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Antineoplastic-related cardiovascular toxicity: A systematic review and meta-analysis in Asia

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ABSTRACT

Background: Cancer and heart diseases are the leading causes of morbidity and mortality in many countries worldwide. Recent advancement in chemotherapy and targeted therapies has led to an improvement in cancer survival rates, but at a cost of higher cardiac side effects. However, report on antineoplastic-related cardiotoxicities incidence in Asia is lacking.

Methods: We systematically searched multiple databases to identify studies reporting incidence of antineoplastic-related cardiovascular toxicity in Asia published from inception to November 2018. Pre-specified subgroups were performed to explore heterogeneity and study quality assessed and reported according to PRISMA guidelines.

Results: A total of 61 studies across 11 countries in Asia reported 8 types of cardiovascular toxicities were included. These studies mostly reported on adult populations, and usually examined cardiotoxicities related to anthracycline use. The most frequently reported cardiotoxicities were heart failure, electrocardiogram abnormalities and left ventricular dysfunction. The pooled estimated incidence of cardiotoxicity was 4.27% (95% CI: 3.53–5.07). Subgroup analysis showed higher incidence in middle income countries compared to high income countries.

Conclusions: Although robust incidence studies are sparse, cardiovascular complications affects approximately one in twenty cancer patients in Asia. This highlights a unique opportunity of cancer patients caring that need cardiologists and oncologist to become familiar with this emerging sub-specialty.

1. Introduction

Cardiovascular (CV) toxicities such as heart failure, systemic hypertension and thromboembolic events are commonly experienced by patients who have received chemotherapy or targeted therapy (Chang et al., 2017a,b). While CV toxicities are commonly associated with older chemotherapeutic agents such as anthracycline, there have been an increasing number of reports associated with targeted therapies such as trastuzumab, bevacizumab and tyrosine kinase inhibitors (Chang et al., 2017a,b). These adverse effects are mainly due to the direct cytotoxic cardiac injury associated with both traditional chemotherapy or the newer targeted therapies and can be classified into either: cardiac systolic dysfunction, cardiac ischemia, arrhythmias, pericarditis and repolarization abnormalities (Hong et al., 2010). While the exact mechanisms are unknown, these adverse effects are thought to be related to the interaction of chemotherapy or targeted therapies with concurrent drugs or changes in physiology of the patient such as hepatic metabolism. It has been reported that 5.3% five years survivors of childhood cancer experienced cardiac conditions such as congestive heart failure, valvular abnormalities, pericardial disease and myocardial infarction (Mulrooney et al., 2009). These rates are expected to increase with the advancement in cancer management (Global Burden

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of Disease Cancer C., 2017).

While understanding the pathophysiology of these adverse effects is important in the development of preventive measures, recognizing the risk and burden is the first crucial step towards developing new strategies to promote cardiac risk prevention, detection and management. Antineoplastic-related CV toxicities have been widely studies and reported in other continents especially North America and Europe (Smith et al., 2010; Moja et al., 2012; Onitilo et al., 2014). Reviews based on data from western countries reported the incidence rate of cancer treatment-induced cardiotoxicity with several chemotherapy and targeted therapies including anthracycline (0.9%–57%) (Chang et al., 2017a; Curigliano et al., 2016; Fulbright, 2011; Conway et al., 2015), cyclophosphamide (2%–28%) (Curigliano et al., 2016; Fulbright, 2011; Conway et al., 2015), trastuzumab (0%–28%) (Curigliano et al., 2016; Conway et al., 2015; Ewer and Ewer, 2015) and bevacizumab (1.7%–10.9%) (Chang et al., 2017a; Curigliano et al., 2016). However, to date there has been no studies that have quantified the incidence of cardiotoxicities in Asia, which may differ due to the presence of interethnic difference (Udagawa et al., 2018). This has been evidence in abacavir- and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis (Fan et al., 2017). Thus, we performed a systematic review to provide collective evidence on the incidence and characteristics of antineoplastic-related CV toxicities which in turn to guide future research in this region.

2. Method

2.1. Search strategy and selection criteria

The following databases were searched: Ovid Medline, EMBASE and Cochrane Central Register of Controlled Studies, without language restriction, for studies reporting antineoplastic related cardiovascular toxicity in Asia (Online Resource 1) from database inception until November 30, 2018. This was supplemented with a manual search of cited references from retrieved articles. Any article which reported the incidence of CV toxicity in cancer patients treated with an antineoplastic agent in Asian countries was included. Studies were excluded if they were case report, reviews and non-patient or lab studies.

2.2. Data extraction and quality assessment

Information about geographic location, study design, participant demographics, types of cancer, frequency of CV toxicity and definition of CV toxicity were extracted independently by two reviewers (SLL and SWHL) using a piloted data extraction table. Any disagreement was resolved through adjudication with input by a third reviewer (NC). All data were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2009).

Study quality was independently assessed by two reviewers (SLL and SWHL) using Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) (Sterne et al., 2016) for non-randomized studies while the Cochrane risk of bias (RoB 2.0) tool (Higgins et al., 2011) was used for randomized studies.

