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Early postoperative atrial fibrillation is associated with late mortality after cardiac surgery: a systematic review and reconstructed individual patient data meta-analysis

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Abstract

Background Early postoperative atrial fibrillation (early-POAF) is the most common complication after cardiac surgery. Although prior studies have demonstrated an association between early-POAF and late outcomes, it is questionable whether these long-term adverse events result from early-POAF or from comorbidities that underlie the development of early-POAF. Therefore, the aim of this study was to investigate the association of early-POAF with late mortality and stroke after adjustment for age and cardiovascular comorbidities.

Methods A systematic search was conducted to identify studies reporting on late mortality after cardiac surgery in patients with and without early-POAF. Articles presenting Kaplan–Meier were included for a pooled analysis of late mortality (primary outcome) and stroke (secondary outcome). Individual time-to-event data were reconstructed from the Kaplan–Meier curves and incorporated into a multivariable mixed-effects Cox model.

Results In total, 33 studies were included in the analysis for late mortality (131 031 patients) and 10 studies in the analysis for late stroke (42 042 patients). Overall, 36 991 patients had early-POAF with a pooled incidence of 31.5% (95% CI: 27.7 to 35.6%). Unadjusted analysis showed that early-POAF was significantly associated with late mortality (Hazard Ratio [HR] = 1.62, 95%CI: 1.58–1.67, $P < 0.001$) and late stroke (HR = 1.72, 95%CI: 1.61–1.85, $P < 0.001$). Early-POAF was significantly associated with late mortality (adjusted HR = 1.19, 95% CI: 1.07–1.33, $P = 0.002$), but not with late stroke (adjusted HR = 1.14, 95% CI: 0.96–1.35, $P = 0.122$) after adjustment for age, comorbidities, surgery type, and the random effects term.

Conclusion Early-POAF after cardiac surgery is significantly associated with late mortality, but not with late stroke, after adjustments for age, sex, cardiovascular comorbidities, and type of surgery.

Keywords Postoperative atrial fibrillation, Cardiac surgery, Meta-analysis, Long-term outcomes

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Introduction

Postoperative atrial fibrillation (POAF) is the most common complication occurring within the first few days after cardiac surgery (early-POAF), with an incidence varying between 30 and 50%, depending on the type of surgery [1, 2]. It is hypothesized that POAF results from acute perioperative stressors, such as inflammation, oxidative stress, and increased adrenergic tone, superimposed on an advanced arrhythmogenic substrate [1, 2]. This substrate is influenced by advanced age and cardiovascular comorbidities, including hypertension, heart failure, diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD) [1, 2].

Previous meta-analyses have identified early-POAF to be associated with an increased incidence of early adverse events, including mortality, stroke, and prolonged hospitalization, as well as long-term mortality and stroke [3–5]. However, these earlier meta-analyses relied on reported event rates or effect size measures from the original studies, which limited the interpretation of the actual time-to-event results. Reconstructed individualized patient data (IPD) from original Kaplan–Meier (KM) curves allows for the aggregation of reconstructed time-to-event data, thereby providing actual survival differences at various timepoints during follow-up and enabling group-level adjustment for potential clinical confounders [6].

Therefore, the main objective of the current study was to determine the association between early-POAF and late mortality and stroke in patients undergoing cardiac surgery, using reconstructed time-to-event data with group-level adjusting for age, cardiovascular risk profile, type of cardiac surgery, and definitions of early-POAF.

Methods

Design

In this systematic review and meta-analysis, reconstructed IPD based on reported KM-curves were used to evaluate the association between early-POAF and both late mortality and stroke. The study was registered in PROSPERO (registration date: 24.07.2023, registration number: CRD42023448183) and adhered to the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020) guidelines as well as IPD PRISMA guidelines [7–9].

Eligibility criteria

Comparative single-center and multicenter studies reporting KM curves with risk tables on late mortality in patients with and without early-POAF after open-chest cardiac surgery were eligible. Early-POAF was defined as new-onset in-hospital AF or AF within 30 days post-surgery. Studies lacking sufficient data to reconstruct individual time-to-event data, including patients with preoperative AF, or using a non-comparative design were excluded. All studies were reviewed for potential overlap of study populations. In case of suspected overlap, the study with the largest population was included in the data synthesis.

Information sources

The PubMed, EMBASE and the Cochrane Library databases were systematically searched on 19 May 2024. Furthermore, the search was supplemented by manual screening of the reference lists of the included articles (cross-referencing).

Search strategy

The databases were searched using an elaborate reproducible search incorporating a combination of disease-associated terms ("postoperative atrial fibrillation"), procedure-associated terms ("cardiac surgical procedures") and outcome-associated terms ('mortality') with inclusion of possible alternative spellings (Supplementary Material 1).

Selection process

The study selection process was conducted independently by two authors (MK and CvdH). Duplicate records were first identified and removed, followed by title and abstract screening. Studies meeting inclusion criteria based on title and abstract were sought for retrieval and screened on full-text. All reasons for exclusion based on full-texts were recorded and presented in the study inclusion process. To optimize the inclusion process, a web-based tool was used (Rayyan.io, http://rayyan.qcri.org) [10]. Any potential disagreements during the inclusion process were resolved through discussion (MK and CvdH).

Data collection process and items

Data were independently collected from the included studies by two authors (MK and CvdH) based on a predefined worksheet of variables of interest (Supplementary Table 1). Potential disagreements in the data collection process were resolved through discussion.

Risk of bias assessment

The risk of bias assessment was performed with the ROBINS I tool [11]. The risk of bias assessment was performed independently by two authors (MJK and CvdH).

Outcomes and effect measures

The primary and secondary outcomes of the current study were defined as mortality and stroke occurring either after hospital discharge or beyond the first 30

postoperative days (late mortality and late stroke, respectively), with at least 12 months of postoperative follow-up. The associations between early-POAF and both late mortality and late stroke were presented in hazard plots, along with hazard ratios (HR) and corresponding 95% confidence intervals (CI). Additionally, differences in late mortality and stroke hazards between patients with and without early-POAF were presented at prespecified time points after discharge (1 year, 3 years, 5 years, and 10 years).

