrawals and drop-outs.

Comparison with Other Studies & Clinical Significance

Overall, there was a moderate-large significant effect of cancer treatment on PWV. We speculated that PWV would increase in response to cancer treatment. This aligns with the results of Parr et al., 2020 that revealed a statistically significant increase in arterial stiffness following cancer treatment. From pre-treatment to post-treatment, Parr et al., calculated an increase of

0.890 m/s which is comparable to 0.643 m/s increase seen in this meta-analysis. Due to the known cardiotoxicity of cancer treatment, these results are expected, but still concerning.

An increase of 1.0 m/s is considered statistically significant as it is associated with a 14% increased risk of a cardiovascular event (cardiovascular death and non-fatal events), 15% increased risk of cardiovascular mortality, and 15% increased risk for all-cause mortality (Vlachopoulos et al., 2010; Kucharska-Newton et al., 2019). The mean difference between pre-treatment and post-treatment was 0.6 m/s which approaches clinical significance. Therefore, further research is needed to identify potential interventional strategies to either i) reduce cardiotoxicity during treatment or ii) reverse the adverse cardiovascular response of treatment once patients enter the survivorship phase.

Implications

This meta-analysis provides an updated summary of the existing literature in this area in hope to investigate the effects of cancer treatment on PWV which was previously investigated by Parr et al., 2020. Such investigations on this and other outcomes are crucial to better understand the cardiotoxicity of cancer treatment and other deleterious effects of cancer treatment. The data indicates that cancer treatment results in a moderate-large significant increase in PWV of 0.634 m/s (SMD) with a mean difference of 0.6 m/s. This worsening in PWV is an indicator of increased CVD risk. In the future, studies should include additional measures of CVD risk to better understand the cardiotoxicity correlated with cancer treatment.

There are important gaps in the current literature which were identified. The current data supports that cancer treatment increases CVD risk however, there are very few studies analyzing interventions to prevent or decrease this risk. For example, there is a low number of trials which investigated the effects of physical activity on PWV in cancer survivors. Direct analysis of the

impacts of physical activity intervention on PWV in cancer survivors could result in improved physical activity recommendations that help improve the lifespan and quality of life of cancer survivors. Improvements in physical activity recommendations for this population could help mitigate the burden that will be placed on our healthcare system as the number of cancer survivors continues to increase in the U.S. due to advances in medical treatments and an aging U.S. population (Bluethmann et al., 2016; Solomou et al., 2019).

CHAPTER VI: CONCLUSION

Cancer treatment, such as chemotherapy and radiation, is associated with increased CVD risk. This meta-analysis consolidated the existing literature on the effect of cancer treatment on PWV in cancer survivors. Furthermore, gaps in the existing literature were identified in order to better inform researchers on the need to investigate potential intervention strategies to mitigate the cardiotoxicity of cancer treatment. The results of this analysis suggest that there are meaningful changes in PWV following cancer treatment (mean difference = 0.6 m/s). These changes are statistically significant and approach clinical significance which is defined as a 1.0 m/s increase in PWV. Further research is needed in order better understand cardiotoxicity of cancer treatment and to better inform healthy lifestyle recommendations for cancer survivors.