2.3. Data analysis

We performed a meta-analysis of proportions to estimate incidence of pre-specified subgroups, using the Freeman-Tukey Double Arcsine Transformation (Freeman, 1950) to establish variance of raw proportions as reported previously (Ang et al., 2017; Lee et al., 2017). DerSimonian-Laird random effects models (DerSimonian and Laird, 1986) was used to combine the transformed proportions and to incorporate heterogeneity anticipated among included studies. Heterogeneity of the studies was assessed using Cochran's Q and I^2 statistics. Pre-specified subgroup analyses were carried out to assess the difference in incidence according to country, country's income as reported in World Economic Situation Prospects (United Nations, 2017) and regions (Physical Map of Asia, 2009), study design, study period, age at diagnosis ($<$ 18 years, $\geq$ 18 years or both), patient's performance status, chemotherapy (anthracycline- vs non anthracycline-based), CV toxicity definition used and type of CV toxicity. All analyses were performed using Stata 15.0 (StataCorp, College Station, TX).

3. Result

3.1. Study characteristics

The initial search yielded 1514 articles, of which 153 articles were selected, and 61 articles met the inclusion criteria (Online Resource 1). These studies were reported across eleven Asian countries, mainly from East Asia (51 studies, 145,849 patients), Middle East (7 studies, 27,271 patients) and South Asia (3 studies, 473 patients). Fourty-four (72%) studies were conducted in high-income countries, including Japan (n = 30), Taiwan (n = 9), South Korea (n = 2), Hong Kong and Israel (n = 1 each). One was a multicentre study expanding across 5 countries (Hong Kong, Japan, South Korea, Singapore and Taiwan). Fourteen studies were from upper-middle income countries (China, Iran and Turkey), with three from lower-middle countries (India and Pakistan). The reported age at diagnosis of the patient populations ranged from birth to 89 years, but most studies reported an adult ($\geq$ 18 years) population (46 studies, 172,499 patients; Online Resource 1). All the studies reported the patient's performance status (n = 25, 42%) measured it using the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al., 1982).

Fourty-three (70%) studies reported CV toxicity among patients who received antineoplastic treatment. Twelve of these studies studied more than one type of CV toxicities. The National Cancer Institute criteria were the most common criteria used to define CV toxicity. Heart failure (n = 17, 28%) was the most frequently reported toxicity followed by electrocardiogram (ECG) abnormalities (n = 11, 18%) and left ventricular dysfunction (n = 9, 15%). In terms of antineoplastic agents, thirty-two (52%) studies reported the effect of anthracycline-based chemotherapy. Nine (15%) studies reported both the combination effect of anthracycline- and non-anthracycline-based chemotherapy. Among studies that reported the effect of non-anthracycline-based chemotherapy, four studies included bevacizumab (7%), one each on 5-fluorouracil, arsenic trioxide, carboplatin, cyclophosphamide-based, gemcitabine, histone deacetylase inhibitor (HBI-8000), nintedanib, paclitaxel, sunitinib and trastuzumab, (2%). The type of antineoplastic agents used was not specified in two studies.

3.2. Quality assessment

Twenty-nine studies were judged to have low risk of bias, three studies had moderate risk of bias and nineteen had serious risk of bias when assessed using the ROBINS-I assessment tool (Online Resource 1). These were mainly due to presence of confounding factor as well as poor reporting and measurement of outcomes. All nine randomized controlled trials were reported to have a low risk of bias (Online Resource 1).

3.3. Pooled incidence according to type of cardiotoxicity

Fifty-nine studies were included in the meta-analysis, as two studies did not report the number of CV cases (Luan et al., 2017; Tokuda et al., 2008). The overall estimated incidence of antineoplastic-related CV toxicity in Asia was 4.27% (95% CI: 3.53–5.07), but there was considerable heterogeneity (I^2 = 94%). Stratification by CV toxicity showed that the most common reported toxicity was hypertension, with a pooled incidence of 22.7% (95% CI, 8.83–40.44, I^2: 95%). Other reported toxicities include ECG abnormality (7.3%, 95% CI, 3.43–12.17,