Subgroup and additional analyses

In the additional analyses, both primary and secondary outcomes were analyzed based on the type of surgery performed (coronary artery bypass grafting [CABG] vs. other cardiac surgical procedures), the definition of early-POAF (intervention-based, which included only early-POAF episodes requiring treatment, and non-intervention-based, which included early-POAF regardless of the need for treatment), and oral anticoagulation use at discharge.

Data synthesis

Data of studies presenting medians and inter-quartile ranges were converted to mean and standard deviation using Wan's method [12]. All comparisons of baseline clinical characteristics between patients with- and without early-POAF were assessed in a meta-analysis of continuous or categorical variables using inverse variance weighting in a random-effects model. Since this part of the analysis focused on assessing baseline differences between patients with and without early-POAF, rather than assessing the primary outcomes, no additional analyses were performed.

For the primary (late mortality) and secondary (late stroke) outcomes the analysis consisted of a dual approach. First all IPD were extracted from reported KM-curves as previously described [6]. Next, based on reconstructed KM-derived IPD a conventional meta-analysis of HRs was performed using inverse variance weighting in a random-effects model. Inter-study variance (τ^2) was assessed with restricted maximum likelihood estimator (REML). Additionally, presence of statistical heterogeneity was defined as a $I^2 > 75\%$. To explore the sources of heterogeneity, an outlier analysis was performed. Also, a meta-regression was performed to assess the impact of preoperative patient characteristics on late mortality and stroke.

The second part of the analysis for the primary (late mortality) and secondary (late stroke) outcomes involved aggregating KM-derived IPD and incorporating them into a mixed-effects Cox model to ensure adequate adjustment for between-study heterogeneity (random effect). These models included clinical and procedure-related variables, selected based on prior literature and unadjusted baseline comparisons, with additional adjustment for the study variable (random effect) [1, 2]. Group-level adjustments accounted for age, sex, preoperative cardiovascular comorbidities, type of surgery, and the random effect term to evaluate the impact of early-POAF on late outcomes. The proportional hazards assumption was assessed visually and tested using Schoenfeld residuals.

All statistical analyses were performed with R Version 4.2.2. (R foundation, Vienna, Austria) using "metafor", "meta", "dmetar ", "survival", "coxme ", "survminer", "maps", and "ggplot2" packages. A significance threshold of $P = 0.05$ was deemed as statistically significant.

Reporting bias and certainty assessment

Potential publication bias was statistically assessed for patient characteristics and late outcomes using the Egger's test. Publication bias of late mortality and stroke was also visually assessed in funnel plots. In case of significant publication bias, a trim-and-fill analysis was performed to assess the patterns of publication bias. There were no separate analyses performed to assess the certainty in the body of evidence for an outcome.

Results

Study selection

The systematic search yielded 12 802 studies. After removal of 2 925 duplicates, 9 877 studies were screened for title and abstract. Based on title and abstract, 9 779 studies were excluded. Of the remaining 98 articles, exclusion based on full-text resulted in the inclusion of 33 studies in the analyses (Fig. 1).

Study characteristics and POAF definition

In total, 33 studies were included, comprising 131 031 patients (Supplementary Table 2). The study sample sizes ranged from 276 to 16 172 patients [13–45]. The majority of studies were single-center ($n = 19$), followed by multi-center studies ($n = 10$) and registries ($n = 4$). Most studies used telemetry ($n = 28$), which was frequently combined with ECG ($n = 22$), for early-POAF assessment, with only 2 studies relying solely on ECG-diagnosed early-POAF (Supplementary Table 3). Additionally, most studies applied a nonintervention-based approach to determine early-POAF occurrence ($n = 19$), compared to 10 studies that used an intervention-based approach. For 3 studies, the monitoring strategy was not described.

Risk of bias assessment

All studies had a comparative design with an overall low to moderate risk of bias (Supplementary Table 4).

