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Original Article

Circulating tumor DNA to predict the risk of venous thromboembolism in locally advanced rectal cancer

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ABSTRACT

Background: Venous thromboembolism (VTE) is a common complication in cancer patients and negatively affects prognosis. Colorectal cancer (CRC) has the second highest incidence of VTE among the four most common cancers. In locally advanced rectal cancer (LARC), circulating tumor DNA (ctDNA) has emerged as a biomarker of residual disease and tumor burden, but its association with thrombotic risk remains unclear. We aimed to explore the association between baseline ctDNA levels and VTE occurrence in LARC.

Methods: We conducted a prospective study of patients with LARC treated with chemoradiation at IEO. Plasma ctDNA was analyzed by droplet digital PCR for tumor-specific mutations identified in tissue samples, including KRAS, NRAS, BRAF, and PIK3CA. Baseline ctDNA, defined as variant allele frequency (VAF), was correlated with VTE occurrence using univariable and exploratory adjusted analyses.

Results: Sixty-one patients underwent ctDNA assessment and were classified as VAF-low (n = 33) or VAF-high (n = 28) according to the median baseline value. Twenty-three patients (38%) were VAF-negative. After a median follow-up of 58 months, 9 VTE events (15%) were observed. Higher VTE cumulative incidence was observed in VAF-high versus VAF-low patients [HR 2.42, 95% CI 0.61–9.59; p = 0.21] and in ctDNA-positive versus ctDNA-negative patients [HR 5.70, 95% CI 0.70–46.1; p = 0.10]. In the KRAS-mutant subgroup, all VTE events occurred in patients with high baseline VAF (p = 0.001).

Conclusions: Higher baseline ctDNA levels may be associated with increased VTE occurrence in KRAS-mutant LARC. These exploratory findings require validation in larger prospective studies.

Introduction

Venous thromboembolism (VTE) is a common complication in cancer patients, which negatively affects treatment delivery and, consequently, prognosis [1]. The pathophysiology of cancer-associated thrombosis (CAT) is extremely complex, relying on cytokine release in response to interactions between tumor cells and macrophages, thus leading to endothelial damage and activation of coagulation [2]. The risk of VTE is influenced by several disease- and treatment-related factors, including cancer type, tumor stage, and exposure to anticancer therapies. Among treatment-related determinants, anti-angiogenic drugs, combined chemotherapy and radiotherapy (CT-RT), and more recently introduced immuno-oncology agents have been consistently associated with an increased thrombotic risk across different tumor types [3,4]. Colorectal cancer (CRC) is generally not classified among the highest-risk malignancies for VTE in commonly used risk-assessment models. even though around 5% of patients with localized CRC developed VTE during the first 6 months after diagnosis [5–7]. Consequently, Given the high incidence of CRC, even a moderate individual risk translates into a substantial clinical burden, contributing to morbidity, healthcare resource use, and mortality. Rectal cancer (RC) comprises approximately 30% of all CRC and the treatment for locally advanced

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disease (LARC) consists of a multimodal approach which includes chemotherapy, radiotherapy, and surgery [8].Within CRC, circulating tumor DNA (ctDNA) has emerged as an increasingly relevant biomarker able to detect minimal residual disease, useful for improving patients' stratification and prognosis [9]. In addition, the variant allele fraction (VAF) of tumor-specific alterations detected at baseline may reflect the amount of circulating tumor-derived material and, consequently, may serve as an indirect marker of tumor burden [10], potentially useful to improve the stratification of the risk of VTE. *KRAS* alterations are detected in around 40% of patients with CRC [11]. Their clinical relevance is well established, as they predict lack of benefit from anti-epidermal growth factor receptor (EGFR) therapy and are associated with poorer prognosis [12]. Beyond their oncogenic role, *KRAS* mutations seem to play a role in the development of a pro-thrombotic phenotype. Preclinical models showed that mutated or activated KRAS could act as mediator of cancer-associated thrombosis increasing the expression of tissue factor [13]. However, most available evidence derives from analyses performed on tumor tissue, which may not adequately capture temporal changes in tumor biology and disease dynamics. On this basis, the present study aimed to investigate whether circulating levels of mutated VAF assessed through ctDNA are associated with the occurrence of VTE in patients with locally advanced rectal cancer.

