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Malignancies and outcome in Takotsubo syndrome: a meta-analysis study on cancer and stress cardiomyopathy

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Abstract

Takotsubo syndrome (TTS) can be induced by a large variety of physical/emotional triggers; several cases, however, are related to either an overt or occult malignancy, as shown in retrospective studies and case reports. The aim of this study was therefore to evaluate the clinical outcome of patients with TTS and cancer in a meta-analysis study. In June 2018, a Pubmed systematic research was conducted for studies assessing outcome in patients with TTS and cancer. We assessed Mantel-Haenszel pooled estimates of risk ratios (RRs) and 95% confidence intervals (CIs) for adverse events at follow-up. After paper retrieval, four studies were included in the meta-analysis, with a total of 123,563 patients. The prevalence of current or previous malignancy among patients admitted with TTS was 6.7% (8258 patients). When compared to control patients, patients with cancer showed an increased risk of clinical events (RR 3.24, 95% CI 3.04–3.45, $p < 0.01$). The risk of in-hospital events was significantly higher in the cancer group (RR 2.08 95% CI, 1.50–2.87, $p < 0.01$) and was mainly due to higher need for respiratory support (RR 1.67, 95% CI, 1.58–1.77, $p < 0.01$). The risk of adverse events at follow-up was also higher in the cancer group (RR 3.30, 95% CI 3.09–3.51, $p < 0.01$). Cancer, either history or active, is associated with an increased risk of adverse events in TTS.

Keywords Cancer · Takotsubo syndrome · Malignancy · Prognosis · Meta-analysis · Stress cardiomyopathy

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Introduction

Takotsubo syndrome (TTS) is a form of acute heart failure, characterized by reversible impairment in cardiac contractility, triggered by usually identifiable physical or emotional stressors. TTS affects mainly postmenopausal women. It has a prevalence of 2% among all patients admitted in emergency room for acute coronary syndrome and about 10% among postmenopausal woman. Four patterns of left ventricular dysfunction have been described in TTS [1]. However, the most typical is the apical ballooning type featured by akinesia/dyskinesia of the left ventricular apex and hyperkinesia of basal segments. Moreover, symptom and biomarker levels may resemble acute coronary syndrome; therefore, coronary angiography is mandatory.

Considerable progress was made regarding diagnosis, clinical characterization, and first-line therapy of TTS. However, the prognosis does not seem to be as benign as thought in the recent past, with a rate of death from any cause of 5.6% per patient-year, and even a significant percentage of in-hospital complications comparable with acute coronary syndrome [1].

One of the comorbidities commonly found in TTS is cancer, either in history or as active neoplasm. Cancer and TTS share several aspects: aged population, stress condition, and physical stressors such as pain or surgery. Chemotherapeutic agents, for instance 5-fluorouracil, may also precipitate TTS, but also rituximab, vascular endothelial growth factor antagonists, and vascular disrupting agents may be implicated in TTS [2].

On the other hand, the rate of incidence of TTS is 11% over a 6-year follow-up in 275 patients with cancer [3].

The link between TTS and cancer, however, is still far from being clearly defined and it is unclear if malignancies significantly influence the clinical course of TTS. The aim of our study was therefore to assess the impact of cancer on TTS patients' outcome in a meta-analysis including representative studies concerning this topic.

Methods

Search strategy and selection criteria

A systematic PubMed research was conducted for studies on malignancies and prognostic impact on TTS patients until June 2018 (see PRISMA statement, Table IS). Key words used for retrieval were "cancer" OR "neoplasm" OR "malignancy" OR "tumor" AND "takotsubo" AND "stress cardiomyopathy" AND "prognosis". References of the articles retrieved that way were also searched through to identify additional references that, not identified by the first search strategy, might be useful for the analysis. Two of the authors (N.T. and F.S.) performed the screening of titles and abstracts, reviewed full-text articles, and assessed their eligibility. The search was limited to the English-language publications. Since the study aimed at evaluating prognostic impact of cancer on Takotsubo, studies without control group were excluded from the analysis.

Study selection, data collection, and quality assessment

Two investigators (N.T. and F.S.) independently abstracted raw data sets related to baseline characteristics of studies, patient populations, and outcomes obtained from original eligible sources, and collected them by using a standardized, ad hoc prepared, data extraction form. In case of uncertainty, data were obtained by a direct contact with the corresponding authors. The two co-primary endpoints were in-hospital events (life-threatening arrhythmias, cardiogenic shock, thromboembolism, need for respiratory support) and events at follow-up (all-cause mortality, re-hospitalization for cardiovascular disease).