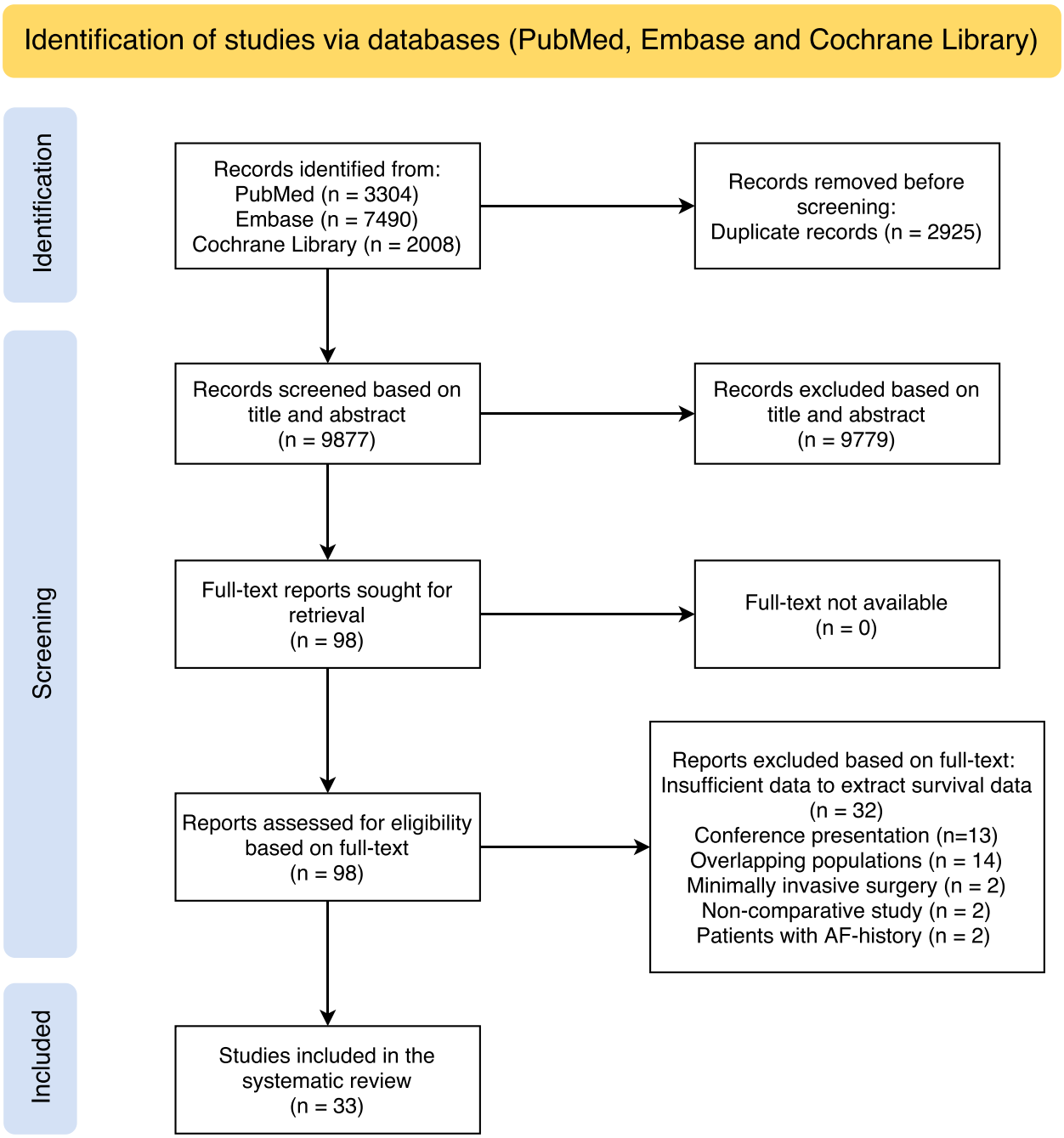

Fig. 1 Study inclusion diagram

Patient characteristics

Most studies were conducted in patients who underwent isolated CABG ($n=$ 17) [14–16, 19, 23–25, 28, 30, 31, 33, 36–38, 41, 43, 44], followed by isolated AVR ($n=$ 6) [18, 21, 26, 39, 42, 45], a combination of different cardiac procedures ($n=$ 6) [17, 29, 32, 34, 35, 40], isolated mitral valve surgery ($n=$ 3) [13, 20, 27], and isolated aortic surgery ($n=$ 1) [22].

Overall, 36.991 patients had early-POAF with a pooled incidence of 31.5% (95% CI: 27.7 to 35.6%) (Table 1). Compared to patients who remained in SR, patients with early-POAF were significantly older (68.1 vs. 63.3 years old, $P<$ 0.001), more frequently had a history of peripheral artery disease (PAD) (9.9% vs. 8.1%, $P=$ 0.003), stroke (9.7% vs. 7.9%, $P<$ 0.001), heart failure (18.0% vs. 15.3%, $P<$ 0.001) and chronic obstructive

Table 1 Patient characteristics and short-term outcomes

Variables	Overall ($n = 131\,031$)	SR ($n = 94\,040$)	POAF ($n = 36\,991$)	Effect size measure (RR or SMD[a])	*P*-value
Patient and surgical characteristics					
Age, in years	65.7 (64.2–67.1)	63.3 (61.2–65.4)	68.1 (66.4–69.8)	SMD = 0.47 (0.40–0.53)	< 0.001
Male subjects, in %	72.1 (65.9–77.4)	71.5 (62.2–79.3)	72.6 (63.9–79.9)	RR = 1.01 (0.97–1.05)	0.791
BMI, in kg/m^2	27.5 (26.9–28.1)	27.4 (26.5–28.2)	27.6 (26.7–28.4)	SMD = 0.04 (−0.01–0.10)	0.125
Hypertension, in %	70.8 (65.5–75.5)	69.5 (61.2–76.7)	72.0 (65.2–77.9)	RR = 1.05 (1.01–1.09)	0.008
Diabetes mellitus, in %	22.9 (19.9–26.1)	22.5 (18.3–27.3)	23.3 (19.3–27.8)	RR = 1.03 (0.97–1.10)	0.315
PAD, in %	9.0 (7.1–11.2)	8.1 (5.7–11.4)	9.9 (7.3–13.3)	RR = 1.16 (1.05–1.27)	0.003
History of MI, in %	27.2 (21.5–33.7)	25.8 (18.0–35.5)	28.5 (20.8–37.8)	RR = 1.05 (0.99–1.12)	0.138
History of stroke, in %	8.7 (7.6–10.1)	7.9 (6.4–9.8)	9.7 (8.0–11.7)	RR = 1.20 (1.10–1.30)	< 0.001
Heart failure, in %	16.6 (12.9–21.2)	15.3 (10.5–21.8)	18.0 (12.6–25.0)	RR = 1.19 (1.11–1.27)	< 0.001
Kidney failure, in %	4.8 (3.9–5.9)	4.3 (3.4–5.5)	5.2 (3.7–7.3)	RR = 1.29 (1.08–1.55)	0.006
COPD, in %	11.6 (9.7–13.7)	10.4 (7.9–13.5)	12.9 (10.2–16.0)	RR = 1.18 (1.10–1.27)	< 0.001
LVEF, in %	56.5 (55.1–57.9)	56.9 (54.8–59.0)	56.0 (54.1–57.9)	SMD = −0.08 (−0.15–0.02)	0.013
LAD, in mm	41.4 (39.7–43.1)	40.5 (38.2–42.7)	42.3 (39.7–44.9)	SMD = 0.27 (0.15–0.39)	< 0.001
CABG, in %	89.8 (64.9–97.7)	90.7 (48.4–99.0)	88.9 (49.2–98.5)	RR = 0.99 (0.99–1.01)	0.833
CPB-time, in minutes	103.5 (96.6–110.4)	101.4 (91.7–111.2)	105.6 (95.7–115.4)	SMD = 0.10 (0.05–0.15)	< 0.001
Clamp time, in minutes	70.0 (61.9–78.0)	68.7 (57.3–80.1)	71.2 (59.5–83.0)	SMD = 0.06 (0.03–0.10)	< 0.001

BMI Body mass index, *CABG* Coronary artery bypass grafting, *COPD* Chronic obstructive pulmonary disease, *CPB* Cardiopulmonary bypass, *LAD* Left atrial diameter, *LVEF* Left ventricle ejection fraction, *MI* Myocardial infarction, *PAD* Peripheral artery disease, *POAF* Postoperative atrial fibrillation, *RR* Relative risk, *SMD* Standardized mean difference, *SR* Sinus rhythm

[a] Cohen's d as measure for standardized mean difference

pulmonary disease (COPD) (12.9% vs. 10.4%, $P < 0.001$) (Table 1).

