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REVIEW

Safety and efficacy of left atrial appendage closure in cancer *versus* non-cancer patients: a systematic review and meta-analysis

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Abstract

There is an ongoing debate regarding the safety and efficacy of left atrial appendage occlusion (LAAO) for atrial fibrillation in patients with cancer. We searched PubMed and Scopus from the database's inception until November 2024 and included studies comparing cancer patients with non-cancer patients undergoing left atrial appendage closure for atrial fibrillation. Our primary outcome was short-term mortality. Secondary outcomes were ischemic stroke, major bleeding, device complications, and pericardial complications. For the dichotomous outcomes, risk ratios (RR) were used, whereas generic inverse variance (GIV) was used to pool the RRs and corresponding 95% confidence interval (95% CI). A random effects model was used to evaluate all the outcomes. Our analysis showed a significantly higher rate of short-term mortality in patients with cancer as compared to non-cancer patients (RR =2.07; 95% CI [1.12 to 3.84]; p=0.02). From secondary outcomes, pericardial complications showed a significantly higher risk in cancer patients (RR: 2.17, 95% CI [1.51, 3.12]; p<0.0001). Meanwhile, other secondary outcomes were found to be insignificant. LAAO in cancer patients was significantly associated with higher short-term mortality and pericardial complications.

Key words: Left atrial appendage closure; cancer; atrial fibrillation; meta-analysis.

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia, affecting more than 33.5 million people worldwide.[1] With a frequency of 1%-2% in the general population, it gradually increases with age and is expected to quadruple in the next 50 years.[2,3] AF is highly associated with ischemic stroke and thromboembolism.[4,5]
Cancer patients often suffer from AF as a comorbidity; the pathophysiological processes of this group of people are associated with the immune system's pro-inflammatory state, as well as treatment, such as the inflammatory response to cancer surgery, and the cardiotoxic effects of radiation and cancer treatments.[6] Patients with cancer and AF are more prone to bleeding complications, thromboembolism, and ischemic stroke-related mortality, and this has been proven by many previous studies and statistics. The data from the ORBIT-AF registry show a higher risk of major bleeding, non-cardiovascular death in patients with AF and cancer.[7] Cancer patients are living longer because of new treatments in the field, and aging is also a risk factor for AF. In this patient population, anticoagulation becomes an inevitable clinical judgment. Low-molecular-weight heparin is mostly advised under current recommendations for cancer patients' prevention of thromboembolism with AF, although the risk of bleeding persists in this regard.[8] As compared to those without cancer, the use of anticoagulation treatment in cancer patients with AF worsens the body's hemodynamic

balance by causing excessive bleeding and other side effects.[9] As far as treatment of individuals with cancer and AF is concerned it can be challenging to mitigate thromboembolic and ischemic stroke risks in these individuals with anticoagulation therapy as anticoagulation therapy further makes the bleeding worse for cancer patients because cancer patients are already taking such anticancer medications which already increases bleeding and disturb the hemodynamic balance of their body so by taking anticoagulation the prognosis gets worst so we need to look upon something different for management of such individuals.

Left atrial appendage occlusion (LAAO) with a Watchman/Amulet device is an alternate approach for stroke risk and thromboembolic risk reduction in cancer patients with AF for whom oral anticoagulation is contraindicated or not deemed appropriate. There is limited information on how LAAO may benefit cancer patients with AF who are contraindicated for anticoagulation therapy. Furthermore, data on the safety and efficacy of LAAO in cancer patients remains scarce. There is a lack of comprehensive evidence regarding in-hospital outcomes such as mortality, stroke, and bleeding complications.

To fill this gap, we conducted a novel meta-analysis to compare the short-term safety and efficacy of LAAO in cancer patients versus non-cancer patients. By focusing on this high-risk group, our study aims to provide better insights into how LAAO can be used to improve care for cancer patients with AF and to identify areas where more research is needed.