Methods

Study procedures

We conducted a prospective observational study enrolling patients with LARC managed with neoadjuvant chemoradiation (capecitabine 1650 mg/m2 concomitant with 50,4 Gy pelvic long course radiotherapy), surgery, plus/minus adjuvant chemotherapy at European Institute of Oncology (IEO) between November 2014 and November 2019 [14]. Blood samples for ctDNA were obtained at pre-planned timepoints: baseline (T0), end of CT-RT (T1), after surgery (T2), end of adjuvant chemotherapy (T3). To determine ctDNA, 20 ml of peripheral blood samples were required. The process for ctDNA preparation should have been performed within 5 h from the blood draw. For plasma preparation, blood must be collected in a tube treated with an anti-coagulant, preferably EDTA (ethylenediaminetetraacetic acid). Supernatant, or plasma were removed by centrifugation. Circulating tumor DNA was extracted from 2 ml of plasma using QIAamp Circulating Nucleic Acid- QIAGEN following the manifacturer's instructions. Mutations detected on tumor biopsy (*KRAS* in exons 2, 3 and 4; *NRAS* in exons 2, 3 and 4; *BRAF* in exons 11 and 15; *PIK3CA* in exons 9 and 20) were evaluated on circulating-free DNA. The analysis was performed with the Droplet Digital PCR (QX200 Biorad), using the appropriate ddPCR Mutation Detection Assays (Biorad). The ctDNA value was defined as variant allele frequency (VAF) in a targeted mutation. Median baseline ctDNA VAF was set as threshold to subdivide patients in high (above median value) and low (below median level). Analogously, negative and positive baseline value of ctDNA were used to subdived patients into negative (VAF undetectable) and positive (VAF > 0).

VTE and survival analysis

In this ancillary study, information regarding VTE events (both symptomatic and incidental) including pulmonary embolism (PE) (segmental, subsegmental multiple and isolated), VVT (visceral vein thrombosis) and DVT (deep vein thrombosis) were captured. Catheter-related VTE were counted as DVT. Visceral vein thrombosis, defined as thrombosis of the splenic, hepatic, portal, mesenteric, renal, or ovarian veins, were included as potentially related to the disease. Venous thromboembolism was considered attributable to cancer if occurred after RC diagnosis or if it was detected within 30 days before the date of RC diagnosis. Continuous data were reported as median and ranges or interquartile ranges. Categorical data were reported as counts and percentages. The cumulative incidence function (CIF) of VTE was estimated according to methods described by Kalbfleisch and Prentice, considering death as competing event [15]. Univariable Fine and Gray regression models were used to assess the association between VAF at baseline and the development of VTE. Poisson exact models were performed to evaluate the association between VAF at baseline and VTE events in the KRAS/mutant subgroup, as no VTE events were observed in the low VAF level. A p-value <0.05 was considered statistically significant. All analyses were performed with the statistical software SAS 9.4 (SAS Institute, Cary, NC, USA). The study was approved by the IEO Ethical committee on December 14th, 2014 (IEO-196) and complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Results

We enrolled 111 patients and tumor molecular characteristics were available for 104 patients (94%). From the whole cohort, 61 patients (59%) which harbored at least one mutation on tumor tissue underwent liquid biopsy detection and were, consequently, included in the VTE risk analysis. Patients' characteristics are reported in Table 1. Baseline Khorana Score (KS) was 0 in 54 patients (89%) and 1 in seven (11%). Fifty-one patients (84%) had a clinical node positive disease at diagnosis, and 84% where tumor located in the medium or distal rectum. According to mutational status, *KRAS* was the most frequent mutation (72%), followed by *NRAS* (13%) *PIK3CA* (10%) and *BRAF* mutation (2%). One patient (2%) had both KRAS and PIK3CA mutations, and another (2%) had both KRAS and BRAF. Median ctDNA value at baseline was 0.10 ng/2 ml (range: 0.00 - 17.40). According to median value, 33 patients were classified as VAF low (54%) and 28 as VAF high (46%), while 23 patients were classified as VAF negative at baseline (VAF $= 0$) representing 38% of the total.

