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REVIEWS

Safety and efficacy of catheter ablation for atrial fibrillation in cancer survivors: a systematic review and meta-analysis

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Abstract

Background Cancer survivors are at increased risk for atrial fibrillation (AF). However, data on the efficacy and safety of catheter ablation (CA) in this population remain limited. Therefore, we aimed to perform a systematic review and meta-analysis comparing outcomes after CA for AF in patients with versus without prior or active cancer.

Methods We systematically searched PubMed, Cochrane Library, and Embase from inception to April 2023 for studies comparing the safety and efficacy of CA for AF in cancer survivors. Outcomes of interest were bleeding events, late AF recurrence, and need for repeat ablation. Statistical analyses were performed using Review Manager 5.4.1. We pooled odds ratios (OR) with 95% confidence intervals (CI) for binary endpoints.

Results We included 5 retrospective cohort studies comprising 998 patients, of whom 41.4% had a history of cancer. Cancer survivors were at significantly higher risk of clinically relevant bleeding (OR 2.17; 95% CI 1.17-4.0; p=0.01) as compared with those without cancer. The efficacy of CA for AF was similar between groups. Late AF recurrence at 12 months was not significantly different between patients with vs. without a history of cancer (OR 1.29; 95% CI 0.78–2.13; p=0.32). Similar findings were observed in the outcome of repeat ablations (OR 0.71; 95% CI 0.37-1.37; p=0.31).

Conclusions These findings suggest that cancer survivors have an increased risk of bleeding after CA for AF relative to patients without cancer, with no significant difference in the efficacy of CA for maintenance of sinus rhythm between groups.

Study registration This systematic review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42023394538.

Keywords Atrial fibrillation · Cancer · Catheter ablation · Cardio-oncology · Cryoablation · Radiofrequency ablation

Abbreviations

AAD	Antiarrhythmic drug
AF	Atrial fibrillation
CI	Confidence intervals
CRNMB	Clinically relevant non-major bleeding
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROSPERO	International Prospective Register of Systematic Reviews
QUIPS	Quality in Prognostic Studies
OR	Odds ratio

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1 Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting up to 2% of the general population, and its prevalence is expected to reach 12.1 million individuals in the USA by 2030 [1, 2]. Cancer survivors are at a higher risk for AF, since malignancy and AF share risk factors and underlying pathophysiology [3, 4]. In addition, neoadjuvant chemotherapy and radiotherapy are associated with an increased risk of incident AF, since individuals not

only live longer while exposed to risk factors but also are subjected to complications of cancer therapy–related cardiovascular dysfunction [5].

Long-term management of AF includes rhythm and rate control strategies. In this setting, catheter ablation may be superior to antiarrhythmic drugs (AADs) for patients with untreated AF, and ablation is recommended to those who remain symptomatic regardless of optimal drug management [6]. As such, catheter ablation for AF could be a reasonable option for rhythm control in cancer survivors. These patients often do not tolerate AADs due to a higher prevalence of bradycardia, QT interval prolongation, and interaction with cancer-targeted therapies [7].

However, cancer survivors are under-referred to catheter ablation because of theoretical concerns over its safety and long-term efficacy. Oncological patients may be at higher risks for AF recurrence and hemorrhagic events depending on past medical history, cancer subtype, and staging [5]. Herein, we aimed to perform a systematic review and meta-analysis comparing the outcomes of cancer survivors versus patients without a history of cancer after catheter ablation for AF, to elucidate the impact of a cancer diagnosis on the safety and efficacy of this procedure.

2 Material and methods

These systematic review, meta-analysis, and reporting were conducted in accordance with Cochrane Handbook for Systematic Reviews of Interventions recommendations and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8, 9]. Accordingly, it was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under protocol CRD42023416797.

2.1 Search strategy and data extraction

We systematically searched Pubmed, Embase, and Cochrane Library from inception to April 2023 with the following medical subject heading terms: "atrial fibrillation," "AF," "AFib," "ablation," "cryoballoon," "radiofrequency," "Pulmonary Vein Isolation," "PVI," "cancer," "tumor," "malignancy," "neoplasm." The exact search strategy is stated in the first section of the Supplemental Material.

