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Review Article

Comorbidity-modified biomarker prediction of postoperative atrial fibrillation after cardiac surgery: a scoping review

Oluwatosin G. Afolabi[1]*, Mayowa E. Oluwajuyigbe[2], Adedamola B. Adegbamigbe[2], Damilola T. Ishola[3], Abiodun I. Okunlola[2]

[1]Faculty of Clinical Sciences, University of Ilorin, Ilorin, Nigeria
[2]Department of Surgery, Federal Teaching Hospital, Ido-Ekiti, Nigeria
[3]Kharkiv National Medical University, Kharkiv, Ukraine

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***Correspondence:**
Dr. Oluwatosin G. Afolabi,
E-mail: otosinafolabi@gmail.com

ABSTRACT

Postoperative atrial fibrillation (POAF) complicates 20–50% of cardiac surgical procedures and is associated with increased stroke risk, prolonged hospitalisation, and mortality. Numerous circulating and clinical biomarkers have been proposed for POAF risk stratification; however, diabetes, chronic kidney disease (CKD), and obesity are typically entered as adjustment covariates rather than assessed as effect modifiers of biomarker performance. This scoping review mapped the extent to which the POAF biomarker literature evaluates comorbidities as modifiers of predictive performance. Following the Arksey and O'Malley framework and PRISMA-ScR reporting guidance, PubMed, Embase, Scopus, Web of Science, and the Cochrane Library were searched from inception, without date or language restriction, alongside backward and forward citation chasing of the included sources. Two reviewers independently screened the records and extracted the data; disagreements were resolved by discussion or by a third reviewer. Data were descriptively synthesised. Out of 1,409 records identified, 887 remained after de-duplication, and 845 were excluded at title/abstract screening, leaving 42 reports for full-text retrieval (one could not be retrieved). Of the 41 reports assessed in full text, 23 studies met the inclusion criteria, and 18 were excluded for documented reasons. Diabetes was the most frequently assessed comorbidity, reported in 21 of 23 studies, almost always as an adjustment covariate or unstratified baseline characteristic rather than a formally tested interaction term. Only two studies performed explicit statistical interaction testing between comorbidities and candidate predictors for POAF, and both found no significant interactions. Chronic kidney disease and obesity were assessed less frequently and with limited methodological rigor. Comorbidities are rarely evaluated as genuine effect modifiers of biomarker performance in POAF prediction research. Although diabetes has been formally tested, it does not appear to modify predictor performance, although the evidence base is too sparse to draw firm conclusions. Future POAF biomarker studies should pre-specify and report comorbidity-stratified or interaction analyses to clarify whether comorbidity-tailored risk models are warranted.

Keywords: Postoperative atrial fibrillation, Biomarkers, Comorbidity, Cardiac surgery, Scoping review

INTRODUCTION

Postoperative atrial fibrillation (POAF) is the most common arrhythmic complication of cardiac surgery, occurring in approximately 20–50% of patients undergoing coronary artery bypass grafting (CABG), valve surgery, or combined procedures.[1,2] A systematic review and meta-analysis has confirmed this incidence range across diverse surgical cohorts.[3] Beyond its acute haemodynamic consequences, POAF is independently associated with increased short- and long-term stroke risk, prolonged intensive care and hospital stay, and

elevated all-cause mortality.[4] Existing clinical prediction tools, including the POAF Score and the multicentre risk index of Mathew and colleagues, retain only modest discriminative ability, with reported C-statistics rarely exceeding 0.65–0.70.[5,6]

A substantial body of literature has examined circulating and clinical biomarkers spanning inflammatory (C-reactive protein, interleukin-6, neutrophil-to-lymphocyte ratio), myocardial injury and stretch (troponin, natriuretic peptides), fibrotic, haematological, and genomic pathways as candidate predictors of POAF.[7,8] Diabetes mellitus, chronic kidney disease (CKD), and obesity are among the most consistently reported clinical risk factors for POAF and for atrial fibrillation more broadly, with diabetes carrying a well-described, if inconsistently replicated, association with atrial structural and electrical remodelling.[9,10]

However, the manner in which these comorbidities are incorporated into POAF biomarker research has not been systematically examined. In most published models, diabetes, CKD, and obesity were entered as adjustment covariates in multivariable regression, used as exclusion criteria, or reported only as unstratified baseline characteristics. Whether these comorbidities modify, rather than merely contribute additively to, the predictive performance of circulating or clinical biomarkers for POAF remains largely unknown. This distinction has direct clinical relevance: if a comorbidity modifies biomarker performance, comorbidity-specific thresholds or models are required for accurate risk stratification; if not, a single model may be applied uniformly across comorbidity strata.

