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Systematic Review

Circulating MicroRNAs as Molecular Biomarkers of Atrial Fibrillation Recurrence After Catheter Ablation: A Systematic Review and Candidate-Centered Evidence Map

Antônio da Silva Menezes, Junior [1,2,3,*], Arthur de Sousa Silva [1], Alcir Júnior de Paula Nunes Meneses [1], Annelyse Vitória Souza Barbosa [2] and Aparecido Divino da Cruz [2,3]

[1] Internal Medicine Department, Faculty of Medicine, Federal University of Goiás, Goiânia 74690-900, Goiás, Brazil; arthur.sousa@discente.ufg.br (A.d.S.S.); alcirjunior@discente.ufg.br (A.J.d.P.N.M.)
[2] School of Medicine, Pontifical Catholic University of Goiás, Goiânia 74605-010, Goiás, Brazil; annelysevitoria@gmail.com (A.V.S.B.); acruz@pucgoias.edu.br (A.D.d.C.)
[3] Postgraduate Program in Genetics, Pontifical Catholic University of Goiás, Goiânia 74605-010, Goiás, Brazil
* Correspondence: a.menezes.junior@uol.com.br

Abstract

Background: Recurrence after atrial fibrillation (AF) ablation remains difficult to predict. Circulating microRNAs may reflect molecular substrates not captured by established predictors. We mapped recurrence-specific evidence and identified priorities for prospective validation. Methods: Six databases were searched from inception through 29 August 2026 for adult AF ablation cohorts measuring circulating microRNAs before or around ablation and reporting atrial tachyarrhythmia recurrence. Recurrence-specific reports were assessed with the Quality in Prognosis Studies (QUIPS) tool. A post hoc candidate-centered framework required direct recurrence evidence in at least two analytically distinct samples and support in at least one additional clinical, mechanistic, or analytical domain. Candidate-specific certainty was evaluated with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework. Results: Thirty-five publications represented 29 linked programs; 26 recurrence-specific reports represented 25 independent cohorts (3309 enrolled; 3205 analyzed), and nine publications provided longitudinal context. Six microRNAs were identified as priorities for prospective validation: miR-21-5p, miR-150-5p, miR-29b-3p, miR-451a, miR-10b-5p, and miR-320a. Their evidence differed in mature-arm identity, matrix, sampling compartment, assay scale, biological source, and mechanistic support. Candidate-specific certainty was very low. Conclusions: The evidence supports candidate-specific prospective validation rather than a uniform circulating-microRNA class effect. Standardized preanalytics, mature-arm and carrier attribution, locked assays, and multicenter incremental-prediction studies are required before clinical utility can be established.

Keywords: atrial fibrillation; catheter ablation; circulating microRNA; molecular biomarkers; recurrence; fibrosis; atrial remodeling; systematic review

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1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with stroke, heart failure, impaired quality of life, and premature mortality [1–3]. Catheter ablation is an established rhythm control strategy, but atrial tachyarrhythmia recurs after a single procedure in many patients [3,4]. Better preprocedural prediction could improve counseling, follow-up intensity, and the design of substrate-directed strategies.

Clinical, imaging, and procedural predictors—including AF type, left atrial size and fibrosis, ventricular function, obesity, and comorbidity burden—capture only part of the biological variability underlying recurrence [5,6]. Circulating microRNAs are short non-coding ribonucleic acids (RNAs) that regulate post-transcriptional gene expression and intersect with atrial fibrosis, inflammatory signaling, calcium handling, electrical remodeling, cellular senescence, and extracellular matrix turnover [7–11]. Extracellular vesicles and protein-associated carriers can protect circulating microRNAs from degradation, whereas cellular leakage, hemolysis, and platelet contamination can confound the measured signal [12–14]. Their compatibility with quantitative polymerase chain reaction supports biomarker development, but molecular identity depends on specimen matrix, carrier fraction, cellular source, mature arm, and assay scale.