We also performed a backward snowballing search for additional studies in the references of previous meta-analyses and included studies [10]. Three authors (T.A.C., N.F., and L.T.) independently extracted the available study characteristics, event rates, and/or adjusted odds ratios (OR) from full-text published articles and relevant scientific abstracts following prespecified search criteria and quality assessment.

2.2 Eligibility criteria

Two investigators (T.A.C. and M.C.) independently screened search records to identify eligible studies. We restricted inclusion in this meta-analysis to (1) clinical studies comparing patients with versus without a history of cancer (either active or in remission), (2) who underwent catheter ablation for AF, (3) reporting safety and/or efficacy endpoints of the procedure, and (4) with a follow-up of at least 30 days. We excluded studies without outcomes of cancers survivors reported separately and studies in patients with previous cardiac surgery (e.g., atrial myxoma excision). We did not apply language restrictions or filters for study screening and selection.

2.3 Endpoints

Our safety outcome was the risk of clinically relevant bleeding, defined as a composite of the prevalence of major bleeding and/or clinically relevant non-major bleeding (CRNMB) complications [11], as defined by the International Society on Thrombosis and Haemostasis guidelines [12, 13]. Per this definition, major bleeding is defined as either fatal bleeding or symptomatic bleeding occurring in a vital area or organ, i.e., intra-cranial, intra-spinal, intra-ocular, retroperitoneal, intra-articular, pericardial, or intra-muscular bleeding occurring with compartment syndrome or bleeding that resulted in a decrease in hemoglobin levels of 2 g/dL or greater or necessitated the transfusion of two or more units of blood [13]. CRNMB is defined as indication or manifestation of hemorrhage, such as bleeding that exceeds what would typically be anticipated in a given medical scenario that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: (1) necessitates medical intervention from a healthcare provider, (2) results in hospitalization or a need for a heightened level of care, or (3) triggers a face-to-face evaluation, as opposed to just a telephone or electronic communication consultation [12].

The efficacy outcomes were as follows: (1) late AF recurrence, defined as the recurrence of AF following a 90-day blanking period after index ablation and before 12 months [14] and (2) the need for repeated ablation within 12 months.

2.4 Risk of bias and sensitivity analysis

Two investigators (M.A.P.B., and M.C.) independently assessed the quality of included studies. Non-randomized studies were appraised with the QUIPS (Quality in Prognostic Studies) tool for prognostic studies, which allows labeling studies as of low, moderate, or high risk of bias in

six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting [15]. We also investigated potential small study effects using funnel-plot analysis of point estimates according to the graphical distribution of similar weight studies against their standard errors.

2.5 Statistical analysis

We pooled OR with 95% confidence intervals (CI) to compare treatment effects for binary endpoints, including adjusted OR from the individual studies whenever available. Cochran Q test and I^2 statistics were used to assess between-study heterogeneity; p-values < 0.10 and $I^2 \geq 25\%$ were considered significant for heterogeneity. We chose a DerSimonian and Laird random-effects model due to the anticipated heterogeneity among studies with respect to baseline characteristics, cancer subtypes and staging, and study design [16]. Review Manager 5.4.1 (Cochrane Centre, The Cochrane Collaboration, Denmark) was used for statistical analyses.

3 Results

3.1 Study selection and characteristics

As detailed in Fig. 1, our initial search retrieved 1122 studies after removing duplicates; 1059 studies were excluded after initial critical examination based on title and/or abstract. After a full-text review of the remaining publications, five retrospective studies were included, comprising 998 patients, of whom 413 (41.4%) were cancer survivors [11, 17–20]. Individual study characteristics are displayed in Table 1.

Most included studies encompassed patients with different subtypes and staging of cancer. Only Haq and colleagues restricted inclusion to patients with a history of breast cancer [20]. The proportion of cancer types were as follows: breast (n = 146, 35.3%), genitourinary (n = 89, 21.6%), hematologic (n = 35, 8.5%), gastrointestinal (n = 23, 5.6%), lung (n = 19, 4.6%), head or neck (n = 13, 3.1%), or other (n = 88, 21.3%). Of note, 60 patients (14.5%) had active cancer by the time of the ablation. Four studies reported the use of oral anticoagulation before the procedure, with direct oral anticoagulants (DOACs) being the most common, reported in 544 patients (59.3%) [11, 17–19]. Only one study acknowledged a significant difference between cancer survivors and controls in AADs use, with a higher use of amiodarone usage in the control group and comparable use of other AADs between groups [18]. Similarly, other studies reported no significant difference in AADs use between groups [17, 19, 20]. Patient characteristics in each individual study are displayed in Table 2.