Given the exploratory nature of this question and the anticipated heterogeneity of study designs, populations, and analytic approaches in this literature, a scoping review methodology was considered most appropriate.[11,12] The objective of this review was to map the extent to which existing studies of biomarkers for POAF prediction report diabetes, CKD or obesity stratified analyses or formal statistical interaction testing and to characterise the methodological approaches used where such testing has been undertaken. Six specific research questions guided the review: the extent to which diabetes, CKD and obesity are assessed via stratified or interaction analyses; whether biomarker performance differs across comorbidity subgroups where such data exist; the proportion of studies treating comorbidity solely as an adjustment covariate; and the range of methodological approaches used to analyse comorbidity in this literature.

METHODS

Protocol and registration

This scoping review was conducted in accordance with the methodological framework of Arksey and O'Malley and reported following the preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR). The protocol was registered prospectively on the Open Science Framework (OSF; https://doi.org/10.17605/OSF.IO/AZK3B) prior to full-text screening.

Eligibility criteria

Eligibility was defined using the Population–Concept–Context (PCC) framework.

Population: adult patients (≥18 years) undergoing cardiac surgery (CABG, valve surgery, or combined procedures).

Concept: Evaluation of one or more circulating, clinical, or genomic biomarkers for predicting POAF, with extractable data on diabetes mellitus, chronic kidney disease, and/or obesity.

Context: Any clinical setting, with no restrictions on country, publication date, or language. Eligible study designs included prospective and retrospective cohort, case-control, cross-sectional, and prediction model derivation/validation studies. Case reports, conference abstracts without accessible full text, animal or in vitro studies, narrative reviews, commentaries, editorials, systematic reviews, and meta-analyses were excluded, as were studies restricted to non-postoperative or non-surgical atrial fibrillation populations.

Information sources and search strategy

To identify relevant literature, we searched PubMed, Embase, Scopus, Web of Science, and the Cochrane Library from inception to June 2026, without language restriction. The reference lists of all included studies and relevant reviews were hand-searched, with backward and forward citation chasing performed for every included source.

The PubMed search strategy combined four concept blocks: postoperative atrial fibrillation ("atrial fibrillation", "postoperative atrial fibrillation", "POAF", "new-onset atrial fibrillation", "new onset atrial fibrillation"); cardiac surgery ("cardiac surgical procedures", "cardiac surgery", "coronary artery bypass", "CABG", "valve surgery", "valvular surgery", "cardiopulmonary bypass", "heart surgery"); biomarker ("Biomarker", "predictor", "C-reactive protein", "neutrophil to lymphocyte ratio", "NLR", "platelet to lymphocyte ratio", "PLR", "natriuretic peptide", "troponin", "inflammatory marker", "risk score", "risk model", "prediction model") , and comorbidities ("diabetes mellitus", "diabetes", "renal insufficiency", "chronic kidney disease", "CKD", "Obesity", "body mass index"). Boolean operators ("AND", "OR", and "NOT") were used to fine-tune the search strategy.

Other databases

For the other databases, the same four concept blocks were adapted to the local syntax. In Embase, the postoperative atrial fibrillation, cardiac surgery, biomarker, and comorbidity blocks were mapped to Emtree explosion terms for atrial fibrillation, heart surgery, coronary artery bypass graft, biological marker, diabetes mellitus, chronic kidney disease, and obesity, combined with the corresponding free-text synonyms used in the PubMed strategy. Scopus searches used TITLE-ABS-KEY() and Web of Science used Topic (TS=) searches, joining the same synonym sets across the four concept blocks with the Boolean operator AND. The Cochrane Library was searched using the History/Search Manager with the same line-by-line concept block structure as PubMed.

