Editorial

Title

Does coronary microvascular dysfunction have a role in cardiovascular oncology?

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Cardiovascular disease (CVD) and cancer are the two leading causes of death worldwide[1]. Substantial evidence showed cancer patients were at increased risk of developing fatal and nonfatal cardiovascular events [2-4]. The overall risk for CVD in cancer patients is 2-6 times higher than the general population[4]. The mechanisms of increased CVD risk in cancer patients may include cancer-associated proinflammatory and hypercoagulability, as well as cancer therapy induced cardiotoxicity with complex mechanisms related to the type of drugs and treatment [2, 5]. Traditional cardio-oncology has focused on cardiovascular risk in patients with cancer treatment. Growing evidence shows the patients with CVD are at increased risk of developing cancer than the general population, suggesting a possible bidirectional link between CVD and cancer, the phenomenon referred to "reverse cardio-oncology"[6-8]. Given that both diseases share common risk factors (i.e., aging, hypertension, diabetes) and pathophysiological pathways (i.e., inflammation, hypoxia), there is gaining interest in exploring the complex relationships between CVD and cancer, for management and prevention of these two diseases [9-11].

Coronary microvascular dysfunction (CMD), a subset of disorders affecting the structure and/or function of the coronary microcirculation, is emerging entity in the evaluation of patients with suspected ischemic myocardial syndromes in the absence of obstructive coronary artery disease (CAD)[12]. CMD is characterised by impaired microvascular vasodilation in response to inadequate increase in blood flow to match myocardia oxygen resulting reduced coronary flow reserve (CFR) [12]. CFR is a gold standard to assess CMD in patients without significant obstructive CAD [13], which can be measured invasively as an adjunct to coronary angiography or noninvasively, such as using positron emission tomography (PET) [14]. Compelling evidence show CMD is associated with increased risk of major adverse cardiac events (MACE) including myocardial infarction, stroke, sudden death in an array of CVD including ischemia heart disease, heart failure and type 2 diabetes[12, 15]. Besides its role in evaluating cardiovascular risk in patients with CVD, emerging evidence showed microvascular dysfunction is associated with future risk of cancer and increased cardiovascular risk in cancer patients[16-18].

In this issue of the *EJPC*, Rajai and colleagues [19] explored the role of CMD in relation to cancer in a cohort of patients with angina and non-obstructive coronary artery disease (NOCAD) using invasively measuredly CFR. Specifically, they assessed 1) association between CMD and the future risk of developing solid tumour; 2) association between CMD and MACE in NOCAD patients with a history of cancer. A total of 1042 patients with NOCAD attended the Mayo Clinic between 2000-2019 for the assessment of chest pain were included in the analysis. The presence of CMD was defined as invasive CFR ≤2.5 based on their previous studies. The outcomes of interest were the incident cancer and MACE. At baseline, patients with CMD had worse CV risk profiles than non-CMD patients. Patients with CMD were older, being female, more likely to have diabetes, hyperlipidaemia, cancer history, poor renal function. During a median of 9 years follow-up, in NOCAD patients who were free of cancer at study entry (n=917), a total of 141 patients (15.5%) were found to have a cancer diagnosis. After adjusting for common CVD risk factors including age, sex, BMI, smoking, diabetes, hypertension, and renal function, the presence of CMD was associated with increased risk of cancer (hazard ratio [HR] 1.45, 95% CI1.02-2.09, P=0.04) (Figure 1). When examining outcome of MACE, CMD was associated with greater risk of MACE in patients with cancer history (odds ratios [OR] 2.50, 95% CI 1.003-6.20, P=0.04) (Figure 2) than those without (OR 1.4, 95% CI 1.01-1.90, P=0.04) after adjustment of common vascular risk factors.