Survival outcomes

In the whole cohort, OS rate at 5 years was 85% (CI 72 - 92) and PFS at was 79% (CI 65–87) (Fig. 1SA and 1SB). PFS were compared between patients with VAF low and high at baseline: 5-y PFS was 83% (CI 64–93) vs 73% (52–87), respectively ($p = 0.236$). (Fig. 1). We also performed KM curves stratified by mutation subgroup (KRAS-mutant vs. other mutations), with no significant differences in OS and PFS in the two groups: 5-y OS was 86% vs 85% [$p = 0.928$] and 5-y PFS was 78% vs 79% [$p = 0.406$], respectively (Fig. 2SA and 2SB).

VTE events and ctDNA levels

After a median follow-up of 58 months, we detected 9 VTE events (15%), with 4 PE, 3 DVT and 2 VVT. The median time from diagnosis to VTE was 14 months (IQR 6 – 51).

Overall, the cumulative incidence function (CIF) of VTE was 3% (95% CI: 1–10) at 6-months, increasing to 7% (95% CI: 2–15) at 12-months and to 10% (95% CI: 4–19) at 36-months. According to baseline VAF value, CIF was higher for VAF high vs VAF low [HR 2.42 (95% CI 0.61–9.59, $p = 0.21$)] as well for VAF positive compared to VAF negative patients [HR 5.70 (95% CI 0.70–46.1, $p = 0.10$)], in univariable analysis (Fig. 2).

However, specifically looking at the KRAS mutant cohort, a statistically significant difference in the risk of VTE was observed between the VAF groups, with 6 VTE events all experienced by VAF high patients (HR not estimable, p value $= 0.001$) (Table 2), with no major differences in baseline risk features compared with other-mutation subgroup (Table 1S). We also performed a series of exploratory adjusted analyses, evaluating the association between baseline ctDNA VAF and VTE while adjusting for one clinically relevant variable at a time (Table 3) which showed that association between VAF and VTE seems to remain

Table 1
Baseline patients' characteristics.

Variable	Level	Overall (N = 61)
Age at diagnosis, median (min-max)		61 (25–79)
Sex, N (%)	Male	40 (66)
	Female	21 (34)
Khorana score, N (%)	0	54 (89)
	1	7 (11)
Tumor site, N (%)	Proximal	10 (16)
	Medium	23 (38)
	Distal	28 (46)
cT, N (%)	1	1 (2)
	2	4 (7)
	3	56 (92)
cN, N (%)	0	8 (13)
	+	2 (3)
	1	24 (39)
	2	25 (41)
	X	2 (3)
cM, N (%)	0	61 (100)
Stage, N (%)	1	11 (18)
	2	50 (82)
Mutation on biopsy tissue, N (%)	Only KRAS	44 (72)
	Only NRAS	8 (13)
	Only PIK3CA	6 (10)
	Only BRAF	1 (2)
	KRAS+PIK3CA	1 (2)
	KRAS+BRAF	1 (2)
Microsatellite status, N (%)	MSS	52 (95)
	MSI	3 (5)
	Missing	6
Capecitabine plus RT as neoadjuvant, N (%)	No	0 (0)
	Yes	61 (100)
pT, N (%)	0	11 (18)
	is	2 (3)
	1	4 (7)
	2	16 (26)
	3	26 (43)
	4	2 (3)
pN, N (%)	0	50 (82)
	1	8 (13)
	2	3 (5)
pM, N (%)	0	61 (100)
Total of lymph nodes, median (min-max)		17 (1–50)
Missing		1
pCR, N (%)	No	49 (80)
	Yes	12 (20)
Downstaging, N (%)	No	12 (20)
	Yes	49 (80)
VAF at baseline, median (min-max) (Q1-Q3)		0.10 (0.00–17.40) (0.00–0.46)
VAF at baseline, N (%)	Low (≤0.10)	33 (54)
	High (>0.10)	28 (46)
VAF at baseline, N (%)	0	23 (38)
	>0	38 (62)

consistent, although estimates should be interpreted with caution due to the limited number of events.