Selection of sources of evidence

Records retrieved from all databases were imported into Rayyan13 for deduplication and screening, which was performed under the supervision of OGA and MEO. Two reviewers (OGA and MEO) independently screened the titles and abstracts and subsequently the full texts against the eligibility criteria; disagreements were resolved by discussion or adjudication by a third reviewer (AIO). Inter-rater agreement, quantified using Cohen's kappa, was 0.78 at the title/abstract stage and 0.95 at the full-text review stage.

Data charting process and items

Data were extracted independently by two reviewers (DTI, ABA) using a standardised, piloted charting form capturing study design, country, population and sample size, biomarker(s) or predictor(s) evaluated, comorbidity variables assessed (diabetes mellitus, chronic kidney disease, obesity), the analytic role assigned to each comorbidity (adjustment covariate, unstratified baseline characteristic, stratified subgroup analysis, or formal interaction term), and associated effect estimates. Discrepancies were resolved through discussion.

Synthesis of results

Findings were synthesised descriptively and narratively, characterising the distribution of biomarker types, comorbidity variables, and analytic approaches across the included studies. No pooled quantitative meta-analysis was undertaken, consistent with the scoping review methodology and the exploratory nature of the research questions.

RESULTS

Selection of sources of evidence

The search of five databases (PubMed, n=674; Embase, n=216; Scopus, n=309; Web of Science, n=118; and Cochrane Library, n=92) yielded 1,409 records. After the removal of 522 duplicates, 887 unique records were screened by title and abstract, of which 845 were excluded for not meeting the eligibility criteria. Forty-two reports were sought for full-text retrieval; one could not be retrieved despite attempts to contact the publisher and was therefore excluded on access grounds rather than content grounds. Of the 41 reports assessed in full text, 23 studies met all eligibility criteria and were included in this review, and 18 were excluded with documented reasons (Supplementary file 1). Notably, several studies provisionally excluded at the title/abstract stage due to the apparent absence of comorbidity data were subsequently confirmed eligible only after full-text retrieval because comorbidity prevalence in this literature is conventionally reported in an unindexed baseline characteristics table that is not reflected in the published abstract; this observation is returned to in the Discussion. The study selection process is summarised in the PRISMA-ScR flow diagram (Figure 1).

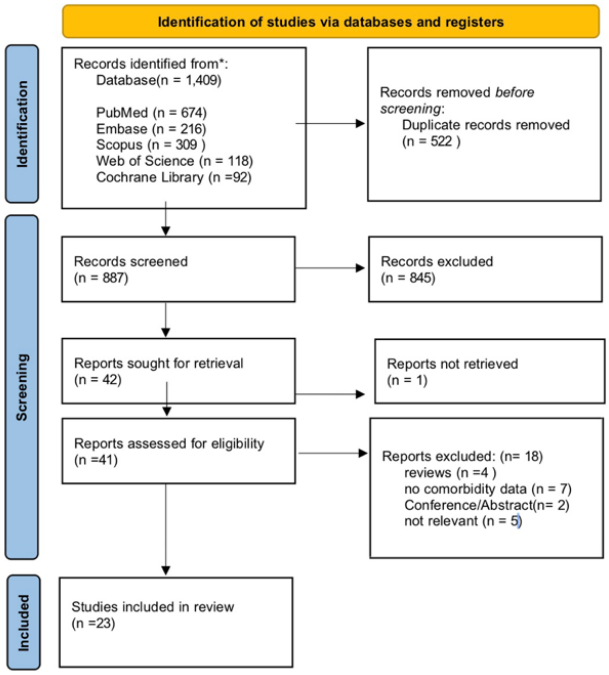

Figure 1: PRISMA-ScR flow diagram of study identification, screening, and inclusion.