APPENDIX

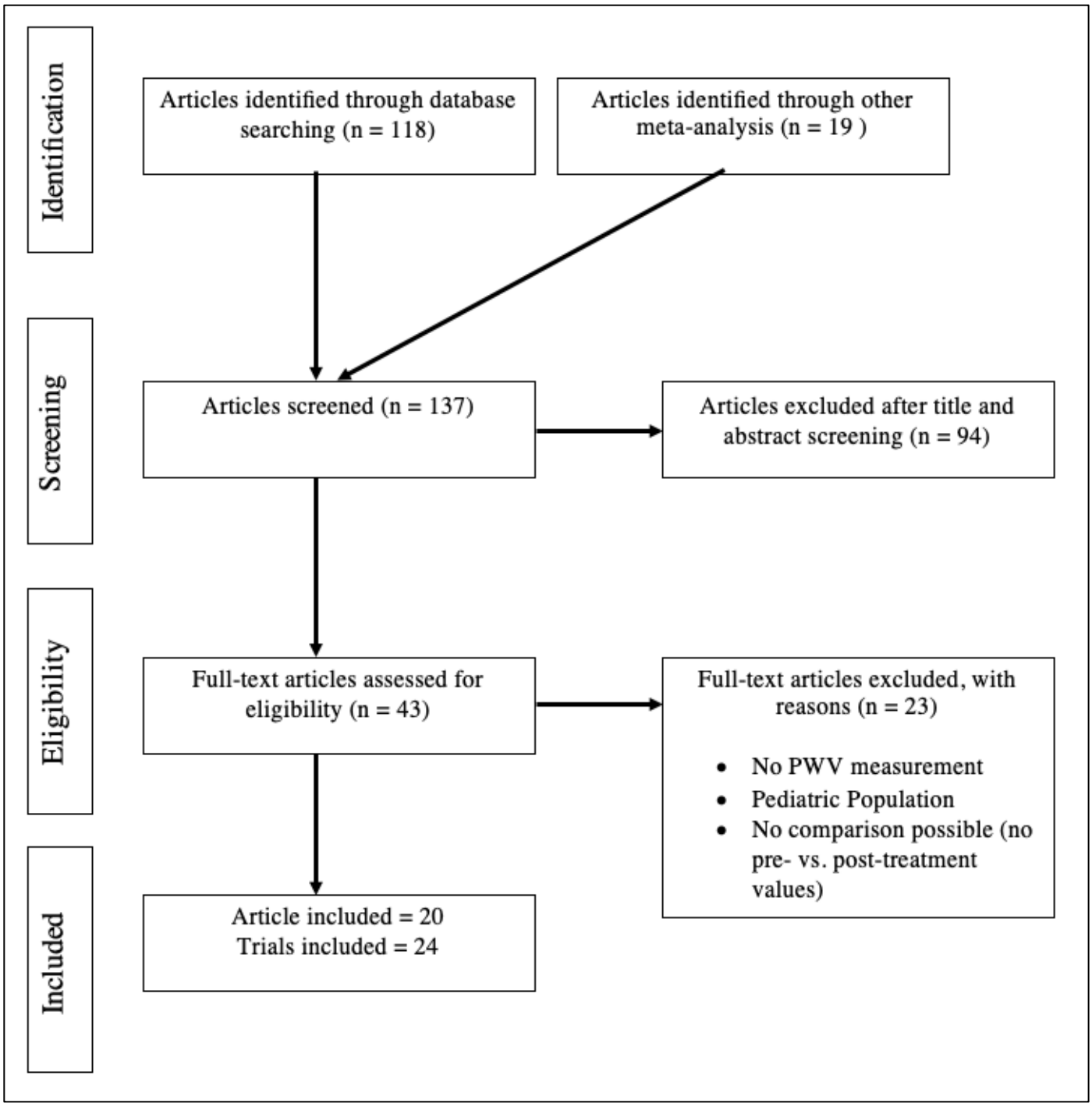

Figure 1. Flow chart outlining literature search and trial selection

PWV, pulse wave velocity

Table 1. Characteristics of included trials

References	Quality	Sample [n (total/F); age (y, mean (SD or range);	BMI mean (SD or range)	Cancer type	Device	Site	Time (weeks)
Alivon et al., 2015	2.0	n=46; age: 59±15	25±4	Mixed	SphygmoCor	CF	7
Burt et al., 2021	2.0	n=12; age: 53±9	27±1.7	Breast	SphygmoCor	CF	28
Catino et al., 2018	2.0	n=43; age -- median(IQR): 62.5(55.8 to 68.0)	median(IQR): 27.9 (24.2 to 33.4)	metastatic renal cell carcinoma	SphygmoCor	CF	33
Chaosuwannakit et al., 2009	2.0	n=40; age: 52±11; race: n=33 CON: n=13; age:53±10	28±6.3 CON: 27.6±5.1	Mixed	Phase-contrast Cardiovascular Magnetic Resonance	ascending to descending thoracic aorta	16
Dockery et al., 2003	2.0	n=16; age: 71±9, CON: n=15; age: 70±7	26.9±3.4 CON: 26.0±4.2	Prostate	COMPLIOR System	AF	12
Dockery et al., (a) 2009	2.0	n=21; age: 71.3±6.6, CON: n=20; age: 69.8±6.2	28.1±5.2 CON: 26.4±3.4	Prostate	COMPLIOR System	CF	24
Dockery et al.,(b) 20	2.0	n=21; age: 71.1±6.1, CON: n=20; age: 69.8±6.3	71.1±6.1 CON: 26.4±3.5	Prostate	COMPLIOR System	CF	24
Drafts et al., 2013	2.0	n=53; age: 50 ± 2 (19 to 80)	29.6 ± 1.6	Mixed	Phase-contrast Cardiovascular Magnetic Resonance	ascending to descending thoracic aorta	24
Grover et al., 2015	2.0	n=27; age: 54±11 CON: n=12; age: 54±13	N/A	Breast	Phase-contrast Cardiovascular Magnetic Resonance	ascending to descending thoracic aorta	56
Kertmen et al., 2022	2.0	n=30; age:41.4±5.9 CON: n=40; age:39.6±6.6	N/A	Mixed	Mobil-O-Graph	CF	4
Lin et al.,(a) 2021	2.0	n=15; age:45±2	21.3±3.3	Breast	dual-channel photoplethymsography	right index finger to right toe	15
Lin et al.,(b) 20	2.0	n=19; age: 42±2	21.0±2.2	Breast	dual-channel photoplethymsography	right index finger to right toe	15
Militaru et al., 2018	2.0	n=30; age: 47.67±13.34	25.77±4.04	acute myeloid leukemia (AML)	Medexpert arteriograph TL2	AO	24
Militaru et al., 2019	2.0	n=35; age: 45.38±11.27	25.57±3.91	acute lymphoblastic leukemia (ALL)	Medexpert arteriograph TL2	AO	12
Mizia-Stec et al., 2013	2.0	n=31; age: 50±9	26.0±4.8	Breast	Not Available	CF	48
Moreo et al., 2016	2.0	n=29; age:63±11	25.2±3.7	Mixed	COMPLIOR System	CF	6