Subjects with active cancer or history of cancer were compared with controls without cancer or history of cancer. Furthermore, different rates of neoplasms and time to the diagnosis of cancer are also given when available.

Statistical analysis

Categorical variables, when available, were reported as percentages and continuous variables as means and standard deviation or medians and interquartile range, as appropriate. From abstracted data, we calculated the risk ratio (RR) of patients with cancer versus non-cancer group using the Mantel-Haenszel method for each study outcome to allow for pooling of similar outcomes. We obtained the average effects for the outcomes and 95% confidence interval (CI) using a random-effects model. Heterogeneity of the effect across studies was assessed by means of the Cochrane Q χ^2 and I^2 statistics. Lack of homogeneity was considered for Cochrane Q χ^2 test $P \leq 0.10$ and/or for an I^2 statistic $\geq 50\%$. When heterogeneity was judged significant, the pooled RR was calculated through the analysis of the variance between studies with the "method of moments" or the DerSimonian and Laird method for random effects. We computed the z statistic for each clinical outcome and considered results statistically significant at a $p \leq 0.05$.

We assessed the likelihood of publication bias using funnel plots by displaying individual study RR with 95% CIs for the endpoints of interest and evaluated it by the Egger regression asymmetry test; $p \leq 0.10$ was considered as indicative of statistically significant publication bias. A meta-regression analysis was also performed in order to ascertain causes of possible bias publication.

Results

After study selection, four retrospective studies were included in the meta-analysis (Fig. 1), one with multicenter [4], two with single-center design [5, 6], and one nation-wide analysis [7] with an overall population of 123,563 patients hospitalized for TTS between 2003 and 2015 (Table 1). Of these, 8258 patients reported a history of active or previous cancer (6.7%). Eighty-eight percent of subjects of the final cohort were female.

Physical stressors, when reported, were present in 58% of patients with cancer compared to 44% of controls ($p = 0.0058$) and apical ballooning in 81% vs 72% of patients ($p = 0.0434$). Gastrointestinal cancer (including esophagus, glands, and biliary ducts) was the most frequent form (23%), followed by breast and lung (both 17%), and by hematologic and skin tumors (10% for each) (Fig. 1S).

After paper retrieval, four studies were included in the meta-analysis, with a total of 123,563 patients. The prevalence of current or previous malignancy among patients admitted with TTS was 6.7% (8258 patients). When compared to control patients, patients with cancer showed an increased risk of clinical events (RR 3.24, 95% CI 3.04–3.45, $p < 0.01$) (Fig. 2). Both risk of in-hospital (RR 2.08 95%, CI 1.50–2.87, $p < 0.01$) and follow-up risk of adverse events were significantly higher in the cancer group (RR 3.30, 95% CI 3.09–3.51, $p < 0.01$).

An additional in-hospital event analysis with available data, however, showed no difference in terms of in-hospital incidence of cardiogenic shock, life-threatening arrhythmias, and length of hospital stay comparing patients with TTS and cancer vs controls (p n.s. in all cases) (Fig. 3). In-hospital rates of need for respiratory support were higher in the cancer group (RR 1.67, 95% CI, 1.58–1.77, $p < 0.01$).

A publication bias with a worse outcome in larger studies was observed at funnel plot analysis and confirmed at Egger's test ($p < 0.05$) (Fig. 4). Non-significant trends of bias were found at meta-regression analysis for number of patients enrolled in the studies included in the meta-analysis and rates of prevalence of cancer or history of cancer in the different populations (Fig. 2S).