Discussion

In our prospective study on patients with LARC, high baseline circulating levels of ctDNA, particularly among KRAS-mutant tumors, were associated with an increased occurrence of venous thromboembolism (VTE). While these findings support a potential relationship between ctDNA burden and thrombotic risk, they should be interpreted cautiously and considered primarily hypothesis-generating. Although colorectal cancer is not listed as a high-risk tumor for VTE by current validated risk assessment models, CRC represents one of the most frequent cancer types associated with thromboembolic complication. In our cohort, despite approximately 90% of patients being classified as Khorana Score (KS) 0, the cumulative incidence of VTE reached 10% at 3 years, further highlighting the limited discriminatory ability of currently

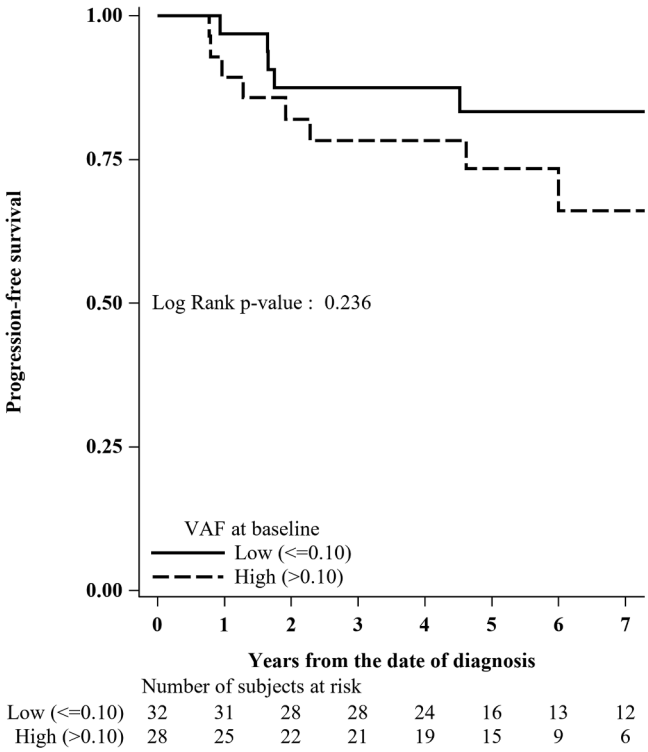

Fig. 1. Progression-free survival by VAD at baseline (N = 60).

available risk stratification tools in this setting. To improve risk stratification and patients' selection in CRC, tumor oncogene status including KRAS/NRAS/BRAF has been proposed as risk factor for VTE, with inconsistent results [16]. In our cohort, no differences in VTE risk have observed between molecular subgroups, previous retrospective reports which showed an increased risk of VTE in BRAF-mut CRC [17]. In this context, KRAS mutation has been proposed to carry a pro-thrombotic profile [13]. However, among KRAS-mutant patients, higher ctDNA VAF values were associated with increased VTE occurrence, whereas no thrombotic events were observed in the low-VAF subgroup. Importantly, these findings should not be interpreted as evidence of a direct mechanistic role of KRAS-mutant ctDNA in promoting thrombosis. Baseline ctDNA levels may instead represent a surrogate marker of tumor burden, biologically aggressive disease, occult micrometastatic dissemination, or other factors associated with systemic inflammation and hypercoagulability. In this regard, ctDNA positivity after neoadjuvant treatment has previously been associated with minimal residual disease and increased relapse risk in CRC [21]. Consistently, in our cohort, patients with high baseline VAF showed numerically lower progression-free survival compared with the low-VAF group, although this difference was not statistically significant. Moreover, only a minority of patients experienced both recurrence and VTE, and the temporal relationship between these events was heterogeneous, suggesting that disease progression alone may not fully explain the observed thrombotic risk.

Liquid biopsy is a non-invasive tool to evaluate treatment response, identify resistance alterations and capture tumor heterogeneity and minimal residual disease (MRD) in colorectal cancer (CRC) [18–20]. The detection of ctDNA after neoadjuvant treatment in LARC is correlated to an increased probability of tumor relapse and may represent a surrogate of the burden of disease, which may also affect VTE occurrence [21]. In our cohort, patients with ctDNA VAF values above the median had an approximately threefold higher risk of VTE compared with patients with lower VAF levels, although this association did not reach statistical significance in the overall population. Exploratory adjusted analyses accounting for clinically relevant baseline variables showed a generally consistent association between higher VAF and VTE risk; however, these