Ng et al., 2020	2.0	n=36; age: 74.67±9.11 CON: n=24; age: 73.25±4.09	23.75±3.08 CON: 23.15±2.83	Prostate	Omron	BA	96
Novo et al., 2021	2.0	n=133; age: 55.64±11.74	26.4 (22.1-29.9)	Breast	Cardiac ultrasoun	CF	48
Res et al., (a) 2018	2.0	n=60; age: 57.9±10.0	26.8±6.0	kidney cancer	COMPLIOR System	CF	Not Available
Res et al., (b) 2018	2.0	n=18; age: 67.4±6.7	25.2±7.7	gastrointestinal stromal tumors (GISTs)	COMPLIOR System	CF	Not Available
Res et al., (c) 2018	2.0	n=93; age:65.2±10.7	28±6.5	Bowel	COMPLIOR System	CF	Not Available
Souza et al., 2018	2.0	n=24; age: 52.33±8.85	31±5.87	Breast	Mobil-O-Graph	CF	48
Steeghs et al., 2008	2.0	n=18; age: 55(22-76)	24.7 (20.5-29.7)	Colorectal	SphygmoCor	CF	5
Visvikis et al., 2020	2.0	n=70; age: 64.9±10.5	24.7±4.4	Colorectal	COMPLIOR System	CF	Not Available

Study quality was assessed using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies (range 1-3).

SD, standard deviation; CON, controls; CF, carotid-femoral; AF, aorto-femoral; AO, aortic; BA, brachial-ankle

Table 2. The effect of cancer treatment on PWV with all trials

	Trials	Quality	Pooled effect					Heterogeneity		
	(n)	/3	Estimate	SE	LCI	UCI	P-value	Q	P-value	I^2
All	24	2	1.096	0.341	0.391	1.8	0.004	371.2	<0.001	96.38%
Device										
PC-CMR	3	2	3.545	0.834	1.912	5.179	<0.001			
no other significant subgroups	23	2								
PWV site										
ascending to descending aorta	3	2	3.235	1.199	0.885	5.584	0.007			
no other significant subgroups	23	2								

Table 3. The effect of cancer treatment on PWV with PC-CMR trials excluded

	Trials	Quality	Pooled effect					Heterogeneity		
	(n)	/3	Estimate	SE	LCI	UCI	P-value	Q	P-value	I^2
All	21	2	0.634	0.118	0.348	0.92	0.002	41.304	0.003	56.27%
Cancer Type								11.195	0.427	13.30%
ALL	1	2	1	0.426	0.164	1.836	0.019			
AML	1	2	-0.12	0.745	-1.581	1.341	0.872			
Bowel	1	2	-0.1	0.472	-1.032	0.832	0.833			
Breast	6	2	-0.939	0.459	-1.839	-0.039	0.041			
Colorectal	2	2	-0.165	0.457	-1.06	0.731	0.718			
GISTS	1	2	-0.4	0.549	-1.475	0.675	0.466			
Kidney	1	2	-0.2	0.476	-1.132	0.732	0.674			
Mixed	3	2	-0.602	0.591	-1.761	0.556	0.308			
Prostate	4	2	-0.013	0.554	-1.099	1.072	0.981			
Renal	1	2	-0.3	1.123	-2.5	1.9	0.789			
Time								18.814	0.222	18.81%
< 12 weeks	6	2	0.569	0.284	0.012	1.126	0.045			
> 13 weeks	11	2	0.317	0.168	-0.013	0.647	0.06			