Characteristics of included sources of evidence

The 23 included studies were published between 2007 and 2026 and comprised prospective cohort studies (n=13), retrospective cohort studies (n=9), and one dose-response meta-analysis of cohort studies addressing obesity specifically.27 Studies originated from Europe (n=11), Asia (n=6), North America (n=3), Oceania (n=1), and the Middle East (n=1), and one multinational meta-analysis. Sample sizes ranged from 49 patients35 to 18,517 patients in a single derivation cohort.33 Diabetes mellitus was the most frequently assessed comorbidity, reported in 21 of the 23 studies (91%); obesity or body

mass index was assessed in six studies (26%); and chronic kidney disease or renal function was assessed in five studies (22%). The full study characteristics, including the specific analytic role assigned to each comorbidity, are presented in Table 1.

Table 1: Characteristics of included studies (n=23).

	Study (ref)	Country	Design	N	Biomarker(s)/ predictor(s)	Comorbidity (ies) assessed	Analytic role of comorbidity	Key comorbidity-related finding
1	Noordzij et al[14]	Netherlands	Prospective cohort	959	13-biomarker panel (inflammatory, metabolic, neuro-endocrine)	Diabetes, obesity (metabolic panel)	Adjustment covariate	Metabolic/neuro-endocrine biomarkers independently associated with POAF; comorbidity not stratified
2	Iglesias-Álvarez et al[15]	Spain	Prospective cohort	123	Orosomucoid, adiposity/inflammation panel	Adiposity-linked markers	Subgroup (sex, not comorbidity)	Sex-stratified only; no comorbidity stratification
3	Altieri et al[16]	Italy	Prospective cohort	105	Ferritin, RDW, platelets	Not stated	Not assessed	No comorbidity data extractable
4	Weedle et al[17]	Ireland	Retrospective cohort	906	Neutrophil-to-lymphocyte ratio (NLR)	Diabetes mellitus	Adjustment covariate (multivariate)	Diabetes independently and significantly protective across all models: aOR 0.63–0.64 (p=0.014–0.018)
5	Coelho et al[18]	Portugal	Retrospective, machine learning	1414	Creatinine, ferritin, platelets, eGFR panel	CKD (eGFR), obesity (implied)	Adjustment covariate/feature	POAF had lowest F1-score of all modelled outcomes
6	Rizvi et al[19]	USA	Prospective cohort	90	PIIINP, miR-29, collagen markers	None reported	Not assessed	No significant baseline comorbidity differences reported
7	Gilbers et al[20]	Netherlands	Prospective cohort (RACE V)	133	Clinical + blood biomarkers	Not stratified	Adjustment covariate	Early/late POAF distinguished; comorbidity not interacted
8	Winters et al2024 [21]	Netherlands	Prospective cohort (RACE V)	147	BMP10	Not stratified	Adjustment covariate	BMP10 associated with late POAF and atrial fibrosis
9	Ohlrogge et al[22]	Germany	Prospective cohort	1047 (425 surgical)	Ang2, BMP10, FGF23, IGFBP7, NT-proBNP	Not stratified	Adjustment covariate	No biomarker significantly associated with POAF specifically
10	Osmanaj et al[23]	China	Retrospective cohort	3481	Inflammatory Burden Index (CRP×NLR)	Not stratified	Adjustment covariate	IBI outperformed SII; comorbidity not interacted
11	Turkkolu et al[24]	Turkey	Retrospective cohort	1191	Multiple biochemical parameters	Diabetes mellitus, HbA1c	Independent predictor (unstratified)	Diabetes OR 1.6 (any POAF), OR 2.1 (persistent POAF); HbA1c OR 2.0 (persistent)
12	Staicu et al[25]	Romania	Prospective cohort	70	NLR, SII, SIRI, CRP, IL-6, IL-17A	Not stratified	Adjustment covariate	NLR and CRP moderately predictive; comorbidity not interacted
13	Vural et al[26]	Turkey	Retrospective cohort	756	Clinical/metabolic risk factors	Diabetes, obesity, metabolic syndrome	Independent predictor (unstratified)	Diabetes OR 2.3, obesity OR 1.65, metabolic syndrome OR 2.46
14	Liu et al[27]	China (meta-analysis)	Meta-analysis, 35 cohorts	33,271/174,713	Body mass index, abdominal adiposity	Obesity	Exposure of interest (pooled)	Non-linear BMI–POAF relationship; obesity RR 1.39
15	Tsai et al[28]	Taiwan	Prospective cohort	266	Clinical/biochemical risk factors	Diabetes, renal function (eGFR)	Independent predictor (unstratified)	eGFR<60 HR 3.174; diabetes univariate only

Continued.