Late mortality

All studies were included in the analysis of late mortality ($n = 33$) [13–45]. The overall median follow-up time was 5.2 years. Early-POAF was significantly associated with late mortality in a conventional meta-analysis of HRs (HR = 1.66, 95% CI: 1.54 to 1.78, $P < 0.001$) with substantial heterogeneity ($I^2 = 81\%$) (Supplementary Fig. 1). To assess the sources of heterogeneity an outlier analysis was performed which identified five studies [17, 37, 40, 42, 45]. Meta-analysis after omitting these studies resulted in a significant association between early-POAF and late mortality (HR = 1.68, 95% CI: 1.59 to 1.77, $P < 0.001$) with moderate residual heterogeneity ($I^2 = 55\%$).

Unadjusted overall 10-year mortality was 30.5% (95% CI: 30.1 to 30.9%), as extracted from reconstructed time-to-event data (Table 2). Unadjusted mixed-effects Cox model showed that early-POAF was significantly associated with increased late mortality hazard (HR = 1.62, 95% CI: 1.58 to 1.67, $P < 0.001$) as compared

Table 2 Unadjusted late outcomes estimated from aggregated hazard plots

Late mortality rate					
Set time points during the FU	**Overall ($n = 131\,031$)**	**SR ($n = 94\,040$)**	**POAF ($n = 36\,991$)**	**Pooled Hazard Ratio (95%CI)**	***P*-value**
1-year mortality	4.0 (3.9–4.1)	3.2 (3.1–3.3)	5.9 (5.7–6.2)	HR = 1.91 (1.80–2.02)	< 0.001
3-year mortality	7.8 (7.7–8.0)	6.6 (6.4–6.7)	11.0 (10.7–11.4)	HR = 1.78 (1.70–1.86)	< 0.001
5-year mortality	12.9 (12.7–13.1)	11.1 (10.8–11.3)	17.8 (17.3–18.2)	HR = 1.72 (1.66–1.79)	< 0.001
10-year mortality	30.5 (30.1–30.9)	27.2 (26.8–27.7)	39.3 (38.4–40.2)	HR = 1.64 (1.59–1.69)	< 0.001
Late stroke rate					
Set time points during the FU	**Overall ($n = 42\,042$)**	**SR ($n = 30\,790$)**	**POAF ($n = 11\,252$)**	**Pooled Hazard Ratio (95%CI)**	***P*-value**
1-year stroke rate	2.9 (2.8–3.1)	2.5 (2.4–2.7)	4.0 (3.6–4.3)	HR = 1.62 (1.43–1.85)	< 0.001
3-year stroke rate	5.1 (4.9–5.3)	4.6 (4.3–4.8)	6.6 (6.2–7.1)	HR = 1.53 (1.39–1.70)	< 0.001
5-year stroke rate	8.0 (7.7–8.2)	7.2 (6.9–7.6)	10.0 (9.3–10.6)	HR = 1.47 (1.35–1.60)	< 0.001
10-year stroke rate	13.4 (12.9–13.9)	12.1 (11.6–12.7)	16.9 (15.8–17.9)	HR = 1.46 (1.36–1.58)	< 0.001

CI Confidence interval, *FU* Follow-up, *POAF* Postoperative atrial fibrillation, *SR* Sinus rhythm

to patients without early-POAF (10-year mortality rate: 39.3% vs. 27.2%, $P < 0.001$, respectively) (Table 2 and Fig. 2A). Multivariable mixed-effects Cox models showed a robust significant association between early-POAF and late-mortality even after group-level adjustment for age, sex, cardiovascular comorbidity profile (hypertension, DM, PAD, and history of heart failure), type of surgery and the random effect term (study parameter) (adjusted HR = 1.19, 95% CI: 1.07 to 1.33, $P = 0.002$) (Table 3). The rationale for variable selection in the adjusted mixed-effects Cox models is provided in Supplementary Table 5.

Additionally a meta-regression was performed to assess the individual impact of the preoperative patient characteristics on late mortality, which showed no significant associations (Supplementary Table 6).