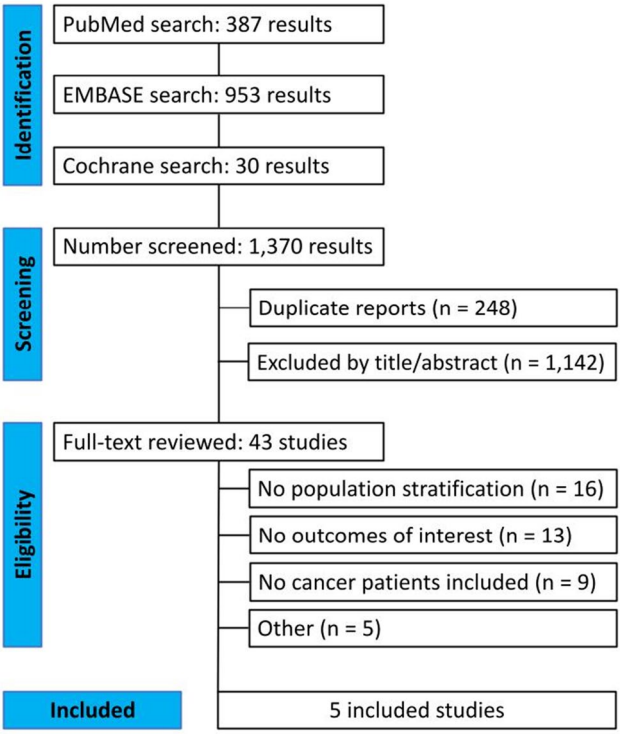

Figure 1. PRISMA flow diagram of study screening and selection

Fig. 1 Study screening and selection

3.2 Pooled analysis of all studies

Our main safety outcome of interest was clinically relevant bleeding, which was reported in all five studies [11, 17–20]. There was a significantly higher incidence (6.5% versus 3.9%) of hemorrhagic events in cancer survivors as compared with patients without a history of cancer (OR 2.17; 95% CI 1.17–4.00; $p = 0.01$; $I^2 = 0\%$; Fig. 2). Of note, one study had no bleeding events in neither study arms, resulting in a "not-estimable" outcome in Fig. 2 [17].

Among 998 patients included in this meta-analysis, 814 were followed for at least 12 months [17–20]. Late AF recurrence among these patients was not significantly different between groups after pooling the existing results from individual studies, including adjusted OR when available (OR 1.29; 95% CI 0.78–2.13; $p = 0.32$; $I^2 = 34\%$; Fig. 3). In addition, there was no significant difference between groups in the need for repeat ablation within 12 months (OR 0.71; 95% CI 0.37–1.37; $p = 0.31$; $I^2 = 42\%$; Fig. 4).

Periprocedural thromboembolic events were rare in the pooled population with a total of 5 events of stroke or transient ischemic attack in the cancer group and 1 event in the control group [11, 18]. Similarly, there were 5 events of cardiac tamponade or pericardial effusion requiring intervention, 3 in cancer survivors, and 2 in the control group [18]. There were no deaths reported in the included studies.