Methods

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist.[10] The data is used from already published literature, and did not collect any new patient data was collected, so this study did not require approval from the institutional review board.

Literature search and search strategy

The research team searched for the published literature on multiple databases, which included PubMed and Scopus. We searched for studies published from inception till 28th November 2024 using the keywords "left atrial appendage occlusion", "atrial fibrillation", "cancer patients", and "non-cancer patients. Moreover, we also identified articles from the reference lists of the relevant studies to be included in our library of studies. A detailed search string containing all the keywords used during the search is outlined in *Supplementary Table 1*.

Study selection and eligibility criteria

We imported all search results into EndNote X9 Reference Manager (Clarivate Analytics, Philadelphia, Pennsylvania), which enabled duplicate removal. Following duplicate removal, two researchers (MA and MK) screened titles and abstracts independently. Full texts of the shortlisted articles were assessed for the presence of relevant intervention and control groups, outcomes of interest, and methodology. Disagreements were resolved with the consensus of the third author (MZ). We finalized four studies that directly compared the outcomes of LAAO for atrial fibrillation in patients with cancer versus those without cancer. We included studies presenting relevant data while excluding those without comparative groups or data that could not be analyzed.

Data extraction

Data extraction was performed separately by two authors (MA and FM) utilizing an Excel sheet to document the results from shortlisted studies. Important data related to the trial (author name, year) and participants at baseline (sample size, age), and baseline characteristics were collected. Primary and secondary outcomes were also recorded in the Excel sheet, which included short-term mortality, ischemic stroke, bleeding complications, device complications, and pericardial complications. Short-term mortality was considered the primary outcome as it is the key measure of surgical success and prognosis in left atrial appendage occlusion. Short-term mortality was defined as in-hospital mortality or 30-day mortality. Device complications were defined as the occurrence of any of the following events: device thrombosis, peri-device leak, or device embolization. Bleeding complications were defined per the Valve Academic Research Consortium (VARC) and Bleeding Academic Research Consortium (BARC) criteria, as reported by individual studies. Major bleeding included events classified as BARC type 3–5, such as intracranial hemorrhage or gastrointestinal bleeding requiring blood product transfusion. In studies that specified anatomical bleeding sites, the following were included: gastrointestinal bleeding, genitourinary bleeding, epistaxis, pelvic hemorrhage, and intracranial hemorrhage. Minor bleeding events were not uniformly reported across studies and were therefore not included in the pooled bleeding outcome. Where applicable, only bleeding events that met criteria for major bleeding were included in the analysis.

Quality assessment

The quality of the studies included was assessed using the Newcastle Ottawa Scale (NOS). All the included studies had a low risk of bias across the three domains of selection, comparability, and outcome.[11] A detailed quality assessment is provided in *Supplementary Table 2*.

Statistical analysis

We utilized Review Manager (V.5.4.1 Cochrane Collaboration, London, UK) for statistical analysis. Risk ratios (RR) were calcu-

lated for dichotomous outcomes. Generic inverse variance (GIV) was used to pool the risk ratio and corresponding 95% confidence interval (95% CI). A random effects model was used to evaluate all the outcomes. The heterogeneity across pooled studies was assessed using Higgins' I^2 statistics. A value of I^2=25%-50% was considered mild, 50%-75% moderate, and greater than 75% severe heterogeneity.[12] To justify heterogeneity, we also performed a sensitivity analysis for the outcomes that had severe heterogeneity. A *p*-value of <0.05 was considered statistically significant throughout our analysis.

Results

Study selection and characteristics

This meta-analysis incorporates five studies, chosen from an initial pool of 144 studies obtained through an extensive literature search, following a thorough screening process that excluded all non-pertinent, redundant, and repetitive studies. Following the PRISMA flowchart, presented in *Supplementary Figure S1*. In the present study, a comprehensive cohort of 61,522 patients was analyzed, a subset of 2,014 individuals was identified as having a confirmed diagnosis of cancer, and the remaining 59,508 participants were classified as non-cancerous. The mean age of cancer patients was 78.05 years, in contrast to a mean age of 76.14 years for the non-cancerous. The patients' characteristics and baseline data have been summarized in Tables 1 and 2.