Published studies of microRNAs after AF ablation vary in specimen compartment, sampling time, extraction and normalization protocols, exposure coding, recurrence definitions, monitoring intensity, and statistical adjustment [5,12–14]. Several reports assess multiple microRNAs or biological compartments within small cohorts, increasing the risk of selective reporting and dependent estimates. What remains unresolved is which individual candidates have sufficiently coherent clinical, analytical, and mechanistic support to justify prospective validation. Therefore, cross-biomarker class-level synthesis is exploratory and requires clear handling of candidate identity, effect direction, and statistical independence. Recent reviews have summarized microRNA biomarkers and other predictors of recurrence after AF ablation [15–17].

The primary objective of this systematic review was to map recurrence-specific evidence and identify candidate microRNAs for prospective validation using a transparent, candidate-specific framework. Secondary objectives were to (1) map peri-ablation longitudinal evidence; (2) distinguish experimentally supported mechanisms from pathway hypotheses and source or carrier inference; (3) explore odds ratio (OR) and hazard ratio (HR) evidence without combining effect measures; and (4) define the analytical and clinical validation pathway for translation.

2. Materials and Methods

2.1. Study Design and Registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and guidance for prognostic factor reviews [18,19]. The protocol and working materials were prospectively made available through the Open Science Framework (https://doi.org/10.17605/OSF.IO/GD4P2; accessed on 29 August 2026). A dated amendment added Wanfang and Chinese-language terms after a coverage gap was identified; eligibility and cohort-linkage rules remained unchanged. The later reviewer-prompted restrictive sensitivity hierarchy is described in Section 2.9 and did not alter eligibility. The final evidence base was frozen on 29 August 2026.

2.2. Eligibility and Evidence Layers

The recurrence-specific layer included adults undergoing catheter ablation for AF, circulating microRNAs measured in blood-derived specimens before or around the index procedure, and recurrence of AF or another atrial tachyarrhythmia during follow-up. A separate contextual longitudinal layer retained eligible pre- and post-ablation circulating microRNA studies that did not report recurrence-specific estimates. Eligibility was based only on population, intervention, biomarker, sampling window, outcome/evidence layer, and original-report criteria; statistical significance, risk of bias, and quantitative usability were not included as eligibility criteria. Surgical ablation, non-separable mixed interventions, tissue-only markers, non-AF populations, ineligible outcomes, and non-original

reports were excluded. Legacy arm-unspecified labels were retained as reported and were not assigned to a mature microRNA arm unless assay documentation confirmed identity.

2.3. Information Sources and Search

PubMed/MEDLINE, Embase, Web of Science Core Collection, Scopus, the Cochrane Library, and Wanfang were searched from inception through 29 August 2026 without language restrictions. The search combined controlled vocabulary and free-text terms for AF, catheter ablation, and microRNA. The recorded Wanfang yield was the 50-record screening set after within-source deduplication; no additional duplicates were recorded against the master library. The original databases were re-evaluated, and citation lists were checked. Exact strategies and dated source accounting are provided in Supplementary Tables S1 and S2.

2.4. Study Selection and Data Extraction

After deduplication, two reviewers independently screened titles and abstracts and assessed full texts; disagreements were resolved by consensus. Inclusion and exclusion were determined before considering effect direction or statistical significance. The same two reviewers independently extracted the prespecified data items using an audited form that included cohort identity, participants, AF phenotype, ablation method, matrix and compartment, sampling time, assay and normalization, recurrence definition, follow-up, effect measure, exposure coding, adjustment set, and report overlap. Reports were linked when author group and institution, recruitment site and period, sample size and AF phenotype, ablation method, biomarker platform, and follow-up characteristics indicated a shared or probably shared cohort. Overlapping publications remained eligible but were assigned a common program or recurrence-cohort identifier so that an independent cohort could contribute at most one estimate to a quantitative sensitivity model. Uncertain linkage was retained as probable rather than treated as confirmed.