Table 1 Individual study characteristics

Study characteristics	GANATRA, 2023	HAQ, 2022	EITEL, 2021	WANG, 2021	GIUSTOZZI, 2019
Population of study	AF	AF	Symptomatic AF	AF	Non-valvular AF
Study design	Multi-center retrospective cohort	Single-center retrospective cohort	Single-center retrospective cohort	Single-center retrospective cohort	Single-center retrospective cohort
Country	USA	USA	Germany	China	Italy
Group of interest	AF with cancer history or exposure to anthracyclines/thoracic radiation	AF with history of breast cancer	AF with history of cancer	AF with history of cancer	AF with history of cancer
Comparison group	AF without cancer history	AF without cancer history	AF without cancer history	AF without cancer history	AF without cancer history
Number of patients (n)	502	82	140	90	184
Follow-up (months)	12	12	12	11	1
Ablation technique	RFA-PVI; CB-PVI	PVI*	CB-PVI	RFA-PVI	RFA-PVI
Clinical follow-up visit procedures	NA	Conducted after 3 and 12 months. All patients underwent 12-lead ECG and Holter monitoring before their clinical follow-up visits	Conducted after 3, 6, and 12 months. All patients underwent assessment of the clinical history, 12-lead ECG, and 24 h Holter ECG	Conducted with telephone and outpatient visits at 1, 3, 6, 9, and 12 months after the RFA procedure	Patients' outcomes follow-up started at time of AF ablation procedure and ended at 30 ± 5 days thereafter
Blanking period definition	3 months	NA	3 months	3 months	NA
Recurrent AF definition	Recurrent AF after post-ablation blanking period	Documented AF on 12-lead ECG and Holter monitoring or on any additional testing that may have been recorded post-ablation, irrespective of symptoms	Recurrent AF after single CB-PVI outside of the blanking period	Recurrent AF, lasting ≥30 seconds, after post-ablation blanking period	NA
Diagnostic modality for detecting recurrent AF	NA	12-lead ECG and/or Holter or any additional testing	12-lead ECG and 24 h Holter ECG	NA	NA
Bleeding event definition	Bleeding requiring investigation or intervention or transfusion (access and non-access site)	Clinically relevant bleeding as described in the ISTH criteria	Major bleeding or CRNMB as described in the ISTH criteria	NA	Major bleeding or CRNMB as described in the ISTH criteria

AF atrial fibrillation, *CB* cryoablation, *CRNMB* clinically relevant non-major bleeding, *ECG* electrocardiogram, *ISTH* International Society on Thrombosis and Haemostasis, *PVI* pulmonary vein isolation, *NA* not available, *RFA* radiofrequency ablation

*Does not specify which ablation modality was used

Table 2 Patient characteristics

Patient characteristics	GANATRA, 2023		HAQ, 2022		EITEL, 2021		WANG, 2021		GIUSTOZZI, 2019	
	Cancer (*n* = 251)	No cancer (*n* = 251)	Cancer (*n* = 41)	No cancer (*n* = 41)	Cancer (*n* = 70)	No cancer (*n* = 70)	Cancer (*n* = 30)	No cancer (*n* = 60)	Cancer (*n* = 21)	No cancer (*n* = 163)
Age, y (mean or median)	61	64	74.6	76.7	71.3	69.7	64.8	63.6	64.3	58.8
Female sex, n (%)	118 (47)	107 (42.6)	41 (100)	41 (100)	31 (44.3)	31 (44.3)	14 (46.7)	28 (46.7)	7 (33)	33 (20)
Paroxysmal AF, n (%)	136 (54.2)	141 (56.2)	25 (61)	24 (58)	22 (31.4)	23 (32.9)	21 (70)	42 (70)	13 (62)	109 (67)
Persistent AF, n (%)	105 (41.8)	103 (41)	16 (39)	17 (41)	48 (68.6)	47 (67.1)	9 (30)	18 (30)	8 (38)	54 (33)
CHA2DS2-VASC score	2 (1–4)	2 (1–3)	5.5 ± 2.0	5.9 ± 2.0	3 (2–4)	3 (2–4)	NA	NA	2.2 ± 1.5	1.4 ± 1.4
HASBLEED score	NA	NA	4.6 ± 1.6	4.3 ± 1.6	NA	NA	NA	NA	1.1 ± 1.0	0.6 ± 0.8
DOACs use, n (%)	141 (56.2)	146 (58.2)	NA	NA	56 (80)	55 (78.6)	14 (46.7)	25 (41.7)	15 (71)	92 (56)
VKA use, n (%)	105 (41.8)	69 (27.5)	NA	NA	14 (20)	15 (21.4)	16 (53.3)	35 (58.3)	NA	NA
Hypertension, n (%)	166 (66.1)	168 (66.9)	NA	NA	49 (70)	55 (78.6)	21 (70)	44 (73.3)	16 (76)	81 (50)
CAD, n (%)	41 (16.3)	36 (14.3)	NA	NA	12 (17.1)	10 (14.3)	6 (20)	13 (21.7)	NA	NA
Heart failure, n (%)	65 (25.9)	68 (27.1)	28 (68)	28 (68)	NA	NA	1 (3.3)	1 (1.7)	2 (9)	16 (10)
CKD, n (%)	NA	NA	20 (49)	17 (41)	22 (31.4)	17 (24.3)	NA	NA	0 (0)	6 (5)
Diabetes mellitus, n (%)	38 (15.1)	51 (20.3)	24 (58)	21 (51)	6 (8.6)	7 (10)	7 (23.3)	14 (23.3)	3 (14)	5 (3)
Active cancer, n (%)	46 (18.3)	-	0 (0)	-	8 (11.4)	-	2 (6.6)	-	4 (19)	-
Two most common cancer types (%)	Breast (20) and Prostate (13)	-	Breast (100)	-	GU (30) and Breast (28.6)	-	GI (30) and GU (26)	-	GI (36) and Breast (23)	-