	Study (ref)	Country	Design	N	Biomarker(s)/ predictor(s)	Comorbidity (ies) assessed	Analytic role of comorbidity	Key comorbidity-related finding
16	Chua et al[29]	Taiwan	Prospective cohort	277	CHADS2, CHA2DS2-VASc scores	Diabetes (embedded in composite score)	Composite score component	Diabetes contributes to score but not interacted separately
17	Girerd et al[30]	Canada	Prospective cohort	2214	Waist circumference, CRP	Obesity (waist circumference)	Independent predictor (unstratified)	Increased waist circumference and CRP independently associated with POAF
18	Nomali et al[31]	Iran	Retrospective cohort	1956 (894 diabetic)	Clinical outcomes comparison	Diabetes mellitus	Direct diabetic vs non-diabetic comparison	Diabetes increased postoperative arrhythmia risk by 30%
19	Bowdish et al[32]	USA (multicentre)	Prospective cohort (RCT ancillary)	2104	Clinical/demographic risk factors	Diabetes, BMI	Formal interaction testing	No significant interactions found for any variable, including diabetes and BMI
20	El-Chami et al[33]	USA	Retrospective derivation/validation	18,517 +1,378	Age, height, weight, PVD risk index	Diabetes, BMI/weight (obesity proxy)	Formal predictor-selection testing (NRI, C-index, R^2)	Diabetes and BMI tested and excluded from final model; no added predictive value
21	Lotter et al[34]	Australia	Retrospective case-control	388	HATCH/HATCH-PC score, P-wave duration	Diabetes mellitus	Univariate testing (unstratified)	Diabetes OR 1.267, p=0.320 (non-significant)
22	Ucar et al[35]	Turkey	Prospective cohort	49	IL-6, hs-CRP	Diabetes mellitus, obesity (BMI)	Baseline comparison (unstratified)	Diabetes (5/14 vs 10/35) and BMI (28.0 vs 27.5) not significantly different
23	Gungor et al[36]	Turkey	Retrospective cohort	125	Platelet-to-lymphocyte ratio (PLR)	Diabetes mellitus	Baseline comparison (unstratified)	Diabetes 42% vs 41% (AF vs non-AF), p=0.261

Extent of comorbidity-stratified or interaction reporting (Research Questions 1–3)

No included study reported a formally pre-specified diabetes, CKD, or obesity-stratified analysis designed a priori to test comorbidities as effect modifiers of biomarker performance. Two studies performed post hoc statistical interaction testing, both addressing clinical risk factors rather than circulating biomarkers. Bowdish et al in a prospective ancillary cohort of 2,104 patients drawn from a multicentre randomised trial, tested interactions between all candidate predictors of POAF, including diabetes mellitus and body mass index, in a multivariable logistic regression model; no interaction reached statistical significance for any variable.[32] El-Chami et al in a derivation cohort of 18,517 patients with external validation in a further 1,378 patients, formally evaluated diabetes and weight/height, used as a proxy for obesity, as candidate predictors using three pre-specified statistical criteria: the net reclassification index, the change in concordance index, and the change in Nagelkerke R^2 when the variable was added to an age-based model.[33] Diabetes contributed a non-significant net reclassification index of 0.002 (p=0.58) and a change in C-index of 0.000, and was excluded from the final four-variable risk index (age, height, weight, and peripheral vascular disease). Body mass index similarly showed no significant unadjusted association with POAF (odds ratio 0.999, 95% CI 0.992–1.006, p=0.77).