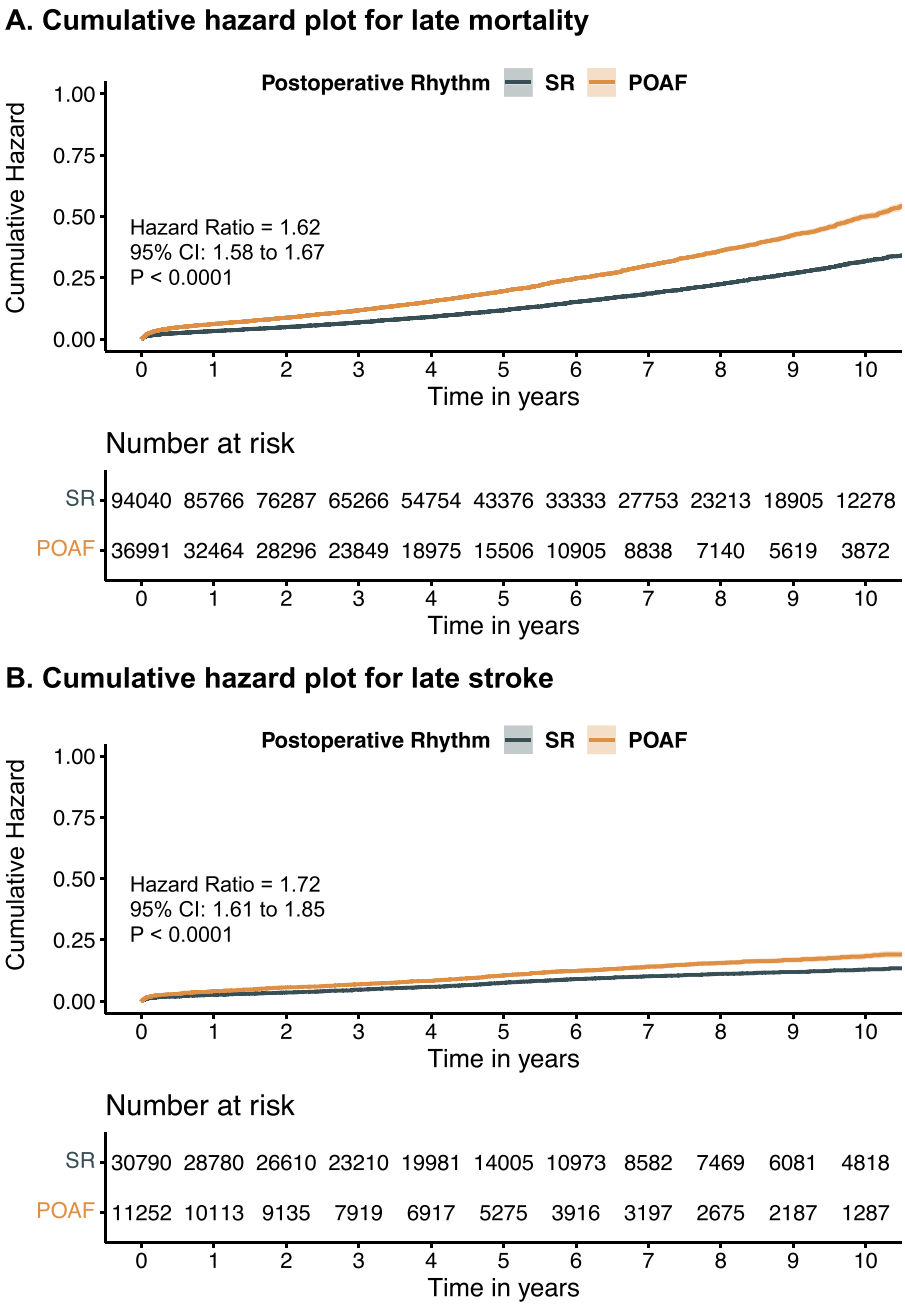

Fig. 2 Hazard plots for late mortality and late stroke. A. Unadjusted late mortality in patients with and without POAF. B. Unadjusted late stroke in patients with and without POAF

Table 3 Adjusted mixed-effects Cox models for late mortality

Variable	*Model 1*		*Model 2*		*Model 3*	
	Hazard ratio (95% CI)	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Age, per 1 year	1.05 (1.04–1.06)	< 0.001	1.06 (1.05–1.07)	< 0.001	1.08 (1.04–1.12)	< 0.001
Males, per 1% increase	0.99 (0.99–1.00)	0.073	1.00 (0.99–1.01)	0.217	1.02 (1.01–1.03)	< 0.001
Valvular surgery, per 1% increase	-	-	1.33 (1.19–1.49)	< 0.001	1.23 (0.89–1.69)	0.226
Hypertension, per 1% increase	-	-	-	-	0.98 (0.96–1.00)	0.066
Diabetes mellitus, per 1% increase	-	-	-	-	1.04 (1.01–1.07)	0.023
PAD, per 1% increase	-	-	-	-	1.01 (0.99–1.03)	0.096
Heart failure, per 1% increase	-	-	-	-	1.02 (0.98–1.06)	0.341
POAF occurrence	1.29 (1.23–1.34)	< 0.001	1.25 (1.17–1.33)	< 0.001	1.19 (1.07–1.33)	0.002
Schoenfeld residuals	-	0.285	-	0.182	-	0.080

CI Confidence interval, *COPD* Chronic obstructive pulmonary disease, *HR* Hazard ratio, *PAD* Peripheral artery disease, *POAF* Oostoperative atrial fibrillation

Late stroke

For the analysis of late stroke, 10 studies were included encompassing a total of 42 042 patients [16, 18, 21, 23, 28, 31, 37, 39, 43, 45]. The overall median follow-up time was 5.0 years. Early-POAF was significantly associated with late stroke in a conventional meta-analysis of HRs (HR = 1.64, 95% CI: 1.37 to 1.96, $P < 0.001$) with substantial heterogeneity ($I^2 = 76\%$) (Supplementary Fig. 2). An outlier analysis was performed which identified one study as a potential source of heterogeneity [37]. Meta-analysis after omitting this study showed a significant association between early-POAF and late stroke (HR = 1.52, 95% CI: 1.40 to 1.66, $P < 0.001$) with no residual heterogeneity ($I^2 = 0\%$).

Reconstructed time-to-event data revealed an overall unadjusted 10-year stroke rate of 13.4% (95% CI: 12.9 to 13.9%) (Table 2). Unadjusted mixed-effects Cox model showed that early-POAF was significantly associated with increased late stroke hazard (HR = 1.72, 95% CI: 1.61 to 1.85, $P < 0.001$) with an increased 10-year stroke rate as compared to patients who did not develop early POAF (16.9% vs. 12.1%, $P < 0.001$) (Table 2 and Fig. 2B). Multivariable mixed-effects Cox models showed no significant association between early-POAF and late stroke after group-level adjustment for age, sex, cardiovascular comorbidity profile (hypertension, DM, and history of stroke), type of surgery and the random effect term (study parameter) (HR = 1.14, 95% CI: 0.96 to 1.35, $P = 0.122$) (Table 4). The rationale for variable selection is provided in Supplementary Table 7.

Additionally a meta-regression was performed to assess the individual impact of the preoperative patient characteristics on late stroke, which showed no significant associations (Supplementary Table 8).