Mean ± SD or Mean (IQR), AF atrial fibrillation, *CAD* coronary artery disease, *CKD* chronic kidney disease, *CKD* chronic kidney disease, *DOAC* direct oral anticoagulant, *GI* gastrointestinal, *GU* genitourinary, *IQR* interquartile range, *n* number of patients, *NA* not available, *SD* standard deviation, *VKA* vitamin K-antagonists

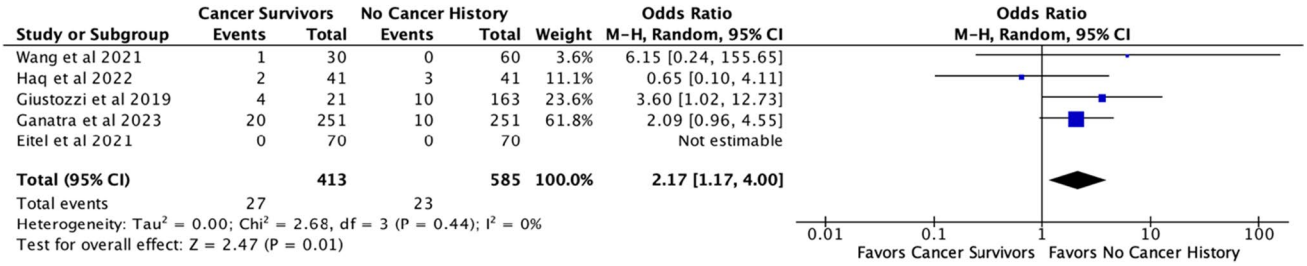

Fig. 2 Clinically relevant bleeding events were significantly increased in patients with a history of cancer ($p = 0.01$)

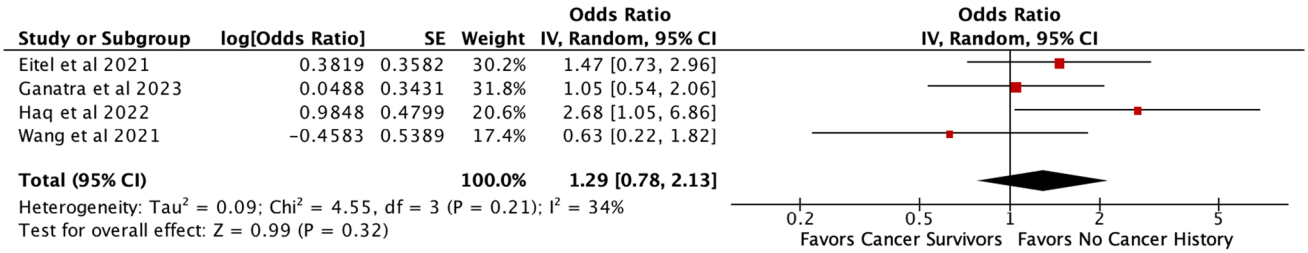

Fig. 3 Late atrial fibrillation recurrence was not significantly different between patients with versus without cancer ($p = 0.32$)