Primary outcome

For our primary outcome, an analysis of four studies revealed a statistically significant association between cancer patients and short-term mortality (RR =2.07; 95% CI [1.12 to 3.84]; *p*=0.02). Notably, the studies included exhibited no significant heterogeneity. The short-term mortality plot is shown in Figure 1.

Secondary outcomes

Ischemic stroke

Our analysis found no significant difference in ischemic stroke risk between cancer and non-cancer populations, yielding a pooled RR of 1.07 (95% CI: 0.71-1.59). Heterogeneity was minimal (I^2 = 0%, *p*=0.76), indicating study consistency. The overall test for effect was not significant (*p*=0.69), suggesting that cancer does not notably impact ischemic stroke risk (Figure 2).

Bleeding complications

In contrast, significant heterogeneity was observed in bleeding complications (I^2 = 94%, *p*<0.00001) with a pooled RR of 2.16 (95% CI: 0.65-7.13). A sensitivity analysis identified Zhang *et al.*[13] as a major contributor to this heterogeneity. Excluding this study reduced heterogeneity (I^2 = 63%) and yielded a revised pooled RR of 1.30 (95% CI: 0.69–2.43), indicating no significant differ-

Table 1. Study characteristics of the included studies

Author, year	Study design	Patient population, n	
		Cancer	Non-cancer
Hobohm *et al.* 2019	Retrospective cohort	206	15,689
Kumar *et al.* 2023	Retrospective cohort	57	332
Shabtaie *et al.* 2023	Retrospective cohort	55	212
Zhang *et al.* 2023	Retrospective cohort	1845	58,535
Zweiker *et al.* 2024	Retrospective cohort	57	429

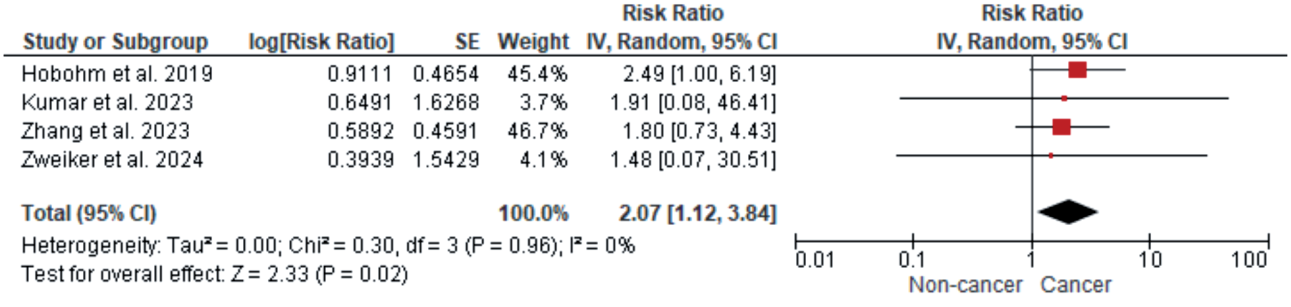

Figure 1. Forest plot for short-term mortality.

ence in bleeding complications between cancer and non-cancer populations (Figure 3).

Device complications

Our analysis showed no significant difference in device complications between cancer and non-cancer populations [RR 1.04 (95% CI: 0.69–1.58); *p*=0.83] (Figure 4).

Pericardial complications

A meta-analysis of two studies showed that pericardial complications were significantly higher in cancer patients as compared to non-cancer patients (RR: 2.17 95% CI [1.51, 3.12]; *p*<0.0001; I^2=0%) (Figure 5).