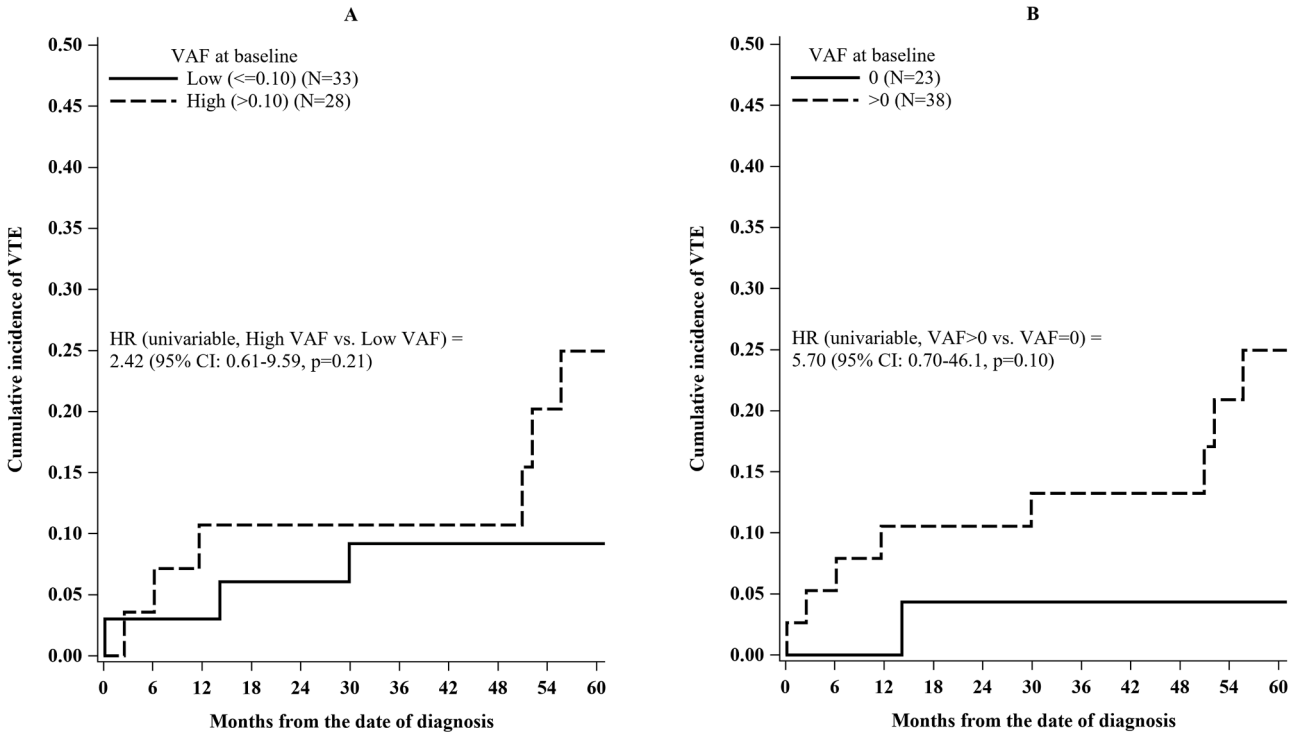

Fig. 2. Cumulative incidence of VTE by VAF at baseline: Low vs. High (Panel A) and 0 vs. > 0 (Panel B) (n = 61).

Table 2
Univariable Fine and Gray regression models for the association between ctDNA and VTE in all patients and in KRAS-mutant subgroup.

Variable	Level	N	VTE	Univariable analysis		
				HR	95% CI	p-value
ctDNA at baseline *(all patients)*	Low (≤0.10)	33	3	Ref.		
	High (>0.10)	28	6	2.42	0.61 - 9.59	0.21
	Negative (0)	23	1	Ref.		
	Positive (0)	38	8	5.70	0.70 - 46.1	0.10
ctDNA at baseline *(KRAS-mut)*	Low (≤0.10)	27	0	Ref.		
	High (>0.10)	19	6	NE	-	0.001
	Negative (0)	20	0	Ref		
	Positive (>0)	26	6	NE	-	0.014

Table 3
Univariable and adjusted Fine and Gray regression models of the association between baseline VAF and VTE (N = 61).