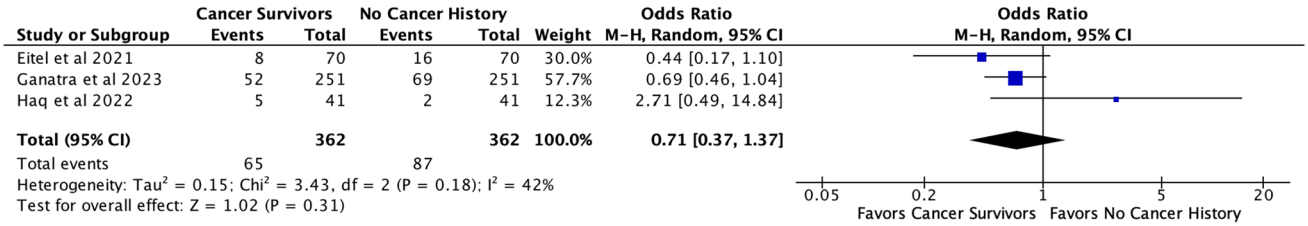

Fig. 4 The need for repeat ablations at 12 months was not significantly different between patients with versus without a history of cancer ($p = 0.31$)

3.3 Quality assessment

Four studies presented moderate concerns with regards to risk of bias due to confounding but were considered with overall low risk of bias [17–19]. Only one study was considered with overall moderate risk of bias [19]. Individual study appraisal of all domains is shown in Supplementary Figure 1. There was no evidence of small study effect (publication bias) in the funnel plot analyses, given that studies with similar weights were symmetrically distributed against their standard errors (Supplementary Figure 2).

4 Discussion

In this systematic review and meta-analysis of 5 observational studies, we compared the safety and efficacy of catheter ablation for AF in cancer survivors versus patients without a history of cancer. Our main findings were as follows: (1) cancer survivors were at a significantly higher risk of bleeding events compared with patients without a history of cancer, and (2) there were no significant differences between groups in late AF recurrence or need for repeat ablation.

Cancer survivors are at a higher risk for AF, especially the elderly and those with preexisting cardiovascular disease, metabolic disorders, and obstructive sleep apnea [21, 22]. Many mechanisms are implicated in this association. First, there are several shared risk factors, such as advanced age, smoking history, alcohol consumption, and comorbidities [21, 23]. Second, systemic inflammation as antineoplastic response may lead to increased inflammatory markers, such as C-reactive protein, which are related to AF burden [21, 23]. Third, it also might be related to autonomic nervous system imbalance, paraneoplastic syndromes, or direct mechanical invasion of tumors into cardiac structures [21, 23]. Finally, cancer-targeted therapies, surgical interventions, and radiation therapy are classically associated with

increased cardiovascular complications, including new-onset AF [21, 23–26].

A recent population-based study comprising 816,811 patients found that cancer may be an independent risk factor for incident AF after adjustment for shared risk factors such as age, smoking, and obesity [23]. A prior meta-analysis showed a 47% higher risk of incident AF after a cancer diagnosis [27]. Moreover, new-onset AF in cancer survivors is associated with a higher risk of thromboembolism/stroke, all-cause mortality, and major bleeding [28]. However, the increased risk of incident AF may vary depending on cancer type and staging, with multiple myeloma holding the highest associated risk of incident AF, for example [23].

Treating AF in cancer survivors may be especially challenging due to complex drug-drug interactions with cancer-targeted therapies and biological particularities of patients with cancer (e.g., heightened thromboembolic and bleeding risks) [21]. Current Cardio-Oncology Guidelines recommend using thrombotic and bleeding risk stratification tools such as CHA2DS2-VASc and HAS-BLED scores to guide anticoagulation strategies in this patient population [28]. Unfortunately, neither tool has been validated for cancer survivors or consider cancer as an independent variable [21, 28].

As for rate and rhythm control strategies, the recommendations for cancer survivors currently align with those for the general population [21, 28]. In patients with a history of cancer, a rhythm control strategy should be considered for persistently symptomatic patients and those unable to achieve rate control despite optimized medical therapy [29]. However, neither AADs nor ablation techniques have been largely studied as rhythm control strategies for cancer survivors [21, 28]. In case of proceeding with ablation, the increased bleeding risk should be considered. Current guidelines recommend continuing oral anticoagulation for 2 months following ablation, regardless of the patient's baseline thromboembolic risk [30, 31]. Moreover, catheter ablation for AF should not be performed in patients who cannot be anticoagulated during and after the procedure [30].