Discussion

To the best of our knowledge, this is the first meta-analysis assessing the impact of cancer on TTS and showing a poor outcome in patients with cancer. Since the first published case reports and cohort studies [8,9], TTS was even hypothesized as a paraneoplastic syndrome. A link between cancer and TTS, however, seems likely. In the largest published registry on TTS, cancer can be found in 16.6% of 1750 patients with TTS, approximately equivalent to chronic obstructive pulmonary disease (16.2%) and coronary artery disease (15.3%), but

Fig. 1 Study selection flow chart

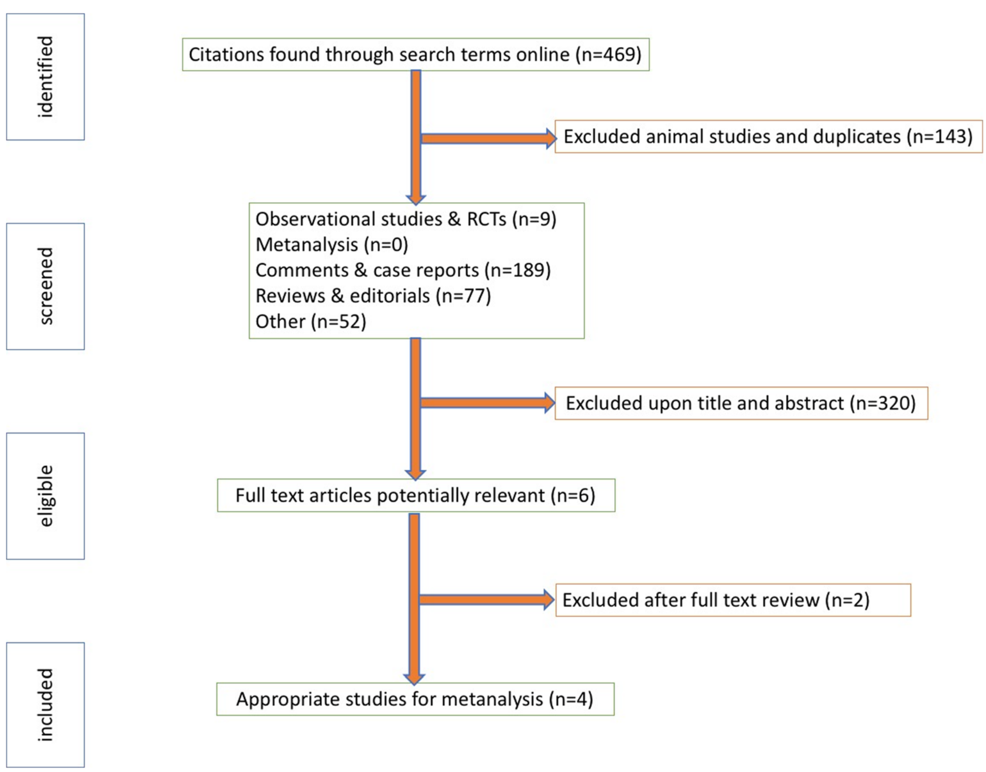


Table 1 Clinical characteristics of the included studies

Authors	Year	Total population	Age (mean)	Female (%)	Cancer pts, *n* (%)	Controls pts, *n* (%)
Girardey	2016	154	67 ± 11	77%	44 (28.5%)	110 (71.5%)
Möller	2017	286	72 ± 10	89%	56 (20%)	230 (80%)
Sattler	2017	114	67 ± 12	77%	25 (14%)	89 (86%)
Joy	2018	122,855	72 ± 7	88%	8089 (6.6%)	114,766 (93.6%)

much less than neurologic and psychiatric disorders (46.8%) [1]. In a systematic review with 1109 TTS patients, malignancies were found in 10% (range 4–29%) [10]. Similarly, Sattler et al. found a cancer prevalence at TTS admission in 14% of patients (21.9% during follow-up) [5], while Möller and Girardey described a prevalence between 20 and 28.5% in their respective studies [4,6]. Prevalence rates in the present meta-analysis (6.7%) may be underestimated due to the different methodology of a NIS-analysis performed in one of the four studies. However, prevalence rate of cancer in other studies, about 20% [4,5,6,11], is substantially higher if compared to age-matched populations from Europe (7.8%) and USA (over 69-year-old population, cancer prevalence > 17.4%) (https://seer.cancer.gov/faststats/selections.php?series=age) [12]. El-Sayed et al. observed a 14.4% prevalence of malignancies in TTS after exploring 24,701 inpatients from the USA, which significantly exceeded the prevalence of an age-matched group of orthopedic (8.8%) and myocardial infarction patients (10.0%) [13].