No study reported a formal interaction test involving chronic kidney disease specifically, despite estimated glomerular filtration rate (eGFR) being identified as an independent multivariate predictor of POAF in a large single-centre cohort (hazard ratio 3.174 for eGFR <60 mL/min/1.73m², 95% CI 1.432–7.037).28 Similarly, no study tested obesity for interaction with a circulating biomarker, although obesity and waist circumference were independently associated with POAF in several studies.[26,27,30] This absence of interaction testing across all three comorbidities, despite their frequent measurement, constitutes the central methodological gap identified by this review.

Differences in biomarker performance across comorbidity subgroups, where reported (Research Question 4)

This research question examined whether the predictive performance of biomarkers differs between comorbidity-positive and comorbidity-negative subgroups in studies that report such comparisons. Answering this question proved to be the most challenging element of this review, precisely because no included study reported a true comorbidity-stratified biomarker performance

comparison, such as separate areas under the receiver operating characteristic curve, sensitivities, specificities, or odds ratios for a specific biomarker calculated separately within diabetic and non-diabetic subgroups, or within obese and non-obese subgroups. This represents an important negative finding in its own right: despite 21 of 23 included studies measuring diabetes, and despite diabetes being tested as an independent predictor in most of them, none progressed to the further analytic step of asking whether a biomarker's discriminative or predictive value changes according to a patient's comorbidity status.

The closest available evidence comes from the two studies identified in Research Questions 1–3. Bowdish et al found that no interaction reached significance when tested across a comprehensive panel of demographic, clinical, and pharmacological candidate predictors, including diabetes and body mass index.[32] El-Chami et al found that diabetes and obesity proxies added no discriminative value when tested using three separate statistical criteria in a cohort of nearly 20,000 patients.[33] Together, these studies constitute the most rigorous evidence currently available for this question. Taken at face value, these findings suggest that, at least for the clinical risk factors examined, comorbidity does not substantially modify the strength of the clinical predictors of POAF. However, both studies addressed clinical and demographic predictors rather than circulating biomarkers, and neither was designed with comorbidity modification as its primary hypothesis; therefore, the null interaction findings should be interpreted as reassuring but preliminary rather than definitive. Whether the same holds true for inflammatory biomarkers such as C-reactive protein or the neutrophil-to-lymphocyte ratio, myocardial injury markers such as high-sensitivity troponin, or genomic and proteomic markers cannot be determined from the currently published literature, since no study has performed the corresponding analysis. This gap represents the principal evidence deficit that this scoping review sought to characterise and directly motivates the recommendation, elaborated in the Discussion, that future primary studies pre-specify and report comorbidity-stratified biomarker performance metrics.

Comorbidity used as covariate or baseline characteristic only (Research Question 5)

Out of the 21 studies assessing diabetes, 19 (90%) reported it only as an unstratified baseline characteristic or an adjustment covariate in multivariable regression, without any stratified or interaction analyses. Several studies found diabetes to be statistically non-significant at either the univariate or multivariate analyses. Gungor et al reported a diabetes prevalence of 42% (21/50) in patients who developed POAF versus 41% (31/75) in those who did not (p=0.261), and diabetes was not included in their final multivariate model.[36] Lotter et al similarly reported a non-significant univariate odds ratio for diabetes of 1.267 (95% CI 0.794–2.022, p=0.320).[34] Ucar and colleagues,35 in a small prospective cohort of 49 patients, found no significant difference in diabetes prevalence (5 of 14 patients with POAF versus 10 of 35 without) or in body mass index (28.0±4.1 kg/m² versus 27.5±3.1 kg/m²) between groups.