To the best of our knowledge, this is the first meta-analysis to focus on the safety and efficacy of catheter ablation for AF in cancer survivors as compared with patients without a history of cancer. The included studies encompassed both radiofrequency and cryoablation techniques in patients with a variety of cancer types. Overall, our results support this procedure as a feasible option for AF rhythm control among cancer survivors, as there were no significant differences in the measurements of efficacy outcomes between groups.

However, we found a significantly higher risk of clinically relevant bleeding in cancer survivors, leading to important safety considerations. Individually, only one study observed an increased bleeding risk in patients with cancer [11]. Of note, that study used bridging with low molecular weight heparin before and after ablation for patients on vitamin K antagonists; there was also an elevated prevalence of malignancies at high bleeding risk, such as gastrointestinal and genitourinary [11, 18]. In contrast, our pooled population included a more diverse group of cancer types, albeit with low heterogeneity between studies ($I^2 = 0\%$), which indicates that results of individual studies are consistent with each other.

Our results are consistent with a recently published population-based study comprising 50,623 weighted AF ablation procedures, which yielded higher bleeding rates in cancer survivors and no significant difference in AF-related readmissions as compared with controls [32]. Unfortunately, their study results could not be pooled with our analysis due to overlapping populations. Ultimately, cancer survivors may benefit from a multidisciplinary individualized assessment before and after the procedure, accounting for procedure-related and patient-related variables implicated in increased bleeding risk, including cancer type, pre-existing cardiovascular disease, and ongoing cancer-targeted therapies.

Our study has limitations. First, the prognostic nature of the clinical question, comparing patients with versus without a history of cancer, cannot be answered by randomized data; therefore, our findings are subject to the risk of confounding. However, most of the studies were at moderate risk of cofounding, due to the use of matched control groups, and we pooled multivariable adjusted OR when available in the individual studies. Second, the absence of individual-level patient data prevented us from conducting subgroup analyses stratifying outcomes by ablation modality, cancer type, cancer status (active versus in remission), antineoplastic therapy received, anticoagulation strategy, and the prevalence of cardiovascular risk factors. Therefore, our findings should be interpreted considering its heterogeneous population, and additional studies are needed to further explore more homogeneous and under-represented subgroups, especially patients with active cancer. Third, we were unable to statistically analyze other relevant safety outcomes, such as pericardial effusion requiring intervention and peri-procedural stroke, due to rarity of events, incomplete reporting, and the absence of individual-level patient data. Finally, our results extend to 1 year, but longer-term results of catheter ablation in this population remain unknown.

5 Conclusion

In this meta-analysis of studies comparing outcomes of catheter ablation for AF in patients with versus without a history of cancer, cancer survivors had comparable rates of late AF recurrence and need for repeat ablation at 12 months, albeit with an increase in the incidence of hemorrhagic events.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10840-023-01677-8.

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Author contribution TAC: conceptualization, study design, data collection, data analysis, data interpretation, writing (original draft), writing (review and editing); NF: conceptualization, study design, data collection, data analysis, data interpretation, writing (original draft), writing (review and editing); MC: data collection, data analysis, writing (original draft); LT: data collection, data analysis, writing (original draft); MAPB: data collection, data analysis, writing (original draft); LTMS: conceptualization, data interpretation, writing (original draft), writing (review and editing).

Data availability This meta-analysis was based on data extracted from previously published research; therefore, all the data and study materials are available in the public domain. The authors of this meta-analysis do not have access to patient-level data of the individual studies. Researchers interested in individual-level data from the studies included in this meta-analysis are encouraged to contact the corresponding author from each individual study for such requests.

Declarations

Ethics approval N/A

Consent to participate N/A

Competing interests The authors declare no competing interests. Author L.T.M.S. is currently an Editorial Training Fellow at the *Journal of Interventional Cardiac Electrophysiology*.

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