Given therefore the large number of patients incurring cancer in the next future (https://www.cancer.gov/about-cancer/understanding/statistics) (http://www.aiom.it/fondazione-aiom/aiom-airtum-numeri-cancro-2017/1,3021,1) [14], it is plausible that a considerable number of patients with cancer may present clinical signs of TTS or that even TTS may be the first presentation of cancer as a paraneoplastic event.

The reasons for the high prevalence of malignancy in TTS remain unclear. Given the time gap between cancer diagnosis and the occurrence of TTS in many patients, it is somehow doubtful that the cancer diagnosis acutely triggered TTS. It is rather more conceivable that cancer and TTS share similar triggering mechanisms. Activation of the sympathetic nervous system with subsequent increased catecholamine levels may be a trigger for malignancies and TTS [15].

Also, the role of genetics in TTS needs to be better elucidated. Enhanced β-adrenergic signaling and higher sensitivity to catecholamine-induced toxicity have been identified in an experimental model of TTS [16]. However, a clear genetic association between TTS and particular loci has still not been found [17]. It is noteworthy to observe a higher percentage of male patients (25% vs 10% found by Templin et al.) and physical stressors in the cancer group in comparison to other studies [1,18]. Cancer, therefore, might represent a risk condition for TTS even in men [19].

Interestingly, patients with TTS and cancer had higher need of respiration support during hospitalization, may be due to the complexity of the comorbidities.

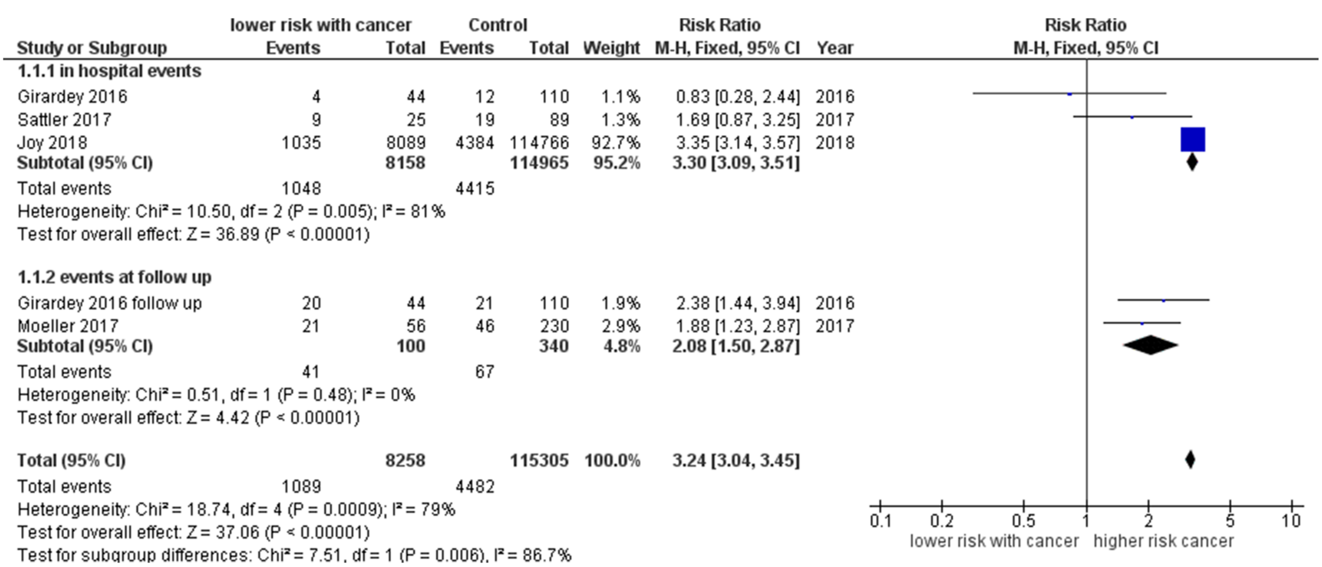


Figure 2 Forest plot comparing outcome in patients with Takotsubo syndrome and cancer vs controls (RR 3.24, 95% CI 3.04–3.45, $p < 0.01$)