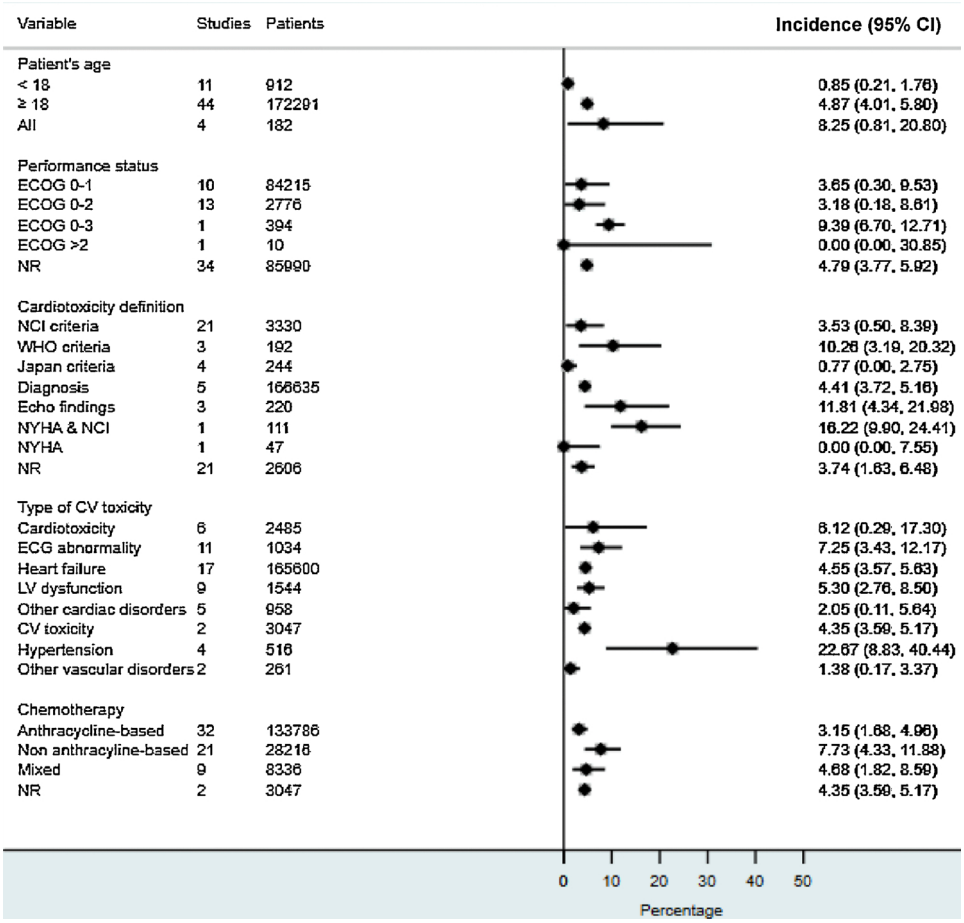

Fig. 1. Pooled estimated incidence of cardiovascular toxicity according to characteristics of participants.
CI, confidence interval; Echo, echocardiogram; ECOG, Eastern Cooperative Oncology Group; NCI, National Cancer Institute; NR: not reported; WHO, World Health Organisation.

I^2: 83%), heart failure (4.6%, 95% CI, 3.57–5.63, I^2: 97%) and left ventricular dysfunction (5.3, 95% CI, 2.76–8.50, I^2: 76%; Fig. 1). When stratified by antineoplastic agent, the highest incidence was observed in patients receiving non-anthracycline based chemotherapy with an incidence of 7.73% (95% CI, 4.33–11.88, I^2: 96%). A relatively lower incidence was reported in patients receiving anthracycline-based chemotherapy, 3.2% (95% CI, 1.68–4.96, I^2: 80%).

3.4. Incidence according to country

We subsequently stratified the incidence of CV toxicities by country's income and found that the incidence was higher in upper-middle income countries, with a pooled incidence of 13.1% (95% CI: 5.45–23.37; Fig. 2). Incidence of CV toxicities was the highest in Pakistan (19.9%, 95% CI, 15.57–24.90) and lowest in India (0.77%, 95% CI, 0.00–3.30). Two countries also reported incidence rate that exceeded 10%: China which had an 18.2% incidence 18.2% (95% CI, 3.50–40.21) and Iran with an incidence of 15.5% (95% CI, 7.35–27.42).

3.5. Incidence of cardiotoxicity by antineoplastic agent

We further stratified the reported incidence of CV toxicities by types of chemotherapy or targeted therapy used. In the thirty-one studies which studied the incidence of cardiac event with anthracycline use, presence of cardiac event was reported in twenty-one (68%) studies. Analysis by type of CV toxicities among this sub-population showed different distribution compare to the overall population (Fig. 3). Among anthracycline recipients, pooled incidence of ECG abnormalities was 9.2% (95% CI, 2.12–19.89). Other CV toxicities reported were cardiotoxicity (unspecified; 8.2%, 95% CI, 3.07–15.24), LV dysfunction (5.5%, 95% CI, 1.57–11.30), heart failure (3.2%, 95% CI, 2.21–4.30) and other cardiac disorders (e.g. dysfunction (Rajendranath et al., 2014) and acute cardiac complications (Hori et al., 2017); 0.7%, 95% CI, 0.05–1.79).

In the twenty-one studies which studied the incidence of cardiac event with non-anthracycline use, presence of cardiac event was reported in fifteen (65%) studies. Among these studies, heart failure had the highest number of cases reported (n = 970), which was mostly due to the use of tyrosine kinase inhibitors (n = 863) (Gronich et al., 2017) and bevacizumab (n = 59). In studies which had reported the incidence of hypertension with use of non-antracycline agents, these were related to the use of either bevacizumab (82%, n = 93) or nintedanib (18%, n = 20). Analysis of type of CV toxicities found that the incidence of hypertension had the highest (22.7%; 95% CI, 8.83–40.4) followed by cardiotoxicity (unspecified; 12.7%, 95% CI, 0.01–39.2), heart failure (9.7%, 95% CI, 2.42–20.7), other cardiac disorders (5.9%, 95% CI, 0.17–3.37) and other vascular disorders (1.38%, 95% CI, 0.17–3.37; Online Resource 1).