2.5. Outcome

The primary outcome was recurrence of AF or another atrial tachyarrhythmia after catheter ablation, as defined by each study. When multiple eligible time points were reported, outcomes beyond the study-specific blanking period were selected consistently using the documented time-point rule. The reviewer-prompted biomarker hierarchy described in Section 2.9 did not alter outcome eligibility. Variations in recurrence definition, rhythm-monitoring method, monitoring intensity, and blanking period were recorded as sources of clinical heterogeneity.

2.6. Risk of Bias and Certainty

Two reviewers assessed recurrence-specific reports using the six-domain Quality in Prognosis Studies (QUIPS) tool [20]. Candidate-specific certainty was evaluated with the GRADE framework for prognostic-factor research [21]. Observational prognostic evidence began at high certainty, as recommended by this framework, and was downgraded for risk of bias, inconsistency, indirectness, imprecision, and suspected publication bias where applicable. Mechanistic plausibility was not used to upgrade certainty for clinical prognosis. Source-based rationales and the complete candidate-specific profiles are provided in Supplementary Table S11.

2.7. Candidate-Centered Molecular Evidence Mapping

Candidate prioritization was post hoc and did not alter eligibility, extraction, or QUIPS judgments. The framework was formalized during evidence mapping and then applied uni-

formly to all microRNAs. A candidate entered the prospective-validation set only when direct recurrence evidence was present in at least two analytically distinct samples—independent cohorts or separately recruited derivation and validation phases—and at least one additional domain supported further study: adjusted prognosis, mechanistic concordance, analytical feasibility, or external evidence. Selection did not depend on effect magnitude, direction, statistical significance, or inclusion in a pooled model. Molecular annotation distinguished experimentally supported targets or pathways, computational enrichment, phenotype-level association, and unresolved cellular or carrier source. The operational criteria and candidate-level evidence are reported in Supplementary Tables S5–S7.

2.8. Effect Selection and Coding

ORs and HRs were not combined. Reported directions were retained exactly as published in the reviewer-prompted restrictive sensitivity analysis; no outcome-informed direction folding was performed. Exposure units remained study-specific and non-commensurate. Reports without a uniquely eligible estimate under the restrictive hierarchy remained in the systematic review and candidate-specific evidence map but did not contribute to the cross-biomarker sensitivity model.

2.9. Statistical Analysis

Candidate-specific mapping was the primary synthesis. In response to peer review, cross-biomarker models were retained only as post hoc sensitivity analyses in the Supplementary Material. One estimate per independent cohort was selected hierarchically: (1) an author-designated primary prognostic biomarker or analysis; (2) the most fully adjusted compatible estimate; and (3) a pre-ablation measure with a prespecified recurrence outcome when otherwise equivalent. If multiple eligible biomarkers remained without a unique author-designated primary estimate, that cohort was excluded from the cross-biomarker model rather than selected by title, abstract order, effect magnitude, direction, or significance. Separate log-OR and log-HR models used restricted maximum likelihood with modified Hartung–Knapp confidence intervals; Q, I^2, τ^2, and prediction intervals were descriptive. The hierarchy is explicitly post hoc and reviewer-prompted. Complete decisions and results are reported in Supplementary Tables S8 and S10.

2.10. Code and Data Availability

The analysis-ready inputs, original and integrity-updated Python (Python Software Foundation; https://www.python.org/; accessed on 26 October 2026) scripts, versioned requirements, and machine-readable outputs are provided in the accompanying Supplementary Data. The protocol is available at https://osf.io/gd4p2/ (accessed on 29 August 2026; https://doi.org/10.17605/OSF.IO/GD4P2).

3. Results

3.1. Study Selection

The original database stream identified 1505 records. After removing 867 duplicates, 638 records were screened; 37 reports were sought, three were not retrieved, 34 were assessed in full, and 25 were excluded, yielding nine eligible publications. Targeted updating, citation searching, and historical evidence reappraisal added a further nine publications. The dated Wanfang amendment screened 50 records, excluded 29 at the title/abstract review stage, assessed 21 full texts, and excluded four, adding 17 more publications. The final review retained 35 publications (Figure 1; Supplementary Tables S2 and S9).

