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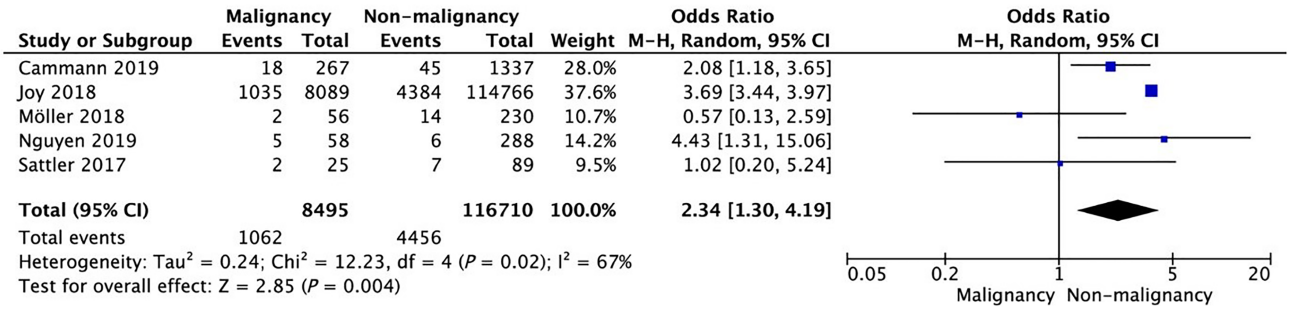
Malignancy predicts short-term mortality in Takotsubo: insights from a meta-analysis of 125 359 patients

Takotsubo syndrome (TTS) is an acute and usually reversible ventricular contractility disorder with unclear pathophysiology. While TTS is commonly triggered by a sudden physical or emotional event, at least 30% of TTS case reports are unrelated to preceding trigger factors. Recent registry data suggest a relationship between malignancy and TTS.[1] We conducted a systematic review with meta-analysis to further explore the link between cancer and TTS.

This meta-analysis was conducted according to guidance from the Cochrane Handbook of Systematic Reviews and is reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[2] and MOOSE (Meta-Analysis of Observational Studies in Epidemiology) recommendations.[3] Two independent reviewers systematically searched databases until October 10, 2020. Studies were excluded if (i) they were review articles, case reports, letters to the editor, and conference papers; (ii) the estimates were presented without standard errors or other information that allowed calculation of standard errors; and (iii) they included $<$20 patients. For statistical analysis, patients were divided into two groups: malignancy and non-malignancy. The main primary outcome was in-hospital or 28-day mortality. The detailed study methodology and patient characteristics are included in the Supporting Information, *Figures S1, S2, S3, S4*; *Tables S1*, *S2*.

Finally, three retrospective and three prospective studies with a total of 125 359 patients were included, from which malignancy was reported in 8539 (6.8%) patients (*Figure 1A*). Emotional stress was a less common factor to induce TTS in patients with malignancy (18%) compared with controls (29%, OR 0.59, 95% CI 0.43–0.83, P = 0.002), whereas physical stressors more often provoked TTS in patients with malignancy (51% vs. 37%) (OR 1.74, 95% CI 1.28–2.37, P = 0.0004). Amongst symptoms, dyspnoea was present in 53.5% of patients with malignancy compared with 44.6% of controls (OR 1.46, 95% CI 1.14–1.87, P = 0.003) and chest pain in 61% of patients with malignancy compared to 73% of controls (OR 0.63, 95% CI 0.48–0.82, $P < 0.001$). There was a lower prevalence of diabetes in TTS patients with malignancy (19% vs. 21%, OR 0.9, 95% CI 0.85–0.95, $P < 0.001$). Current tobacco use had no impact on the incidence of TTS in either group. The most important differences between both groups were related to in-hospital outcomes assessed in five included studies of 125 205 patients (*Figure 1B*). TTS patients with malignancy had a higher in-hospital or 28-day risk of death (OR 2.34, 95% CI 1.3–4.19, Z = 2.85, P = 0.004) than controls. Higher demand for mechanical respiratory support was observed in TTS patients with malignancy (22.6% vs. 14.8%, OR 1.67, 95% CI 1.58–1.76, $P < 0.001$) (Supporting Information, *Table S3*).

Figure 1 Forest plot of in-hospital or 28 day mortality in malignancy and not malignancy group. The centre of each square represents the weighted odds ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.