4. Discussion

To our best knowledge, this is the first and only systematic review which assessed the incidence and characteristics of CV toxicity in Asia. We found a total of sixty-one studies, reporting frequency of various types of CV toxicity related to various types of antineoplastic agent. Results from our meta-analysis suggest that nearly one in every twenty

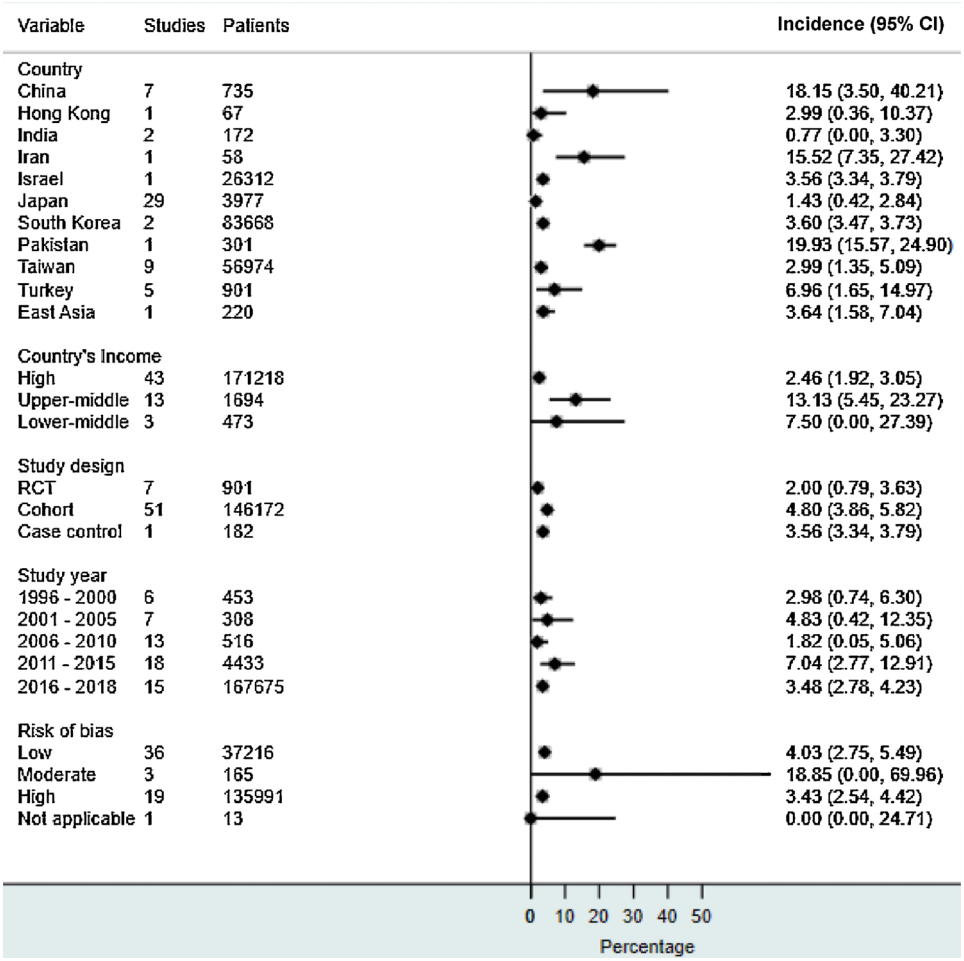

Fig. 2. Pooled estimated incidence of cardiovascular toxicity according to characteristics of included studies.
CI, confidence interval; NR: not reported; RCT, randomised controlled trial.

recipients of antineoplastic agents will develop CV related toxicity, with higher incidence in middle-income countries. Given that cancer affects nearly 13.2 million people in Asia, this translates to 620,000 recipients of antineoplastic agents who will develop some form of CV toxicity in their lifetime (Ferlay et al., 2015). Commonly reported CV toxicities were targeted therapies related hypertension and anthracycline-related ECG abnormalities and left ventricular dysfunction.

Over the past few years, there has been increasing reports of adverse events associated with antineoplastic use, which had led to a new branch of interest of onco-cardiology. As noted in our review, we found that the number of studies reported has increased from an average of one study per year during 1996 to 2000 to five studies per year over the past 2 years (Fig. 4). This increase is mainly fuelled by an in increasing in number of studies for newer targeted therapies such as bevacizumab (Totzeck et al., 2017) and trastuzumab (Guenancia et al., 2016). This increasing prevalence has potential ramification to the healthcare systems, as studies have shown that the economic burden of cardiotoxicities are very high, ranging from international dollar (Int$) 908 to Int $40 971 per patient (Shafie et al., 2018) for treatment of heart failure to USD 485.06 to USD 817.73 per 100 patients per month (Alefan et al., 2009). Indeed, as shown in our analyses, the incidence of CV toxicities was higher among middle income countries compared to high-income countries. This could be related to the large sample size and the availability of monitoring and preventive measures in these countries, since health care spending had been found to correlate with better health outcomes (Nixon and Ulmann, 2006; Bein et al., 2017).