Estimate: trivial, small, moderate, and large effect are defined as <0.2, 0.2, 0.5, and 0.8, respectively. I^2: 25, 50, and 75% represent low, moderate, and high heterogeneity, respectively.

Estimate, SMD; SE, standard error; LCI, lower confidence interval; UCI, upper confidence interval

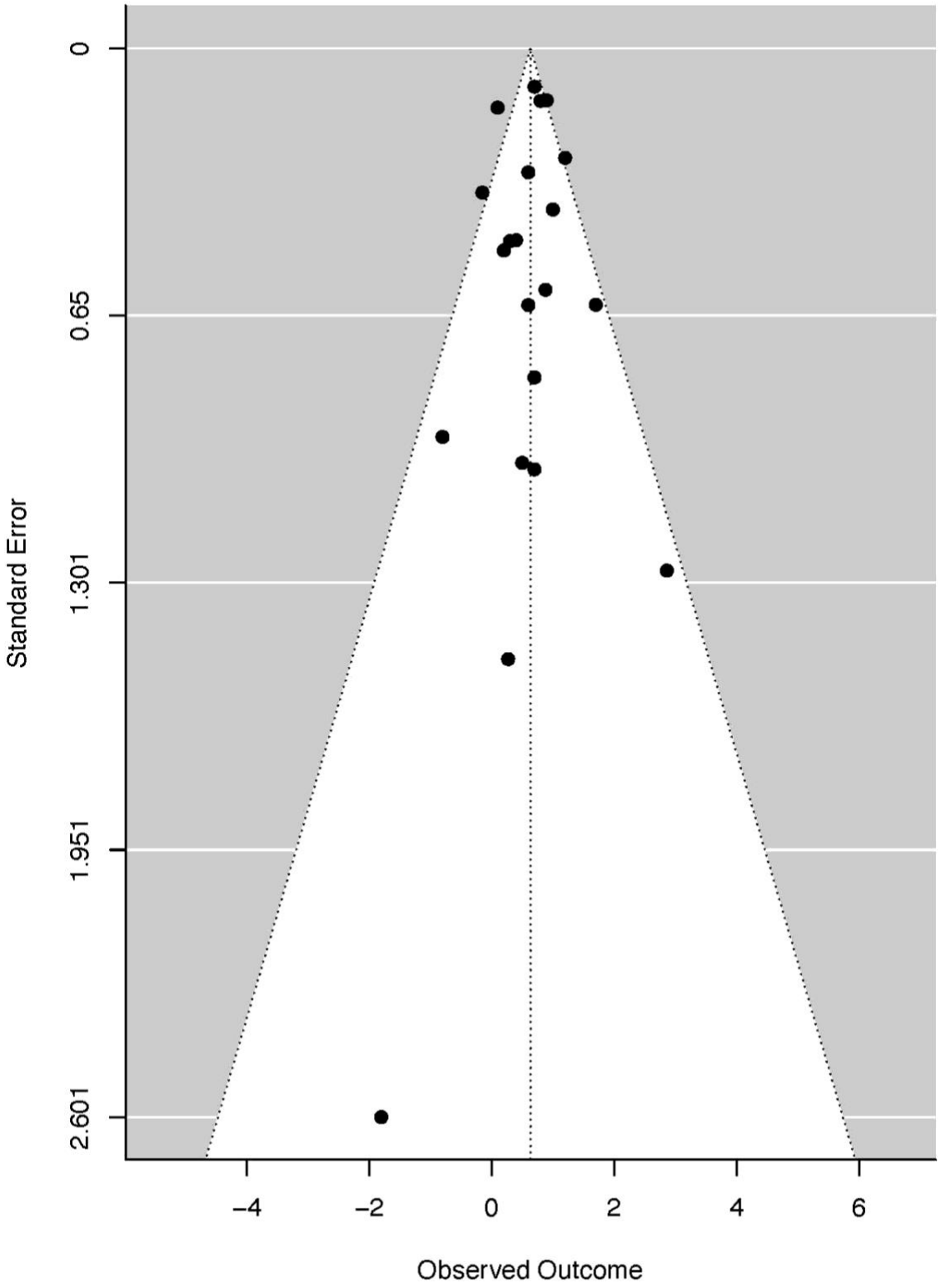