Sensitivity analysis

A leave-one-out sensitivity analysis was conducted to address the high heterogeneity observed in the initial analysis (Figure 2). This iterative process identified Zhang *et al*.[13] as the primary contributor to the heterogeneity. Upon excluding this study, the revised analysis (*Figure S2*) revealed a substantially reduced heterogeneity of 63%. The remaining studies demonstrated stability in the pooled risk ratio for bleeding complications (RR = 1.30, 95% CI: 0.69-2.43). Due to different definitions of major bleeding across the studies, high heterogeneity was seen.

Figure 2. Forest plots for ischemic stroke.

Figure 3. Forest plots for bleeding complications.

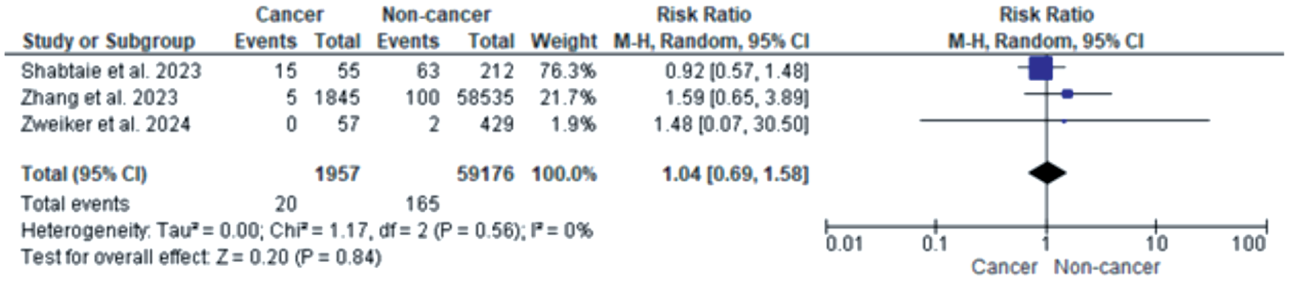

Figure 4. Forest plots for device complications.

Discussion

We conducted a meta-analysis and systematic review including five studies to assess LAAO for AF in cancer versus non-cancer patients. Our primary outcome shows that the rate of short-term mortality is statistically significant and is higher in cancer patients as compared to non-cancer patients undergoing the procedure. As for our secondary outcomes, including ischemic strokes, bleeding, and device complications, no significant result was observed.

As per the rate of mortality, our study showed that it is higher in patients with cancer undergoing LAAO as compared to non-cancer patients. LAAO benefits cancer patients significantly as it avoids the risk of bleeding complications from anticoagulation for AF. According to the study conducted by Zhang *et al.*, there was conflicting evidence about whether cancer is a risk factor for in-hospital mortality after the LAAO procedure, as it showed no statistical evidence. Still, it showed that cancer patients had to stay in the hospital for longer durations due to complications like pericardial effusion, which required open or percutaneous pericardial effusions, and major bleeding risks like intracranial and gastrointestinal, which ended up requiring transfusions in patients.[13] Moreover, one in six patients receiving LAAO dies within the first 2 years, having risk factors of older age, valvular diseases, HF, vascular disease, and altered renal and liver function, which increases the mortality rate by 46%[14] making cancer patients more prone to mortality, as up to two-thirds of cancer patients have one of the long-term comorbidities, and half of them have multiple long-term conditions at the time of diagnosis.[15] As cancer patients are subjected to anti-cancer and chemotherapy agents, they are associated with increased cardiovascular toxicities, which increase cardiovascular risks in patients, including hypertension, HF, thrombosis, cardiomyopathy, and arrhythmias.[16] HF and cancer share similar risk factors, as HF can develop from exposure to cardiotoxic drugs or radiotherapy, which leads to overall higher all-cause mortality in cancer patients.[17] Chemotherapy also induces acute systemic inflammation for months after treatment completion in cancer patients, which also contributes to many comorbidities.[18] In a multivariable analysis by Agarwal *et al.*,[19] the presence of active cancer was significantly associated with higher odds of in-hospital mortality in cancer patients than without cancer (10). The multivariate analysis of Hobohm *et al*. also supports our findings for early in-hospital mortality in cancer patients receiving LAAO.[20]