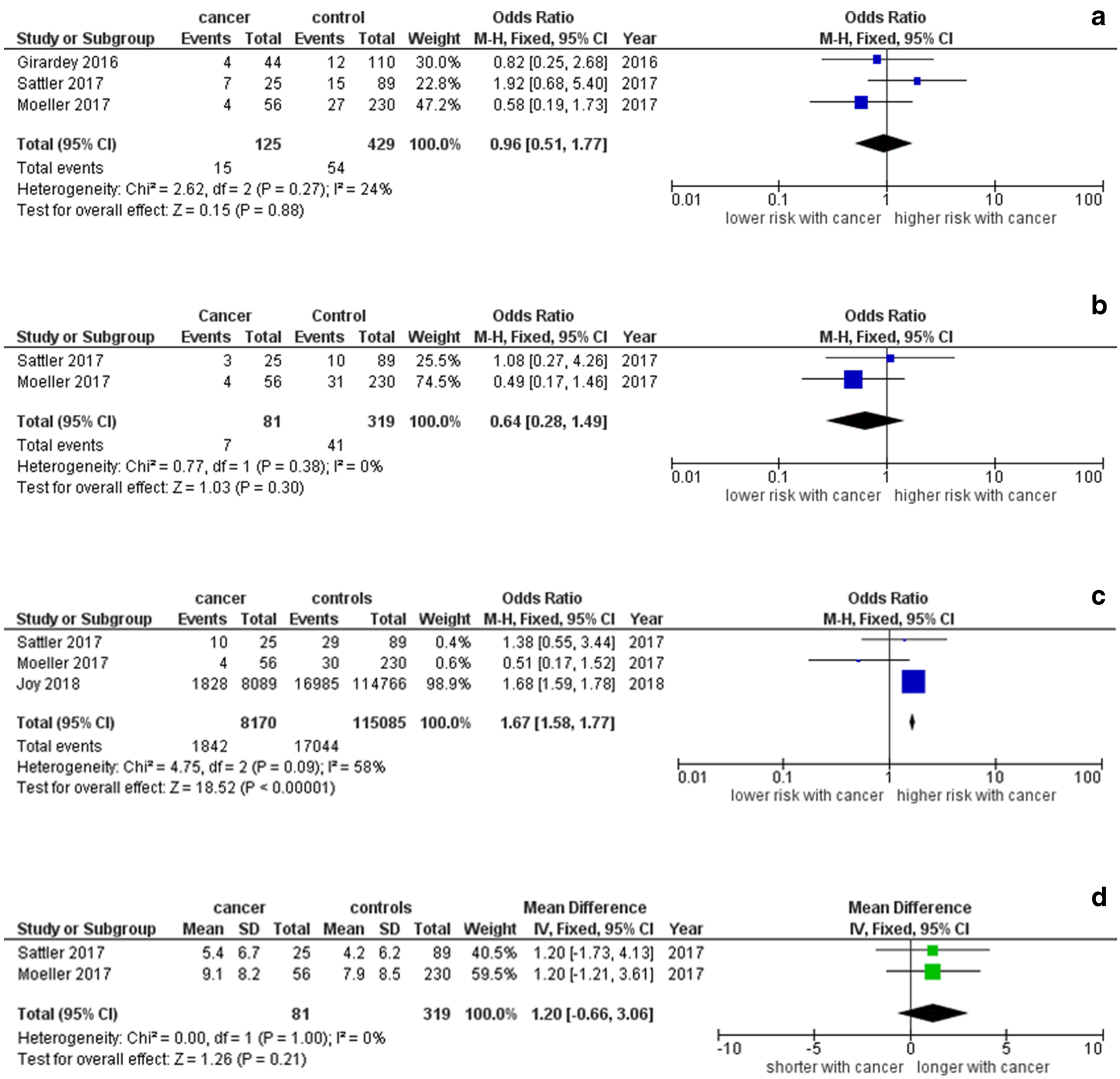
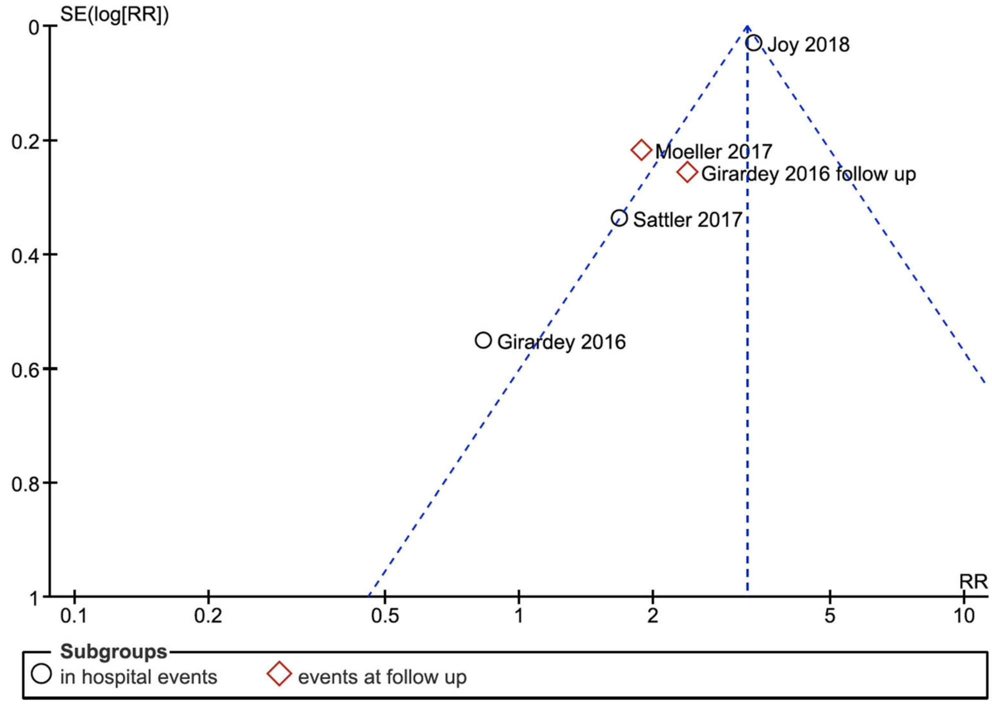