These findings provide new evidence that presence of CMD may have a prognostic role to evaluate the future risk of cancer in patients with NOCAD. The observed relation between CMD and incident cancer is less likely explained by reverse causality because authors used landmark time of 1, 3 and 5 years and showed patients with CMD were significantly likely to develop cancer at all three time points. Results of the present study support the findings from the previous study by the same group of authors using the reactive hyperaemia peripheral arterial tonometry (RH-PAT) index to assess microvascular dysfunction in relation to cancer risk[18]. In this study, Toya et al showed the presence of microvascular dysfunction defined as RH-PAT index<=2.0, was associated with increased risk of incident solid-tumour in patients with chest pain and/or cardiovascular risk [18](HR 2.79, 95% CI 1.24-6.41 Figure 1). Together, these

findings may support the shared pathophysiologic pathways including chronic inflammation, excess oxidative, hypoxia for both CVD and cancer [20, 21]. Impaired microcirculation may contribute to the creation of a pro-oncogenic environment by potentially activating angiogenetic pathway and promote tumour growth [18]. Inflammatory markers including C-reactive protein (CRP), interleukin (IL)-6 are associated with CAD and in malignant process like metastasis, angiogenesis, immune evasion, and cancel cell invasion [11, 22]. Indeed, in patients with stable CVD, chronic systemic low-grade inflammation, measured by CRP, is a risk factor for cancer, in particularly lung cancer [10]. The results from Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) further support this concept by showing lowering CPR with interleukin-1β antibody can improve cardiovascular outcome, reduce the cancer incidence and mortality[23].

Another important finding is that the presence of CMD in NOCAD patients with the history of cancer was associated with greater risk of MACE than those without cancer (OR 2.5 vs OR 1.4). These findings correspond to a previous study by Divakaran et al [16]that assessed the impact of impaired microcirculation on cardiovascular risk in cancer patients. In this study, the authors examined the association between CMD measured by myocardial flow reserve (MFR) using PET and adverse cardiovascular events in a cohort of 87 breast cancer patients with no clinically overt CAD[16]. After adjusting common vascular risk factors, family history of CAD and chronic kidney disease, those in lowest MFR tertile (<1.7) had higher incidence of MACE during a median follow up of 7 years compared with patients in the highest MFR tertile (>2.24) (HR 4.91, 95% CI 1.68-14.38, p=0.04, Figure 2). These results demonstrated a consistent risk of MACE associated with CMD across different diagnostic modalities in cancer patients and is independent of known vascular risk factors.

The exact mechanisms that contribute to impaired CFR and increased risk of MACE in cancer patients remain unclear and are likely multifactorial. Cancer-associated proinflammatory and hypercoagulability can increase the risk of thromboembolic events including stroke[2]. It may also result from the interplay

between cancer therapy induced microcirculation injury including radiation or chemotherapy such as doxorubicin and chronic inflammation that led to myocardial ischemia, resulting increased cardiovascular risk in cancer patients[17, 24]. This is supported by a recent study that showed increased mean cardiac radiation dose was strongly correlated to the decreased global MFR using PET in a cohort of cancer patients following radiotherapy [17]. However, the lack of details of cancer treatment regime in this study limits further interpretation.

The main strength of this study is CMD was confirmed by gold-standard invasive measurement, which provides enhanced accuracy of diagnosis compared to non-invasive diagnostic modalities to understand microvascular function and its relation to cancer risk. The other strengths include long follow-up and taking into account of reverse causality by performing landmark analysis. However, when interpreting these results, the main consideration is that this is a retrospective analysis in a single centre, in which their original study design has not been powered to the cancer outcomes. The small sample size may have an impact on statistical power to detect true effects. Because cancer is a general term that refers to large groups of heterogeneous diseases, validation of this relationship in future studies with detailed cancer phenotyping are required. Although this analysis adjusted the common risk factors shared by both CVD and cancer, other important interactions between CVD and cancer such as inflammatory markers, cancer therapy, cardioprotective medication were not included, which require a more careful design before the conclusion can be drawn.

Taken together, the findings of this study advance our current understanding of complex relationship between CVD and cancer. The results provide new evidence that the presence of CMD defined by invasively measured CRF may have a role to evaluate cancer occurrence in patients with NOCAD, supporting the need for further studies to better understand the cancer risk in patients with CVD. Among patients with a history of cancer, assessment of CMD could potentially have a role in early detection of

cancer treatment related cardiovascular complications, which help to identify at high-risk group to guide diagnosis and preventive therapies.