To the best of our knowledge, we present the largest analysis evaluating the impact of malignancy on mortality in TTS. Recent meta-analyses examining the malignancies and outcomes in TTS reported a 2.08-fold to 2.23-fold increase in mortality rate.[4,5] Our study confirmed these findings documenting malignancy as a powerful predictor of in-hospital death in TTS. In line with previous studies, we found no impact on the occurrence of cardiogenic shock and a higher need for respiratory support in TTS patients with malignancy.[4–6] Although no significant differences in life-threatening arrhythmias or length of in-hospital stay were previously reported, there was an increased risk of in-hospital and follow-up events (i.e. mortality and hospital readmission for cardiovascular disease). However, this observation included only a total of 440 patients at follow-up with its unknown duration. On the contrary, our in-depth analysis included a greater representation of patients with cardiopulmonary resuscitation, cardiogenic shock, respiratory support, life-threatening arrhythmias, ECG results, drugs use at admission, and associated risk factors (i.e. smoking, hypertension, hyperlipidaemia, and overweight).

In conclusion, the co-existence of malignancy substantially deteriorated the short-term prognosis of TTS patients. We acknowledge that the lack of information regarding the type, stage, or treatment of cancer is a limitation of our meta-analysis, which might have influenced the outcomes. Nevertheless, our meta-analysis draws attention to the potential mutual relationship between TTS and malignancy. Both entities may at least partly share the same pathophysiological background, including elevated concentrations of pro-inflammatory cytokines and catecholamines.[7] Further studies to assess the hypothetical association between malignancy and TTS are required to determine whether TTS might be seen as a paraneoplastic phenomenon in patients with malignancy and whether the risk of malignancy is higher in patients after a TTS episode. Altogether, it is important to raise the oncological vigilance of the clinicians to the potential co-existence of both entities.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. The PRISMA flow diagrams demonstrates the pathway leading to final article selection in our systematic review.
Figure S2. Forest plot of female gender in malignancy and not malignancy group. The center of each square represents the weighted odds ratio for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.
Figure S3. Forest plot of patients age in malignancy and not malignancy group. The center of each square represents the weighted mean difference for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.
Figure S4. Forest plot of left ventricle ejection fraction at admission in malignancy and not malignancy group. The center of each square represents the weighted mean difference for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.
Table S1. Characteristics of included studies.
Table S2. Patient characteristics at admission in the included studies.
Table S3. Characteristics of in-hospital events.

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References

1. Cammann VL, Sarcon A, Ding KJ, Seifert B, Kato K, Di Vece D, Szawan KA, Gili S, Jurisic S, Bacchi B, Micek J, Frangieh AH, Napp LC, Jaguszewski M, Bossone E, Citro R, D'Ascenzo F, Franke J, Noutsias M, Knorr M, Heiner S, Burgdorf C, Koenig W, Thiele H, Tschöpe C, Rajan L, Michels G, Pfister R, Cuneo A, Jacobshagen C, Karakas M, Banning A, Cuculi F, Kobza R, Fischer TA, Vasankari T, Airaksinen KEJ, Dworakowski R, Kaiser C, Osswald S, Galiuto L, Dichtl W, Delmas C, Lairez O, Horowitz JD, Kozel M, Widimský P, Tousek P, Winchester DE, Gilyarova E, Shilova A, Gilyarov M, El-Battrawy I, Akin I, Ukena C, Bauersachs J, Pieske BM, Hasenfuß G, Rottbauer W, Braun-Dullaeus RC, Opolski G, MacCarthy P, Felix SB, Borggrefe M, Di Mario C, Crea F, Katus HA, Schunkert H, Münzel T, Böhm M, Bax JJ, Prasad A, Shinbane J, Lüscher TF, Ruschitzka F, Ghadri JR, Templin C, Clinical features and outcomes of patients with malignancy and Takotsubo syndrome: observations from the international Takotsubo registry. *J Am Heart Assoc* 2019; **8**: e010881.
2. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.
3. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008–2012.
4. Guo S, Xie B, Tse G, Roever L, Xia Y, Li G, Wang Y, Liu T. Malignancy predicts outcomeof Takotsubo syndrome: a systematic review and meta-analysis. *Heart Fail Rev* 2020; **25**: 513–522.
5. Brunetti ND, Tarantino N, Guastafierro F, de Gennaro L, Correale M, Stiermaier T, Möller C, di Biase M, Eitel I, Santoro F. Malignancies and outcome in Takotsubo syndrome: a meta-analysis study on cancer and stress cardiomyopathy. *Heart Fail Rev* 2019; **24**: 481–488.
6. Möller C, Stiermaier T, Graf T, Eitel C, Thiele H, Burgdorf C, Eitel I. Prevalence and long-term prognostic impact of malignancy in patients with Takotsubo syndrome. *Eur J Heart Fail* 2018; **20**: 816–818.
7. Burgdorf C, Kurowski V, Bonnemeier H, Schunkert H, Radke PW. Long-term prognosis of the transient left ventricular dysfunction syndrome (Takotsubo cardiomyopathy): focus on malignancies. *Eur J Heart Fail* 2008; **10**: 1015–1019.