Type of surgery and late outcomes

Unadjusted subgroup analysis based on the type of surgery showed that early-POAF was significantly associated with increased late mortality in patients undergoing CABG (HR = 1.69, 95% CI: 1.64 to 1.75, $P < 0.001$) as well as in those undergoing other cardiac surgical procedures (HR = 1.42, 95% CI: 1.34 to 1.50, $P < 0.001$) (Fig. 3A-B).

Table 4 Adjusted mixed-effects Cox models for late stroke

Variable	*Model 1*		*Model 2*		*Model 3*	
	Hazard ratio (95% CI)	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Age, per 1 year	1.07 (1.04–1.10)	< 0.001	1.07 (1.04–1.10)	< 0.001	1.06 (1.01–1.11)	0.026
Males, per 1% increase	1.01 (1.00–1.02)	0.001	1.01 (1.00–1.02)	< 0.001	1.01 (1.01–1.02)	< 0.001
Valvular surgery, per 1% increase	-	-	1.58 (0.69–3.63)	0.284	1.69 (0.83–3.46)	0.152
Hypertension, per 1% increase	-	-	-	-	0.98 (0.96–1.01)	0.148
Diabetes mellitus, per 1% increase	-	-	-	-	1.01 (0.99–1.03)	0.266
Stroke history, per 1% increase	-	-	-	-	1.06 (1.02–1.11)	0.006
POAF occurrence	1.14 (0.98–1.31)	0.094	1.15 (0.99–1.34)	0.075	1.14 (0.96–1.35)	0.122
Schoenfeld residuals	-	0.141	-	0.146	-	0.173

CI Confidence interval, *COPD* Chronic obstructive pulmonary disease, *HR* Hazard ratio, *PAD* Peripheral artery disease, *POAF* Postoperative atrial fibrillation

Similarly, early-POAF was significantly associated with late stroke in patients undergoing CABG (HR = 1.78, 95% CI: 1.65 to 1.93, $P < 0.001$) as well as in those undergoing other cardiac surgical procedures (HR = 1.51, 95% CI: 1.28 to 1.77, $P < 0.001$) in an unadjusted subgroup analysis (Fig. 3C-D).

Early-POAF definition and late outcomes

A sensitivity analysis was conducted to assess the impact of the definition of early-POAF, categorized as nonintervention- or intervention-based, on late mortality and stroke. An intervention-based approach was significantly associated with increased late mortality among early-POAF patients compared to a nonintervention-based approach (HR = 1.12, 95% CI: 1.06–1.17, $p < 0.001$; Table 5). Further sensitivity analysis stratifying the nonintervention approach by early-POAF duration (any duration, less than 30 min, or at least 30 min) revealed that any duration and episodes lasting less than 30 min were associated with a lower late mortality hazard (Table 5) compared to the intervention-based approach. Conversely, studies defining early-POAF as lasting at least 30 min showed no significant difference in late mortality compared to the intervention-based definition (Table 5).

Similar results were observed for late stroke, where an intervention-based definition was associated with an increased risk of late stroke compared to a nonintervention definition (HR = 1.36, 95% CI: 1.21–1.53, $p < 0.001$; Table 5).

Oral anticoagulation and late stroke

In studies reporting on late stroke incidence, the overall OAC initiation rate at discharge was 14.4% (95% CI: 3.9 to 40.9%) [21, 23, 31, 39, 45]. The OAC initiation rate was significantly higher (RR = 3.12, 95% CI: 1.37 to 7.11, $P = 0.007$) in early-POAF patients (28.0%, 95% CI: 11.1 to 54.9%) compared to no-POAF patients (8.9%, 95% CI: 1.7 to 36.4%). Multivariable mixed-effects Cox analysis showed a significant association between a higher OAC initiation rate at discharge and reduced late stroke