Hypertension had the highest-incidence among all types of CV toxicity found in this study, which were related to nintedanib (Dai et al., 2015) and bevacizumab (Wang et al., 2015; Xu et al., 2012; Zhou et al., 2015). Although the underlying pathophysiological mechanism for antineoplastic related hypertension remains unknown, increase in vascular tone due to inhibition of VEGF-mediated vasodilation is the most accepted hypothesis for the mechanism of hypertension by these agents (Li and Kroetz, 2017). Given that tyrosine kinase inhibitors and VEGF-A inhibitors acts on this pathway, it is expected to cause some degree of increase in blood pressure. As such recipients of these agents should be considered at higher risk for CV toxicity if they have systolic blood pressure of more than 160 mmHg or diastolic blood pressure of more than 100 mmHg; diabetes mellitus, established CV disease (Curigliano et al., 2016) or genetic marker(s) (Leong et al., 2018). Strategies such as serial monitoring of blood pressure and aggressive management of blood pressure elevations are necessary to avoid cardiac dysfunction and early termination of cancer therapy. Besides, an improved collaboration between oncology and cardiology is needed to address the clinical gaps experienced by this at risk patient population (Virani et al., 2019).

Among all antineoplastic agents, ACT related CV toxicity is the most commonly reported and well defined, with incidences ranging from 0.9% to 26%, depending to type and cumulative dose of anthracycline (Yeh and Bickford, 2009). This is unsurprising since the drug has been in the use for several decades. Our study further confirms finding from other reviews which have reported risk factors for cardiotoxicity, including the use of doxorubicin at doses of 550 mg/m^2 (Swain et al., 2003). In addition, our study found that the use of synthetic anthracycline amrubicin (Murakami et al., 2014; Sawa et al., 2006; Shimokawa et al., 2009; Takeda et al., 2007) and pirarubicin (Hori

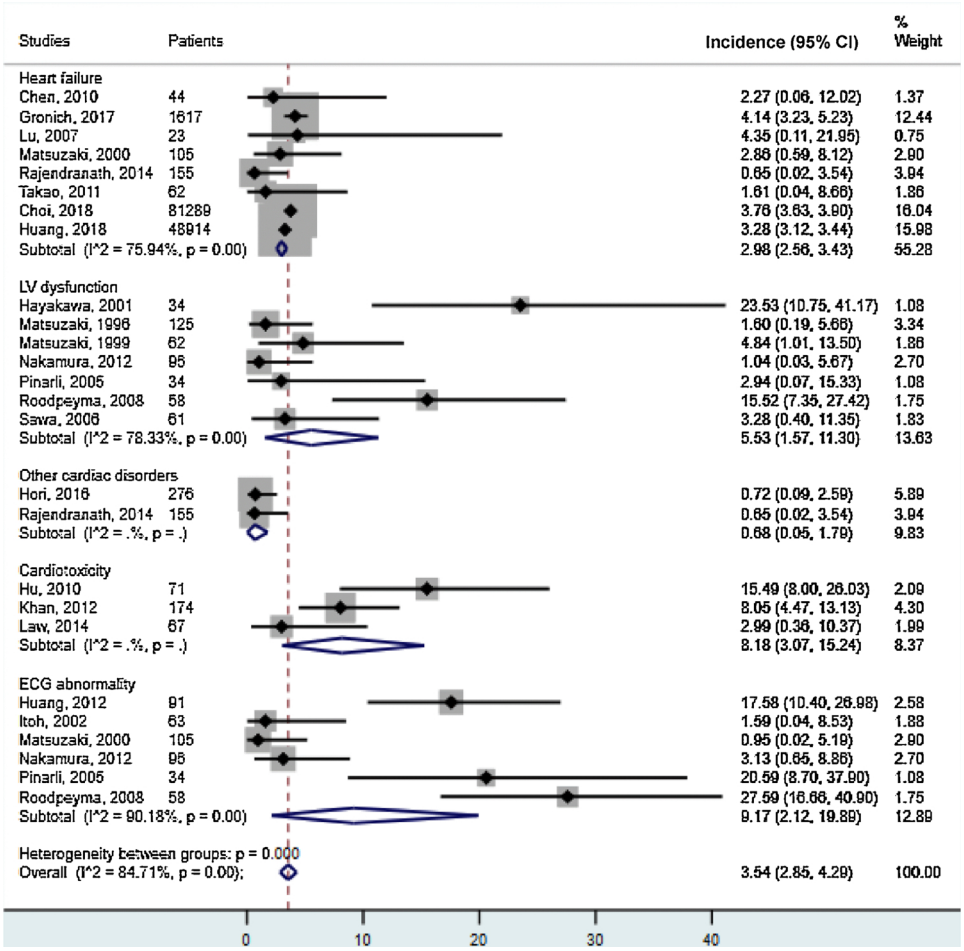

Fig. 3. Type of CV toxicities among anthracycline recipients.
CI, confidence interval; ECG, electrocardiogram; LV, left ventricular.