	VAF at baseline			
	HR (95% CI)		P-value	
Adjusted for	High vs. Low	Positive vs. Negative	HR (95% CI)	P-value
-	2.42 (0.61–9.59)	0.21	5.70 (0.70–46.1)	0.10
Age	2.65 (0.63–11.2)	0.18	6.85 (0.79–59.1)	0.080
Khorana score	2.73 (0.72–10.4)	0.14	5.73 (0.79–41.8)	0.085
Tumor site	3.42 (0.70–17.0)	0.13	7.65 (0.81–72.2)	0.076
Stage	2.54 (0.65–9.90)	0.18	5.70 (0.70–46.3)	0.10
Microsatellite status	2.05 (0.52–8.10)	0.30	4.99 (0.62–40.2)	0.13

analyses should be interpreted cautiously given the limited number of thrombotic events and the consequent statistical instability of the estimates. These new results need to be confirmed in larger multicentric prospective trials, but they are partially consistent with results derived from the larger Memorial Sloan Kettering Cancer Center dataset in which 4141 cancer patients have been analyzed with a ctDNA 129-gene NGS assay and with cell-free DNA (cfDNA) for the prediction of the risk of thrombosis. The ctDNA detection was associated with an increased risk of VTE in a dose-dependent way and the LB positive group outperformed the Khorana score in both the cross-validation and external lung cohort [22]. Interestingly, in that study, ctDNA positivity was not associated with VTE risk specifically among CRC patients. Differences in patient populations, disease stage, and ctDNA methodologies may partly explain these discrepancies. In particular, our use of droplet digital PCR (ddPCR) enabled highly sensitive detection of predefined tumor mutations but did not allow broader characterization of the genomic landscape, tumor mutational burden, or other potentially relevant biological features that could influence thrombotic risk.

Our study presents several key limitations. First, the use of ddPCR restricted ctDNA analyses to mutations previously identified in tumor tissue and limited the evaluation to a predefined molecular subset of patients, potentially reducing the generalizability of the findings. Contemporary broad-panel NGS approaches, whole-exome sequencing, or genome-wide assays may provide more comprehensive biological information and better characterize the relationship between tumor genomics and thrombosis; However, such analyses were not feasible in the present study, which was originally designed more than ten years ago, before comprehensive molecular profiling became routinely integrated into clinical trials. Consequently, these data are not available for this cohort, and retrospective analyses could have introduced significant methodological bias related to incomplete samples and non-standardized archival material. Secondly, the population of this analysis represented a selected subgroup of the original trial cohort, and the relatively small sample size together with the limited number of VTE events may have reduced statistical power and increased the risk of model overfitting Thirdly, ctDNA level was assessed only at baseline,

whereas serial sampling could potentially improve sensitivity and better reflect dynamic changes in tumor burden over time [23].Several studies demonstrated that specificity and sensitivity of LB significantly increase with more determinations at close timepoints, reducing false negative cases [23]. Finally, some patients were receiving anticoagulant therapy at baseline for concomitant medical conditions, which may have influenced VTE occurrence.

In conclusion, our study suggests a possible association between elevated baseline ctDNA levels and increased VTE risk in patients with KRAS-mutant LARC, providing a potential additional parameters for VTE risk prediction. However, these observations should be considered exploratory and do not establish a causal or mechanistic relationship between KRAS alterations and thrombosis. Rather, ctDNA burden may represent a composite marker reflecting tumor biology, disease burden, and systemic prothrombotic activation. Translational and interventional studies using deeper molecular techniques and wider populations are required to clarify the potential role of ctDNA as an adjunctive tool for VTE risk stratification in CRC and other malignancies.

CRediT authorship contribution statement

Lorenzo Gervaso: Writing – original draft, Formal analysis, Conceptualization. **Davide Ciardiello:** Writing – original draft, Data curation. **Samuele Frassoni:** Writing – review & editing, Methodology, Formal analysis. **Vincenzo Bagnardi:** Writing – review & editing, Methodology, Formal analysis. **Giuliana Gregato:** Writing – review & editing, Methodology. **Chiara Alessandra Cella:** Writing – review & editing. **Lavinia Benini:** Writing – review & editing. **Darina Tamayo:** Data curation. **Francesca Spada:** Writing – review & editing. **Francesco Bertolini:** Writing – review & editing, Validation, Methodology. **Nicola Fazio:** Writing – review & editing, Supervision. **Maria Giulia Zampino:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2026.101316.

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