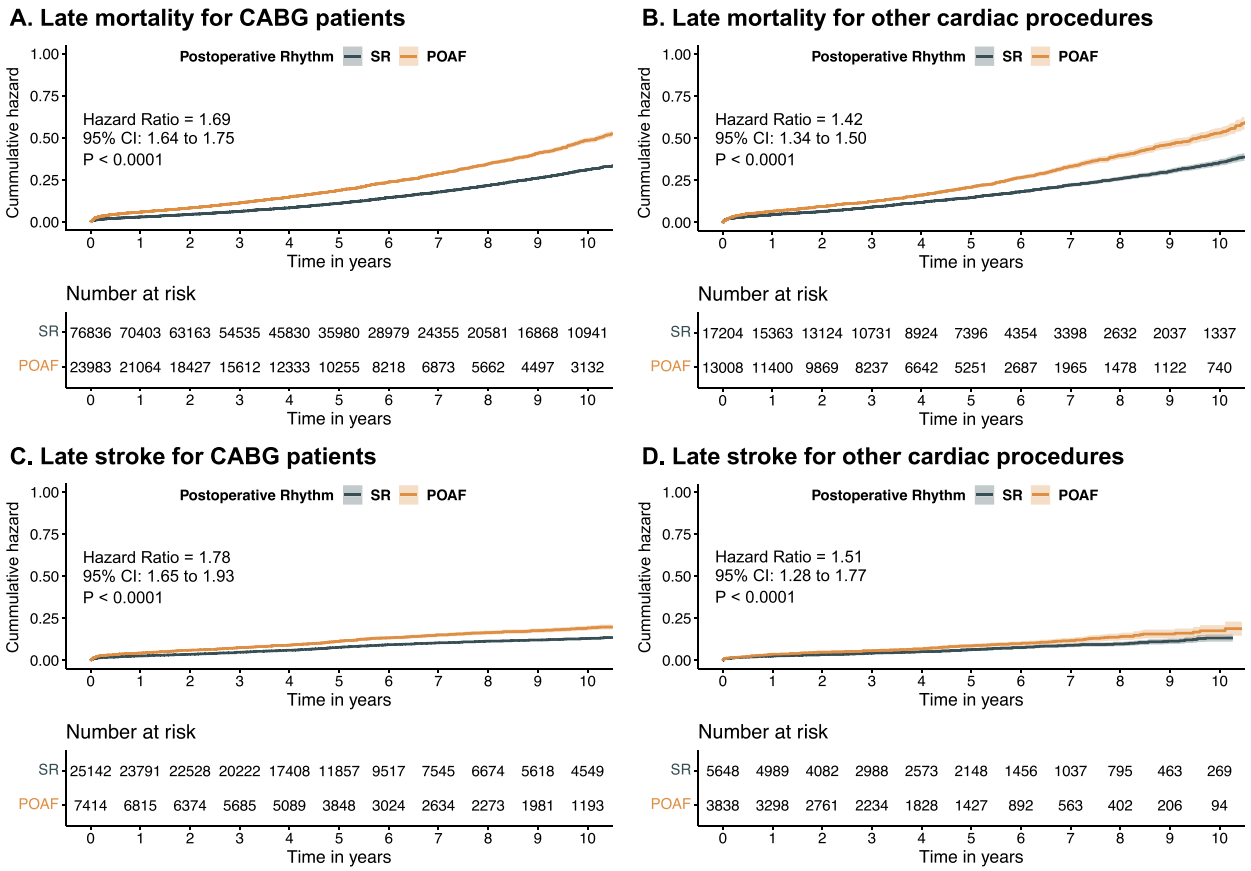

Fig. 3 Hazard plots for late mortality and late stroke for different surgical procedures. **A** Unadjusted late mortality hazard in patients with and without POAF undergoing CABG. **B** Unadjusted late mortality hazard in patients with and without POAF undergoing other cardiac procedures. **C** Unadjusted late stroke hazard in patients with and without POAF undergoing CABG. **D** Unadjusted late stroke hazard in patients with and without POAF undergoing other cardiac procedures

Table 5 Subgroup analysis by definition of early-POAF

Comparison	Number of studies	Number of patients	Hazard Ratio (95% CI)	*P*-value
Late mortality				
Early-POAF definition according to treatment				
Nonintervention	23	22 082	reference	
Intervention	10	14 909	1.12 (1.06–1.17)	< 0.001
Early-POAF definition according to treatment and episode duration				
Intervention	10	14 909	reference	
Nonintervention (any duration)	8	13 608	0.90 (0.85–0.95)	< 0.001
Nonintervention (< 30 min)	10	6 061	0.94 (0.89–0.99)	0.045
Nonintervention (≥ 30 min)	5	2 413	0.94 (0.86–1.03)	0.201
Late stroke				
Early-POAF definition according to treatment				
Nonintervention	7	6 077	reference	
Intervention	3	5 175	1.36 (1.21–1.52)	< 0.001
Early-POAF definition according to treatment and episode duration				
Intervention	3	5 175	reference	
Nonintervention (any duration)	3	3 562	0.53 (0.45–0.62)	< 0.001
Nonintervention (< 30 min)	4	2 515	0.54 (0.48–0.62)	< 0.001
Nonintervention (≥ 30 min)	0	0	*NA*	*NA*

CI Confidence interval, *NA* Not available, *POAF* Oostoperative atrial fibrillation

after group-level adjustment for age, sex, cardiovascular comorbidity profile (hypertension, DM, and history of stroke), type of surgery, early-POAF, and the random effect term (study parameter) (HR = 0.98, 95% CI: 0.97 to 0.99, $P = 0.004$). Unfortunately, no analyses considering bleeding complications could be performed due to missing data.

Publication bias

There was no significant publication bias for patient features and procedural characteristics (Supplementary Table 9). Also, there was no significant publication bias for both late mortality ($P = 0.352$) and stroke ($P = 0.138$) (Supplementary Fig. 3).

Discussion

While previous meta-analyses have shown an unadjusted association between early-POAF and late mortality, this is the first to demonstrate that early-POAF is independently associated with late mortality after adjusting for age, cardiovascular comorbidities, type of surgery, and study heterogeneity. For late stroke, early-POAF was significantly associated only in the unadjusted model, with this association disappearing after adjustments for age, cardiovascular comorbidities, type of surgery, and study parameters. Subgroup analysis further revealed that an intervention-based definition of early-POAF was a stronger predictor of late mortality and stroke compared to a non-intervention-based definition.

Late mortality

While cardiac surgeons are mainly confronted with early postoperative complications, the benefits of performing extensive cardiac procedures are primarily focused on improving long-term outcomes. Although early-POAF is still often considered a relatively harmless short-term adverse event that is mainly self-terminating, the results of the current study suggest otherwise. Specifically, the unadjusted 10-year mortality rate was 12.1% (95% CI: 11.6 to 12.5%) higher in early-POAF patients compared to patients who did not develop early-POAF, and the association between early-POAF and late mortality remained significant after adjusting for cardiovascular comorbidities, acting as relevant clinical confounders. Nevertheless, the pathophysiological mechanisms contributing to this association are mostly unknown, primarily due to the multifactorial nature of POAF involving many interacting risk factors and processes [1, 2]. However, a possible explanation might lie in the strong association between new-onset early-POAF and late post-discharge AF recurrences (late-POAF), demonstrated in several studies conducted with implantable loop recorders (ILRs) [46–48]. In those studies, late-POAF occurred in more than half of patients who had new-onset early-POAF, and early-POAF proved to be an strong independent predictor of late-POAF after adjusting for clinical confounders [46, 47]. In the non-surgical AF-patients, it is widely recognized that AF is associated with increased mortality and that both heart failure, due to the development

of arrhythmia-induced cardiomyopathy, and sudden cardiac death are the leading causes of this association [49, 50]. Therefore, it may be hypothesized that patients with early-POAF are more likely to develop late-POAF and experience AF-related adverse events, such as arrhythmia-induced heart failure, which contribute to an increased long-term mortality risk.

Late stroke

Currently, thrombus formation in the left atrial appendage during AF is considered the leading cause of stroke in AF patients, but previous studies have suggested a threefold relationship between a hypercoagulable state, AF, and stroke itself [51]. Moreover, the temporal relationship between AF and stroke, along with the specificity of this association, is still a matter of debate [52]. While the association between AF and stroke is clear, it remains questionable whether this association is fully causative, mostly due to the vast interplay of different comorbidities and processes contributing to hypercoagulability and atrial remodeling in AF patients. This complex association was also apparent in our meta-analysis, as early-POAF was strongly associated with increased late stroke in the unadjusted analysis, but this independent association disappeared after adjusting for multiple clinical cofounders. Based on these results, it is likely that while early-POAF plays an important role in the increased stroke risk, other cardiovascular comorbidities might interact in this association and contribute to the pathophysiological pathway preceding stroke.