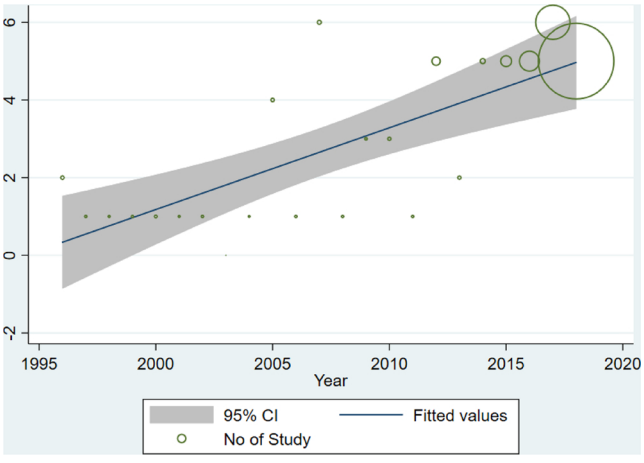

Fig. 4. Scatter plot of study distribution according to years weighted by number of participants.

et al., 2017) were relatively safe. Among the 367 patients received amrubicin or pirarubicin, only two (0.5%) patients reported to have decreased left ventricular ejection fraction of more than 15% from baseline. Other factors identified to be associated with ACT risk include extreme age, female gender, pre-existing cardiac disease, mediastinal radiation, concurrent treatment with cyclophosphamide, paclitaxel and trastuzumab as well as risk single nucleotide polymorphism (Leong et al., 2017).

Nevertheless, we urge caution while interpreting the results of this study given the varying definitions used by study. For example, the World Health Organisation (WHO) define hypertension as transient increase more than 20mmHg (Anon., 2003) while National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 define hypertension as transient (< 24 h) increase in diastolic by more than 20 mmHg or to more than 150/100 if previously within normal limit (National Cancer Institute, 2006). Thus, studies using WHO definition (Furuse et al., 1997; Huang et al., 2012; Wang et al., 1998) would not report hypertensive event when blood pressure from 120/80 mmHg to 145/90 mmHg. However, similar event would be reported as hypertensive event studies using NCI-CTCAE v3 (Atagi et al., 2005; Matsui et al., 2005). With the increase of baseline blood pressure for hypertension definition to 140/90 mmHg as recommended by Eighth Joint National Committee (JNC 8) (James et al., 2014), hypertensive events is expected to increase in studies using NCI-CTCAE after 2014 (Dai et al., 2015; Wang et al., 2015; Zhou et al., 2015).

There are several strengths of this systematic review and meta-analysis. Our study is the first o to quantify incidence estimates, derived using a comprehensive search strategy and included additional studies that are not found in academic sources. We also attempted to explore the sources of heterogeneity by conducting subgroup analyses. Results of our study suggest that further research is needed in this area to identify for the sources of these large variance.

Despite its strengths, some aspects in this study need to be considered when interpreting our findings. Due to the diversity of language in Asia, our search may have missed studies which were not published in English. Most of the studies had not adequately controlled for

baseline CV functions at the start of follow-up with missing crucial data on definitions and measurements, except for several characteristics such as gender and age. This information is important for further methodological analyses to identify for sources of heterogeneity and how different cardiac outcomes definitions, measurements and study period affect incidence estimates. As such, future studies might benefit from examining in different sub-populations such as elderly and children as this would provide a basis for developing effective strategies to prevent and respond to CV related toxicities due to antineoplastic use.

5. Conclusion

Cardiovascular toxicities due to antineoplastic use affects almost one in every twenty (approximately 620 thousand) people in Asia. These findings strengthen the case to expand for efforts to identify and prevent CV related toxicities due to antineoplastic use, and the need for early CV screening in this population. Considering the serious health consequences, more efforts are needed to raise awareness of, and provide guidance especially to both oncologists and cardiologist on the best way to respond to this and become familiar with this emerging subspecialty.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2019.05.017.

References

Alefan, Q., Ibrahim, M., Razak, T., Ayub, A., 2009. Cost of treating hypertension in Malaysia. Asian J. Pharm. Clin. Res. 2 (1).

Ang, B.H., Chen, W.S., Lee, S.W.H., 2017. Global burden of road traffic accidents in older adults: a systematic review and meta-regression analysis. Arch. Gerontol. Geriatr. 72, 32–38.

Anon, 2003. WHO Toxicity Grading Scale for Determining The Severity of Adverse Events. Accessed 23 December 2018, 2018. http://www.icssc.org/documents/resources/aemanual2003appendicesfebruary_06_2003%20final.pdf.

Atagi, S., Kawahara, M., Tamura, T., et al., 2005. Standard thoracic radiotherapy with or without concurrent daily low-dose carboplatin in elderly patients with locally advanced non-small cell lung cancer: a phase III trial of the Japan Clinical Oncology Group (JCOG9812). Jpn. J. Clin. Oncol. 35 (4), 195–201.

Bein, M.A., Unlucan, D., Olowu, G., Kalifa, W., 2017. Healthcare spending and health outcomes: evidence from selected East African countries. Afr. Health Sci. 17 (1), 247–254.

Chang, H.M., Moudgil, R., Scarabelli, T., Okwuosa, T.M., Yeh, E.T.H., 2017a. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 1. J. Am. Coll. Cardiol. 70 (20), 2536–2551.

Chang, H.M., Okwuosa, T.M., Scarabelli, T., Moudgil, R., Yeh, E.T.H., 2017b. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 2. J. Am. Coll. Cardiol. 70 (20), 2552–2565.