In contrast, Weedle et al in the largest single-centre cohort in this review (n=906), found that diabetes mellitus was independently and significantly protective against POAF across all multivariate models: adjusted odds ratio 0.64 (95% CI 0.45–0.93, p=0.018) in the preoperative NLR model, 0.63 (95% CI 0.44–0.91, p=0.014) in the day-1 NLR model, and 0.64 (95% CI 0.45–0.93, p=0.017) in the day-2 NLR model.[17] This finding was directionally consistent across every multivariate specification the authors constructed, although diabetes was never tested for interaction with the neutrophil-to-lymphocyte ratio; the authors speculated that rigorous institutional diabetes management from the preassessment stage onwards may have attenuated the proinflammatory contribution of diabetes to POAF risk otherwise expected from the literature. Turkkolu et al reported the opposite direction of association, with diabetes as an independent predictor of both POAF (odds, 1.6) and persistent POAF (odds, 2.1), alongside glycated haemoglobin as a predictor of persistent POAF (odds, 2.0).[24] Similar to Weedle et al diabetes was not tested for interaction with any co-measured biomarkers. Obesity was treated similarly across studies: Vural and Ağlar and Girerd et al reported obesity and waist circumference as independent risk factors for POAF, without testing whether obesity modified the performance of any co-measured biomarker, such as C-reactive protein.[26,30]

Methodological approaches identified (Research Question 6)

Five broad analytic approaches to comorbidity were identified across the 23 included studies. First, comorbidity was an exclusion criterion, in which patients with pre-existing renal replacement therapy or uncontrolled diabetes were removed from enrolment altogether, precluding the assessment of comorbidity-related variation within the study population. Second, comorbidity as an unstratified baseline characteristic, the most frequent pattern, in which prevalence was reported in a demographic table without further analytic use, exemplified by the sex-stratified but not comorbidity-stratified analysis of Iglesias-Álvarez et al.[15]

Third, comorbidity as an adjustment covariate, in which the variable was entered into multivariable regression alongside the biomarker of interest to control for confounding rather than to test effect modification, exemplified by Noordzij et al 13-biomarker panel analysis.[14] Fourth, subgroup comparison without formal interaction testing, in which the study population was divided by a variable other than comorbidity, typically sex, while comorbidity itself was never used as a

stratifying variable. Fifth, and rarest, formal statistical interaction testing, identified only in Bowdish et al and El-Chami et al.[32,33]

No study in this review employed machine-learning-based feature-importance or SHAP-value methods to interrogate comorbidity-biomarker interactions for POAF, in contrast to methodologically comparable work in the heart failure literature, where atrial fibrillation itself has been formally tested as, and found to be, a significant modifier of the prognostic performance of biomarkers such as galectin-3 and soluble ST2.[38]

DISCUSSION

This scoping review mapped 23 studies evaluating biomarkers for POAF prediction with respect to how diabetes, chronic kidney disease, and obesity were incorporated into their analyses. The central finding was that comorbidity is almost universally treated as a covariate for statistical adjustment, an exclusion criterion, or an unstratified baseline characteristic, rather than as a variable whose effect-modifying role on biomarker performance is formally tested. Only two studies, both addressing clinical risk factors rather than circulating biomarkers, performed genuine interaction testing and both reported null findings for diabetes and obesity.[32,33] No study addressed chronic kidney disease with comparable rigor, and no study reported a true comorbidity-stratified comparison of biomarker performance corresponding to Research Question 4.

The consistent, independent replication of a null diabetes interaction finding across two large, methodologically distinct cohorts is noteworthy. Bowdish et al analysed a multicentre randomised trial ancillary population using comprehensive interaction testing across all candidate variables, while El-Chami et al analysed a single-centre derivation-validation cohort of nearly 20,000 patients using three complementary statistical criteria for variable selection.[32,33] Despite differing substantially in design, geography, and era, both studies converged on the same conclusion that diabetes does not meaningfully add to or interact with clinical predictors of POAF, lending this finding more weight than either study alone would provide. However, the generalisability of this conclusion to circulating biomarkers, as opposed to clinical and demographic variables, remains untested and should not be assumed.

A directly relevant methodological precedent exists in the heart failure literature, where atrial fibrillation, rather than diabetes, has been shown to modify the prognostic performance of circulating biomarkers. Tan et al formally tested the interaction between atrial fibrillation status and twelve circulating biomarkers in a cohort of 1,099 patients with heart failure, finding significant interactions for galectin-3 and soluble ST2, such that these markers predicted heart failure hospitalisation and mortality only, or more strongly, in the presence of atrial fibrillation.[38] This demonstrates that the statistical approach required to answer the underlying question of the present review, namely formal interaction testing between a modifying condition and a biomarker's predictive performance, is both feasible and clinically informative when applied. This approach has been transplanted into the atrial fibrillation-as-modifier literature in heart failure but not into the comorbidity-as-modifier literature in POAF prediction, representing a clear and actionable methodological gap.