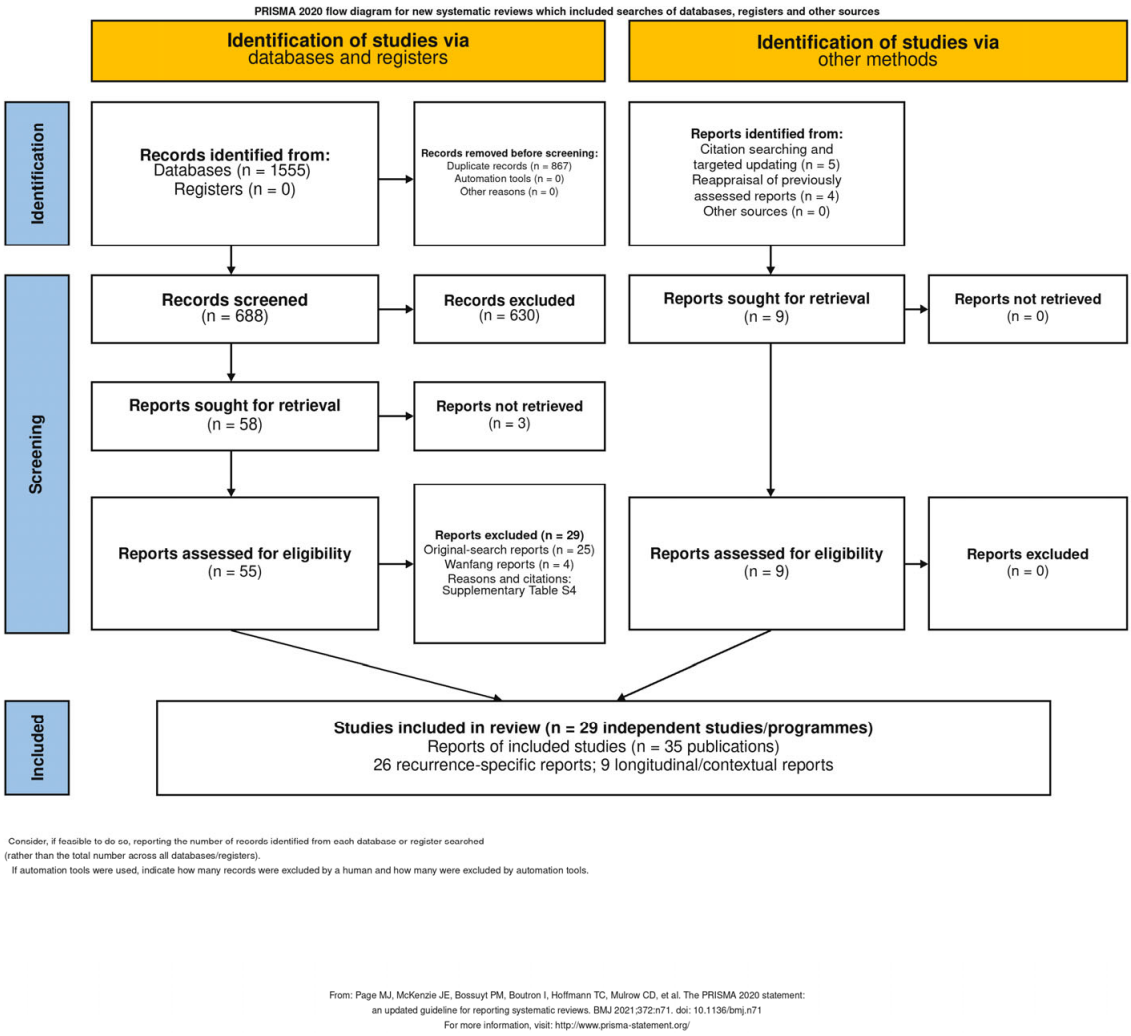


Figure 1. PRISMA 2020 flow diagram. The database stream contributed 26 publications after the dated Wanfang amendment; targeted updating, citation searching, and historical evidence reappraisal contributed nine. The final evidence base contained 35 publications representing 29 linked study/cohort programs. Of these, 26 addressed recurrence-specific prognosis, and nine contributed contextual longitudinal evidence. Adapted from the PRISMA 2020 flow diagram [18].