Conway, A., McCarthy, A.L., Lawrence, P., Clark, R.A., 2015. The prevention, detection and management of cancer treatment-induced cardiotoxicity: a meta-review. BMC Cancer 15, 366.

Curigliano, G., Cardinale, D., Dent, S., et al., 2016. Cardiotoxicity of anticancer treatments: epidemiology, detection, and management. CA Cancer J. Clin. 66 (4), 309–325.

Dai, W., Luo, B., Wu, Z., Chen, J., Feng, G., Guan, P., 2015. A multi-center phase II study of nintedanib as second-line therapy for patients with advanced non-small-cell lung cancer in China. Am. J. Cancer Res. 5 (10), 3270–3275.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7 (3), 177–188.

Ewer, M.S., Ewer, S.M., 2015. Cardiotoxicity of anticancer treatments. Nat. Rev. Cardiol. 12, 547.

Fan, W.L., Shiao, M.S., Hui, R.C., et al., 2017. HLA association with drug-induced adverse reactions. J. Immunol. Res. 2017 3186328.

Ferlay, J., Soerjomataram, I., Dikshit, R., et al., 2015. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer 136 (5), E359–386.

Freeman, M.F.T.J., 1950. Transformations related to the angular and the square root. Ann. Math. Stat. 21, 607–611.

Fulbright, J.M., 2011. Review of cardiotoxicity in pediatric cancer patients: during and after therapy. Cardiol. Res. Pract. 2011 942090.

Furuse, K., Naka, N., Takada, M., et al., 1997. Phase II study of 3-hour infusion of paclitaxel in patients with previously untreated stage III and IV non-small cell lung cancer. West Japan Lung Cancer Group. Oncology 54 (4), 298–303.

Global Burden of Disease Cancer C, 2017. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol. 3 (4), 524–548.

Gronich, N., Lavi, I., Barnett-Griness, O., Saliba, W., Abernethy, D.R., Rennert, G., 2017. Tyrosine kinase-targeting drugs-associated heart failure. Br. J. Cancer 116 (10), 1366–1373.

Guenancia, C., Lefebvre, A., Cardinale, D., et al., 2016. Obesity as a risk factor for anthracyclines and trastuzumab cardiotoxicity in breast cancer: a systematic review and meta-analysis. J. Clin. Oncol. 34 (26), 3157–3165.

Higgins, J.P., Altman, D.G., Gotzsche, P.C., et al., 2011. The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 343 d5928.

Hong, R.A., Iimura, T., Sumida, K.N., Eager, R.M., 2010. Cardio-oncology/onco-cardiology. Clin. Cardiol. 33 (12), 733–737.

Hori, H., Kudoh, T., Nishimura, S., et al., 2017. Acute and late toxicities of pirarubicin in the treatment of childhood acute lymphoblastic leukemia: results from a clinical trial by the Japan Association of Childhood Leukemia Study. Int. J. Clin. Oncol. 22 (2), 387–396.

Huang, B.T., Zeng, Q.C., Yu, J., Liu, X.L., Xiao, Z., Zhu, H.Q., 2012. High-dose homoharringtonine versus standard-dose daunorubicin is effective and safe as induction and post-induction chemotherapy for elderly patients with acute myeloid leukemia: a multicenter experience from China. Med. Oncol. 29 (1), 251–259.

James, P.A., Oparil, S., Carter, B.L., et al., 2014. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eighth joint national committee (jnc 8). JAMA 311 (5), 507–520.

Lee, S.W.H., Chan, E.M.C., Lai, Y.K., 2017. The global burden of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a systematic review and meta-analysis. Sci. Rep. 7 (1), 7984.

Leong, S.L., Chaiyakunapruk, N., Lee, S.W., 2017. Candidate gene association studies of anthracycline-induced cardiotoxicity: a systematic review and meta-analysis. Sci. Rep. 7 (1), 39.

Leong, S.L., Chaiyakunapruk, N., Tassaneeyakul, W., Arunmanakul, P., Nathisuwan, S., Lee, S.W.H., 2018. Roles of pharmacogenomics in non-anthracycline antineoplastic-induced cardiovascular toxicities: a systematic review and meta-analysis of genotypes effect. Int. J. Cardiol.

Li, M., Kroetz, D.L., 2017. Bevacizumab-induced hypertension: clinical presentation and molecular understanding. Pharmacol. Ther.

Luan, X.D., Zhao, K.H., Hou, H., et al., 2017. Changes in ischemia-modified albumin in myocardial toxicity induced by anthracycline and docetaxel chemotherapy. Medicine 96 (32), e7681.

Matsui, K., Hirashima, T., Nitta, T., et al., 2005. A phase I/II study comparing regimen schedules of gemcitabine and docetaxel in Japanese patients with stage IIIB/IV non-small cell lung cancer. Jpn. J. Clin. Oncol. 35 (4), 181–187.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann. Intern. Med. 151 (4), 264–269 w264.

Moja, L., Tagliabue, L., Balduzzi, S., et al., 2012. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst. Rev.(4) Cd006243.