Figure 2. Funnel plot for second analysis that excluded trials that used PC-CMR

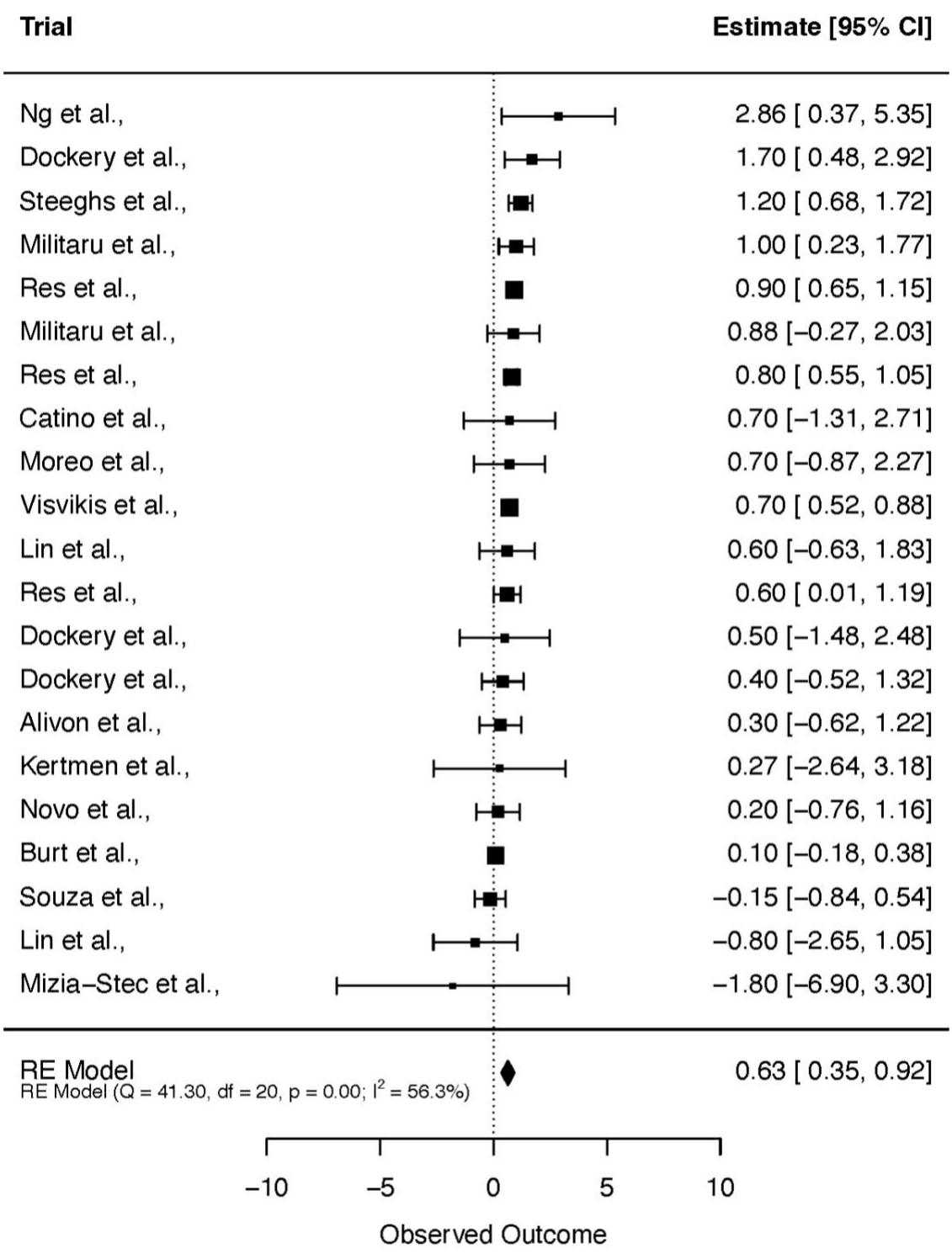

Figure 3. Forest plot for second analysis that excluded trials that used PC-CMR

Estimate, SMD; CI, confidence interval; df, degrees of freedom

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