This gap should be understood within the broader context of the persistent methodological weaknesses in POAF prediction research. A recent systematic review and critical appraisal of multivariable prediction models for atrial fibrillation after cardiac surgery found that, although some models achieved reasonable apparent discrimination (median C-statistic 0.71 on internal validation), every model reviewed was judged to be at high risk of bias, driven principally by small sample size, data-driven predictor selection, and inadequate internal validation.[37] That review did not specifically examine whether comorbidity modification had been considered during model development; the present scoping review extends that critique by showing that, even where comorbidity data are collected, they are rarely analysed beyond simple adjustment.

Obesity was addressed as an independent risk factor for POAF in several included studies, including a dose-response meta-analysis of 35 cohorts and over 174,000 patients demonstrating a non-linear relationship in which risk rose steeply above a body mass index of approximately 30 kg/m², with neither underweight nor mild overweight conferring significant additional risk.[27] A mechanistic proteomic study of the epicardial fat secretome, excluded from this review's primary analysis because it did not stratify findings by obesity status, nonetheless illustrates that biologically plausible pathways linking adiposity to POAF are under active investigation, describing differential expression of gelsolin and other adipokines preceding the onset of arrhythmia.[39] Despite this substantial descriptive literature on obesity as a POAF risk factor, no study in the present review tested whether obesity modifies the discriminative performance of any specific circulating biomarker, leaving the clinical question of whether obese patients require a different biomarker threshold, or a different biomarker altogether, entirely open.

Chronic kidney disease was the least studied comorbidity in this context, assessed in only five of the 23 included studies, generally as an adjustment covariate or an exclusion criterion rather than an analytic variable of interest. An estimated glomerular filtration rate below 60 mL/min/1.73m² was identified as a strong independent predictor of POAF in a large single-centre cohort, with a hazard ratio of 3.174, the single largest comorbidity-related effect size identified across all included studies.[28] Given the well-established bidirectional relationship

between renal dysfunction, volume status, and atrial electrophysiological re-modelling, the near-absence of CKD-stratified biomarker analyses represents a notable evidence gap, particularly since several of the biomarkers evaluated in this literature, including natriuretic peptides and creatinine-adjacent hematological indices, are themselves influenced by renal function, raising the possibility that CKD could confound as well as modify their apparent predictive performance.

Limitations

The principal strength of this review is its methodologically rigorous dual-reviewer screening and extraction process, with high inter-rater agreement at both screening stages. A key limitation is that one study meeting all other eligibility criteria could not be retrieved in full text owing to publisher paywall restrictions and was excluded on access grounds. As a scoping review, no formal quality or risk-of-bias appraisal of the included studies was undertaken, consistent with current scoping review guidance, and the findings describe the extent and nature of existing evidence rather than its certainty. Finally, the small number of studies performing any form of comorbidity-stratified analysis precluded any quantitative synthesis of Research Question 4, which had to be answered narratively as a description of an evidence gap rather than as a substantive finding.

CONCLUSION

Diabetes, chronic kidney disease, and obesity are frequently measured but rarely tested as effect modifiers of biomarker performance in the literature on postoperative atrial fibrillation prediction. When diabetes and obesity proxies were formally tested for interaction with clinical predictors, no significant modification was found; however, this evidence was derived from only two studies addressing clinical rather than circulating biomarkers. Future primary studies of POAF biomarkers should pre-specify and report comorbidity-stratified or interaction analyses, following the precedent set in adjacent cardiovascular literature, to determine whether comorbidity-specific risk models are necessary. Journal reporting standards and prediction-model reporting guidelines, such as TRIPOD, could be extended to require an explicit statement of how candidate comorbidities were analytically treated, including whether interaction terms were tested and, if so, with what result.

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