3.2. Study Characteristics

The 35 publications represented 29 linked studies or cohort programs under the overlap rules. Twenty-six publications reported recurrence-specific data from 25 independent recurrence cohorts: 3309 participants were enrolled and 3205 were analyzed. Nine publications contributed contextual longitudinal evidence. Follow-up ranged from 3 to 24 months, and sampling included baseline peripheral serum or plasma, intracardiac blood, and early post-ablation specimens. Recurrence definitions ranged from AF alone to AF or another atrial tachyarrhythmia after study-specific blanking periods. Rhythm surveillance ranged from scheduled electrocardiography or ambulatory monitoring to more intensive or symptom-triggered assessment, depending on the study. Intermittent surveillance may miss asymptomatic episodes and can therefore alter event detection and prognostic estimates. Study characteristics are summarized in Table 1; Table 2 lists only the estimates retained in the reviewer-prompted restrictive sensitivity set. Full assay details remain in Supplementary Tables S4–S6 [22–56].

Table 1. Characteristics of included studies and study populations.

Study	Country	Design	AF Population	Ablation	Enrolled/Analysed	Follow-Up, Mo	Evidence Role	Quantitative Status
Lai 2026 [38]	China	Retrospective single-center clinical cohort with GEO discovery/cross-validation	AF patients undergoing RFA; mixed AF phenotype	Radiofrequency ablation with circumferential pulmonary vein isolation	122/122	12	Prognostic cohort and two-miRNA risk-stratification model	Qualitative evidence retained; not selected in restrictive model
Šustr 2024 [34]	Czech Republic	Prospective monocentric discovery and qRT-PCR validation cohort	Paroxysmal and persistent AF	Catheter ablation guided by EnSite mapping systems	49/48	6	Prognostic discovery/validation study	Restrictive OR sensitivity set
Yue 2021 [24]	China	Longitudinal pre/post-ablation observational study	90 AF patients: 30 paroxysmal, 30 persistent, 30 permanent; 90 healthy controls	Radiofrequency ablation	90/—	3	Longitudinal peri-ablation expression study	Longitudinal only
Lage 2023 [31]	Spain	Prospective single-center cohort	Paroxysmal, persistent, and long-standing persistent AF	Point-by-point radiofrequency pulmonary vein isolation	42/42	24	Prognostic cohort with peripheral and left-atrial sampling	Restrictive OR sensitivity set
Zhan 2024 [35]	China	Prospective single-center cohort	Non-valvular AF undergoing first RFCA	Radiofrequency circumferential pulmonary vein isolation	134/100	12	Prognostic cohort and pre/post expression study	OR sensitivity only
He 2023 [33]	China	Prospective cohort as described by the authors	Paroxysmal AF undergoing first cryoablation	Cryoballoon ablation	66/66	12	Prognostic cohort	Systematic review only
Vardas 2026 [39]	Greece	Nested discovery case–control phase plus independent prospective validation cohort	Paroxysmal or persistent AF	Radiofrequency or pulsed-field ablation	155/126	12	Two-phase biomarker discovery and prospective validation	Restrictive OR sensitivity set
Liu 2016 [23]	China	Prospective AF-control discovery and longitudinal peri-ablation study	100 AF patients and 100 matched healthy controls	Radiofrequency catheter ablation	100/—	1–3	Longitudinal peri-ablation expression study	Longitudinal only
Pradhan 2023 [30]	Germany	Clinical validation cohort with mechanistic in vitro experiments	Paroxysmal and persistent AF; first and redo ablations	Radiofrequency pulmonary vein isolation	175/175	12	Prognostic validation and mechanistic study	Restrictive HR sensitivity set