Fig. 3 Forest plots comparing in-hospital incidence of cardiogenic shock (**a**), life-threatening arrhythmias (**b**), in-hospital rates of need for respiratory support (**c**), and length of in-hospital stay (**d**) in patients with Takotsubo syndrome and cancer vs controls (p n.s. in all cases except for **c**, $p < 0.01$)

Stress from surgery and diagnostic procedures, chronic and acute cancer-related pain may increase the susceptibility to sympathetic surge [11,20–23] whereas vomiting, fever, anemia, or bleeding, very frequent in oncologic patients, may induce dehydration or alter the hemorheology, leading to cardiac hyperkinesia and with afterload increase [24, 25]. Circulating cytokines from chronic inflammation or superimposed infections can exert cardio-depressive effects [26, 27]; free radicals from chronic psycho-physical stressor generated by radiotherapy can damage myocardium [28–32] and also common metabolic disturbances in oncologic setting (e.g., hypophosphatemia, low T3 syndrome) may alter systolic function at a substantial extent [33–36]. Some chemotherapy drugs are actually recognized as precipitating factors of TTS [37]; capecitabine, 5-fluorouracil, combrestatin are able to induce coronary vasospasm and were related to some cases of TTS [38–40], as well as bevacizumab, may be because of its thrombogenic action [19, 41]. Rituximab and IL-2 can cause a dysregulation in cytokine interplay, leading, respectively, to modification of cardiac extracellular matrix and increased nitric oxide production, and, consequently, reduced cardiac contractility [42–44]. Additionally, some of these agents can influence the brain-heart axis through collateral polyneuropathy [45–47].

Fig. 4 Funnel plot showing possible publication bias among the included studies



Significant emotional disorders affect near half of cancer patients [48, 49], possibly modulating the impact of further external stressors.

Clinical implications

Subjects with history or presence of active cancer represent a special subset of TTS patients. Due to higher prevalence of in-hospital complications, they may require a longer stay in intensive care unit. Additionally, a strict routine cardiological follow-up may be required.

Limitations

Principal limitations of this study are represented by the observational nature of the studies included in the meta-analysis and by publication bias: small studies report better in-hospital outcome when compared to larger studies.

Most clinical, therapeutic, lab, and echocardiographic variables were not available for the analysis in each study, and furthermore, no details can be retrieved regarding the most frequent type of cancer.

Detailed in-hospital outcome and long-term follow-up data are not provided in larger studies, not allowing reliable analysis.

Conclusions

Either history of or current cancer are associated with an increased risk of adverse events in TTS patients. Therefore, a careful follow-up may be recommended after an episode of TTS in subjects with cancer.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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