Mulrooney, D.A., Yeazel, M.W., Kawashima, T., et al., 2009. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the childhood cancer survivor study cohort. BMJ 339.

Murakami, H., Yamamoto, N., Shibata, T., et al., 2014. A single-arm confirmatory study of amrubicin therapy in patients with refractory small-cell lung cancer: Japan Clinical Oncology Group Study (JCOG0901). Lung Cancer 84 (1), 67–72.

National Cancer Institute, 2006. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Accessed 23 December 2018, 2018. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.

Nixon, J., Ulmann, P., 2006. The relationship between health care expenditure and health outcomes. Evidence and caveats for a causal link. Eur. J. Health Econ.: HEPAC: Health Econ. Prev. Care 7 (1), 7–18.

Oken, M.M., Creech, R.H., Tormey, D.C., et al., 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am. J. Clin. Oncol. 5 (6), 649–655.

Onitilo, A.A., Engel, J.M., Stankowski, R.V., 2014. Cardiovascular toxicity associated with adjuvant trastuzumab therapy: prevalence, patient characteristics, and risk factors. Ther. Adv. Drug Saf. 5 (4), 154–166.

Physical Map of Asia, 2009. Physical Map of Asia. . Accessed 28 October 2017. http://www.physicalmapofasia.com/regions-of-asia/.

Rajendranath, R., Veeraiah, S., Ramesh, A., Sagar, T.G., 2014. Late effects of treatment in survivors of childhood cancer from a tertiary cancer center in South India. South Asian J. Cancer 3 (1), 60–65.

Sawa, T., Yana, T., Takada, M., et al., 2006. Multicenter phase II study of amrubicin, 9-amino-anthracycline, in patients with advanced non-small-cell lung cancer (Study 1): West Japan Thoracic Oncology Group (WJTOG) trial. Invest. New Drugs 24 (2), 151–158.

Shafie, A.A., Tan, Y.P., Ng, C.H., 2018. Systematic review of economic burden of heart failure. Heart Fail. Rev. 23 (1), 131–145.

Shimokawa, T., Shibuya, M., Kitamura, K., et al., 2009. Retrospective analysis of efficacy and safety of amrubicin in refractory and relapsed small-cell lung cancer. Int. J. Clin. Oncol. 14 (1), 63–69.

Smith, L.A., Cornelius, V.R., Plummer, C.J., et al., 2010. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of

randomised controlled trials. BMC Cancer 10, 337.
Sterne, J.A., Hernan, M.A., Reeves, B.C., et al., 2016. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355 i4919.
Swain, S.M., Whaley, F.S., Ewer, M.S., 2003. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 97 (11), 2869–2879.
Takeda, K., Takifuji, N., Negoro, S., et al., 2007. Phase II study of amrubicin, 9-amino-anthracycline, in patients with advanced non-small-cell lung cancer: a West Japan Thoracic Oncology Group (WJTOG) study. Invest. New Drugs 25 (4), 377–383.
Tokuda, Y., Tajima, T., Narabayashi, M., et al., 2008. Phase III study to evaluate the use of high-dose chemotherapy as consolidation of treatment for high-risk postoperative breast cancer: Japan Clinical Oncology Group study, JCOG 9208. Cancer Sci. 99 (1), 145–151.
Totzeck, M., Mincu, R.I., Rassaf, T., 2017. Cardiovascular adverse events in patients with cancer treated with bevacizumab: a meta-analysis of more than 20 000 patients. J. Am. Heart Assoc. 6 (8).
Udagawa, C., Nakamura, H., Ohnishi, H., et al., 2018. Whole exome sequencing to identify genetic markers for trastuzumab-induced cardiotoxicity. Cancer Sci. 109 (2), 446–452.
United Nations, 2017. World Economic Situation and Prospects 2017. Accessed 23 October 2017. http://www.refworld.org/docid/587f35e24.html.
Virani, S.A., Dent, S., Brezden-Masley, C., et al., 2019. Canadian cardiovascular society guidelines for evaluation and management of cardiovascular complications of cancer therapy. Can. J. Cardiol. 32 (7), 831–841.
Wang, W.S., Chen, P.M., Chiou, T.J., et al., 1998. Weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin in patients with advanced colorectal cancer: taiwan experience. Jpn. J. Clin. Oncol. 28 (1), 16–19.
Wang, G., Ye, Y., Zhang, X., Liu, H., Song, J., 2015. A single-arm clinical study of continuous usage of bevacizumab as second-line chemotherapy for Chinese patients with metastatic colorectal cancer. Med. Oncol. 32 (5), 163.
Xu, B.H., Jiang, Z.F., Shen, Z.Z., et al., 2012. Safety and efficacy of first-line bevacizumab combined with taxane therapy in Chinese patients with HER2-negative locally recurrent or metastatic breast cancer: findings from the ATHENA study. Chin. Med. J. 125 (5), 764–769.
Yeh, E.T., Bickford, C.L., 2009. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J. Am. Coll. Cardiol. 53 (24), 2231–2247.
Zhou, C., Wu, Y.L., Chen, G., et al., 2015. BEYOND: a randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer. J. Clin. Oncol. 33 (19), 2197–2204.