Our analysis did not find any significant results for ischemic stroke between cancer and non-cancer patients, as the incidence of ischemic stroke in cancer patients was about 1.12%, and in non-cancer patients was 0.28%. According to the study conducted by Shabtaie *et al*., there was no significant result regarding ischemic stroke in cancer and non-cancer patients as well.[21] The study conducted by Tung *et al*. also stated that ischemic stroke occurred in 1.4% of patients in one year and 3.4% of patients in 5 years, irrespective of their history of malignancy, having insignificant differences between the two groups.[22] Agarwal *et al*. also showed an insignificant outcome for stroke in both patient groups.[19] A study conducted by Isogai *et al.* showed a statistically significant result for increased risk of ischemic stroke associated with active cancer, but not with prior cancer patients.[23] As we have both active and prior cancer patients included in our study data, this could be a reason for our findings to be insignificant.

Our analysis related to bleeding complications showed no significant outcome. As stated by Tung *et al*.,[22] major bleeding did not have any significant difference between cancer and non-cancer groups, as most of the patients continued warfarin or direct oral anticoagulant therapy for the first 45 days after LAAO implantation, followed by lifelong aspirin. Hence, most of the major bleeding complications occurred while receiving the initial anticoagulation therapy. Shabtaie *et al*.[21] showed no significant difference as well. Agarwal *et al*. showed a significant difference between patients with active cancer and non-cancer patients. Since our study data was limited to cancer patients altogether (active and prior cancer patients), our result was found to be insignificant.[19]

The analyses performed showed insignificant results for device complications in cancer and non-cancer patient groups. According to a study conducted by Zweiker *et al*., LAAO-associated complications occurred only in one cancer patient out of 57 (1.8%) and seven non-cancer patients out of 429 (1.6%).[24] Our analyses showed 1.05% complications in cancer and 0.27% in non-cancer patients, with no significant difference between the two groups.

Our analysis also showed that pericardial complications were statistically significant in cancer patients. Pericardial effusion

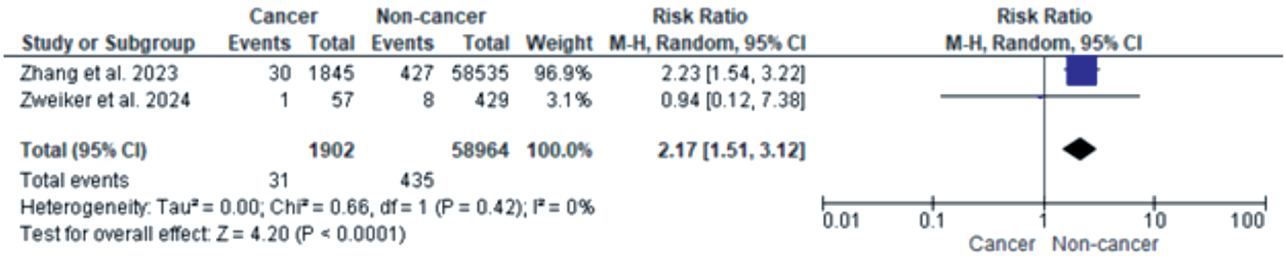

Figure 5. Forest plots for pericardial complications.

Table 2. Baseline characteristics of patients.