Additionally, in a subgroup analysis of five studies reporting OAC initiation rates, we found a significant adjusted association between a higher OAC initiation rate and lower late stroke hazard. However, this analysis included a heterogeneous population of patients undergoing CABG and valvular surgery, which complicates the interpretation of these findings. Considering the guidelines for early-POAF patients (Class IIb, level of evidence B) along with our results, we believe it is crucial to assess each patient's stroke risk before prescribing (N)OAC treatment, rather than initiating it in all early-POAF patients [53]. Additionally, no randomized controlled trials (RCTs) have yet evaluated the long-term efficacy and safety of (N)OAC treatment in early-POAF patients. Therefore, while prescribing (N)OAC may seem intuitive, it is important to carefully assess the individual cardiovascular risk profile and thoroughly inform patients about the potential benefits and harms, especially given the lack of high-quality data supporting (N)OAC use for stroke prevention in early-POAF patients.

Importantly, our findings should be interpreted in the context of emerging strategies to reduce stroke risk in AF patients, with left atrial appendage (LAA) exclusion being one of the most prominent. Currently, LAA exclusion is recommended only for patients with a history of preoperative AF, but future studies are expected to explore its potential role in patients without preoperative AF [54]. A recent meta-analysis of six studies, involving a total of 4,130 patients without a history of preoperative AF who underwent LAA exclusion concomitant to cardiac surgery, demonstrated a reduced risk of CVA, no difference in the incidence of early-POAF, and a significant overall survival benefit in a 4-year landmark analysis [55]. Based on the findings from our study, we hypothesize that preoperative thromboembolic risk factors, rather than the individual risk of new-onset POAF alone, should be considered when selecting patients for LAA exclusion. Nonetheless, further studies are warranted to evaluate these clinical considerations more thoroughly.

Impact of early-POAF definition

The definitions for diagnosing early-POAF vary across cardiac surgical centers, leading to significant heterogeneity in assessing therapeutic strategies and long-term adverse events associated with early-POAF. In this study, we found that an intervention-based definition was associated with a higher late mortality and stroke hazard compared to a nonintervention-based definition. Interestingly, dividing the nonintervention-based definition by the minimum duration of early-POAF episodes revealed that studies including patients with episodes lasting less than 30 min had significantly lower late mortality than those using the intervention-based definition. These findings suggest that patients with more sustained early-POAF, characterized by longer episodes or the need for treatment, may face an increased late mortality hazard. Previous studies have already shown that patients with prolonged early-POAF are at higher risk for late-POAF recurrences compared to those with shorter early-POAF episodes [56, 57]. Therefore, it can be hypothesized that patients with sustained early-POAF may have an increased risk for late adverse events, such as mortality or stroke, potentially even mediated by a higher risk of late-POAF recurrences and associated AF-related complications, such as arrhythmia-induced heart failure.

Limitations

Despite the strengths of the current study, such as a large number of patients, adjustment for clinical confounders and the absence of publication bias, there are some important limitations that should be mentioned.

First, our meta-analysis is inherently influenced by the quality and methodology of the original studies included. Nevertheless, we carefully assessed study quality and

found an overall satisfactory standard among the included studies.

Second, pooling data from multiple studies may introduce heterogeneity, primarily due to differences in patient characteristics. Furthermore, because survival data were extracted from reported Kaplan–Meier curves, it was not possible to perform a competing-risk analysis for stroke and death. However, we attempted to address clinical and study-level heterogeneity by performing adjusted analyses that included correction for the study variable, allowing us to account for residual unexplained heterogeneity.

Third, there was variability in the definitions used to diagnose POAF across studies. In addition, a significant number of studies did not use telemetry for POAF detection, which may have led to underestimation of its true incidence, particularly in the intervention group. Nonetheless, we performed multiple subgroup analyses to evaluate the impact of these differing definitions on the overall results.

Fourth, sensitivity analyses for late mortality, especially for cardiovascular versus non-cardiovascular mortality, were not feasible due to limited data availability. Similarly, it was not possible to analyze whether patients were in sinus rhythm or AF at the time of death or stroke. Due to insufficient reporting, we were also unable to perform sensitivity analyses on the impact of graft material, recurrent angina, graft occlusion, or repeat revascularization on long-term outcomes.

Lastly, while treatment strategies in POAF patients may influence late outcomes, adjustment for therapy was not possible due to insufficient data. For example, it was unknown whether patients were receiving OAC therapy or whether they had persistent or paroxysmal AF at the time of stroke. Data on subsequent ablation procedures or LAA occlusion during follow-up were also lacking. Although we conducted a sensitivity analysis to assess the effect of OAC initiation on late stroke risk, it was limited by a small number of studies and notable between-study heterogeneity.

Conclusion

Early-POAF appears to be associated with increased late mortality, independent of clinical confounders such as age, type of surgery, and comorbidities. In the unadjusted analysis, early-POAF was independently associated with an increased late stroke hazard; however, this association disappeared after adjusting for age, type of surgery, and comorbidities. The definition of early-POAF may impact the association between early-POAF and late outcomes, potentially introducing bias into studies assessing this relationship.

Supplementary Information

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Supplementary Material 1.

Authors' contributions

MJK. conception and design, writing and revision of the manuscript, final approval. CvdH. conception and design, writing and revision of the manuscript, final approval. JGM. conception and design, revision of the manuscript, final approval. US conception and design, revision of the manuscript, final approval. MK conception and design, revision of the manuscript, final approval. PS conception and design, revision of the manuscript, final approval. EB conception and design, writing and revision of the manuscript, final approval. BM conception and design, writing and revision of the manuscript, final approval.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Competing interests

The authors declare no competing interests.

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