Figure legend

Figure 1 Association between CMD and incident cancer by comparing current study by Rajai et al 2022 with the previous study by Toya et al 2021; Figure 2 Association between CMD and major adverse cardiac events (MACE) by comparing current study by Rajai et al 2022 with the previous study by Divakaran et al 2021. In Rajai et al 2022, Coronary microvascular dysfunction (CMD) was defined as invasive coronary flow reserve (CFR)<=2.5. In Toya et al 2020, microvascular dysfunction was defined by reactive hyperaemia peripheral arterial tonometry (RH-PAT) index<=2.0. In Divakaran et al 2021, CMD was measured by myocardial flow reserve (MFR) using PET.

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Figure 1 Association between CMD and incident cancer

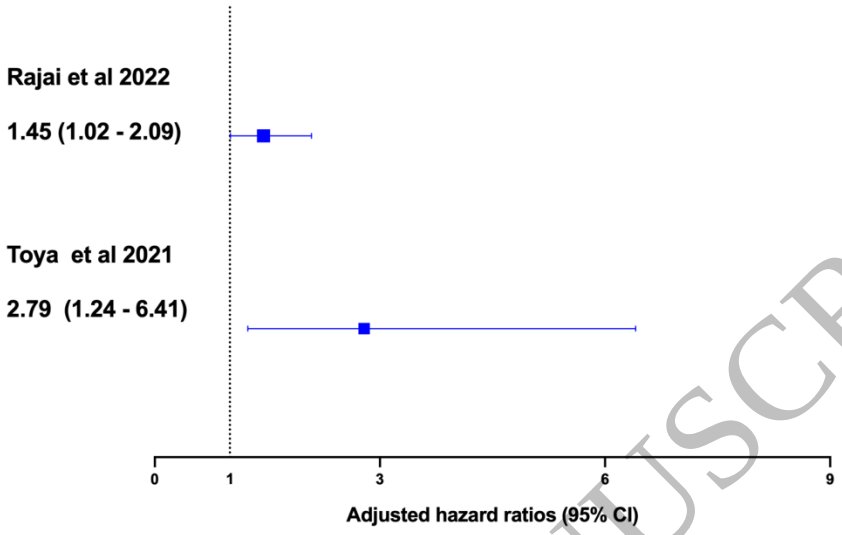
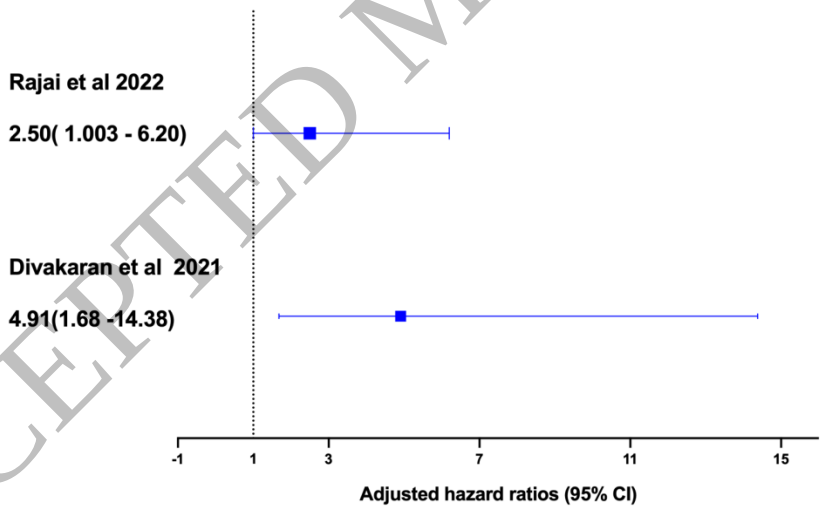


Figure 2 Association between CMD and MACE in cancer patients



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