Author, year	Age, mean (SD) / median (IQR)		Male sex, n (%)		Coronary artery disease, n (%)		Hypertension, n (%)		Diabetes mellitus, n (%)		Heart failure, n (%)		Stroke, n (%)		Chronic obstructive pulmonary disease, n (%)		Anemia/thrombocytopenia, n (%)	
	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer	Cancer	Non-cancer
Hobohm *et al.* 2019	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kumar *et al.* 2023	78 (74-83)	78 (71-82	37 (65)	195 (59)	NR	NR	48 (84)	297 (89)	22 (39)	116 (35)	21 (37)	84 (25)	11 (19)	49 (15)	NR	NR	2 (3.5)	16 (4.8)
Shabtaie *et al.* 2023	79.0 (6.1)	76.8 (7.4)	44 (80.0)	143 (67.5)	27 (49.1)	94 (44.3)	52 (94.5)	194 (91.5)	17 (30.9)	63 (29.7)	18 (32.7)	56 (26.4)	21 (38.2)	73 (34.4	10 (18.2)	30 (14.2)		
Zhang *et al.* 2023	77.26 (0.37)*	76.09 (0.09)*	1280 (69.38)	33,985 (58.06)	955 (51.76)	29,074 (49.67)	1610 (87.26)	50,844 (86.86)	630 (34.015)	20,493 (35.01)	775 (42.01)	22,858 (39.05)	NR	NR	350 (18.97)	12,854 (21.96)	140 (7.59)	2827 (4.83)
Zweiker *et al.* 2024	78 (74-81)	75 (70-79)	38 (66.66)	274 (63.86)	27 (47.4)	171 (39.9)	53 (93)	379 (88.3)	13 (22.8)	125 (29.1)	18 (31.6)	111 (25.9)	11 (19.3)	115 (26.8)	8 (14)	53 (12.4)	34 (59.6)	169 (39.4)

* Data has been reported in standard error; SD, standard deviation; IQR interquartile range; NR not reported.

is one of the most common cardiac complications seen in patients undergoing percutaneous LAAO.[25] A possible explanation is that pulmonary artery pressure is associated with pericardial effusion in AF patients undergoing LAAO, which can result in pericardial complications.[26] Direct involvement of the pericardium due to metastases can predispose to complications such as effusion or tamponade in patients undergoing LAAO.[27]

Limitations

This meta-analysis includes several limitations that need to be addressed. For our meta-analysis, we could only find retrospective cohort studies, which may have selection and information bias and may not have a controlled and selective environment like randomized controlled trials (RCTs). Moreover, we had limited data on cancer patients, whether they were active cases or had prior cancer, which had been treated. This could have some significance in our outcomes. Another limitation is the limited data regarding the cancer therapies being given to active cancer patients or patients recovered, as many cancer therapies contribute to cardiovascular complications. In addition to that, we did not have enough data about the LAAO devices being used in both patient groups, as different devices have their shortcomings and complications. A key limitation of our study is that most patients were treated with earlier-generation LAAO devices, which typically required short-term post-procedural anticoagulation due to a higher risk of incomplete closure and device-related thrombus formation. In contrast, newer-generation devices such as the Watchman FLX, approved by the FDA in 2020, feature enhanced design elements that allow for more reliable deployment and sealing of the appendage, potentially eliminating the need for even short-term anticoagulation. As such, the bleeding risks reported in this study may overestimate the true risk associated with current-generation devices. This evolution in device technology should be acknowledged when interpreting our findings. Surgeon preferences and experience with LAAO devices can influence the outcome of our study, as data for devices being used was insufficient. Moreover, we could not perform meta-regression to assess the effect of confounding variables as there was not enough data available.

Conclusions

Our meta-analysis concluded that there was a significant rate of short-term mortality in patients with cancer undergoing LAAO procedures rather than in non-cancer patients. On the other hand, there were no significant differences between the two groups in terms of complications like ischemic strokes, bleeding, and device complications. Furthermore, more RCTs and larger sample sizes will be of benefit to a better outcome.

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Online supplementary material:
Figure S1. PRISMA flow chart.
Figure S2. Leave-one-out analysis of bleeding complications.
Table S1. Detailed search strategy used in each database.
Table S2. Newcastle-Ottawa Quality assessment for cohorts.