Table 1. *Cont.*

Study	Country	Design	AF Population	Ablation	Enrolled/Analysed	Follow-Up, Mo	Evidence Role	Quantitative Status
Galenko 2019 [27]	United States	Observational registry cohort	AF patients undergoing RFCA	Radiofrequency catheter ablation	141/141	12	Prognostic cohort	Restrictive OR sensitivity set
Zhou 2018 [26]	Germany	Prospective observational cohort	Persistent AF undergoing first left-atrial ablation	Cryoballoon or radiofrequency PVI with optional substrate modification	102/102	12	Prognostic cohort and fibrosis-substrate study	Restrictive HR sensitivity set
Liu 2022 [29]	China	Single-center cohort	65 paroxysmal and 22 non-paroxysmal AF patients	Second-generation cryoballoon ablation	87/87	6	Prognostic cohort with peripheral and left-atrial sampling	Restrictive HR sensitivity set
Ruan 2025 [37]	China	Retrospective single-center study	Paroxysmal or persistent AF undergoing RFCA	Radiofrequency catheter ablation	43/43	6	Exosome-derived prognostic biomarker study	Systematic review only
McManus 2015 [22]	United States	Prospective miRhythm cohort with AF-control and pre/post-ablation analyses	112 AF patients and 99 controls; 47 ablation patients with paired samples	Catheter ablation	112/—	1	Longitudinal peri-ablation expression study	Longitudinal only
Vaze 2017 [25]	United States	Prospective miRhythm recurrence cohort	Symptomatic AF undergoing catheter ablation	Cryoballoon ($n = 33$) or radiofrequency ($n = 50$)	83/83	12	Prognostic recurrence cohort with a longitudinal subset	Qualitative evidence retained; not selected in restrictive model
Harada 2023 [32]	Japan	Prospective single-center two-stage sequencing and clinical validation study	AF ablation cohort; separate AF vs. SVT screening cohort	Cryoballoon or RF for paroxysmal AF; RF for persistent AF	141/141	12	Prognostic expression study with cardiac-specific discovery	Systematic review only
Ren 2025 [36]	China	Single-center observational cohort	Persistent AF undergoing first RFCA	Radiofrequency pulmonary vein isolation with optional linear ablation	126/126	12	Prognostic cohort	Qualitative evidence retained; not selected in restrictive model
Kiliszek 2020 [28]	Poland	Prospective discovery and independent ddPCR validation study	First-time AF ablation; predominantly paroxysmal AF	Radiofrequency pulmonary vein isolation with contact-force catheter	109/109	12	Prognostic discovery study with negative independent validation	Systematic review only
Liu Meichen 2025 [40]	China	Master's thesis; single-centre observational cohort	AF undergoing radiofrequency catheter ablation	Radiofrequency catheter ablation	150/150	12	Prognostic recurrence cohort	Qualitative evidence retained; not selected in restrictive model
Li 2023 [41]	China	Single-centre observational cohort	AF undergoing radiofrequency catheter ablation	Radiofrequency catheter ablation	158/158	6	Prognostic recurrence cohort	OR overlap sensitivity

Table 1. *Cont.*

Study	Country	Design	AF Population	Ablation	Enrolled/Analysed	Follow-Up, Mo	Evidence Role	Quantitative Status
Zhou 2024 [42]	China	Single-centre longitudinal recurrence cohort	AF undergoing radiofrequency catheter ablation	Radiofrequency catheter ablation	86/86	12	Recurrence-specific qualitative cohort	Systematic review only
Wang 2024 [43]	China	Single-centre observational cohort	Persistent AF undergoing radiofrequency catheter ablation	Radiofrequency catheter ablation	180/180	6	Prognostic recurrence cohort	Qualitative evidence retained; not selected in restrictive model
Li 2024 [44]	China	Single-centre observational cohort	Paroxysmal AF undergoing first radiofrequency catheter ablation	Radiofrequency catheter ablation	120/120	12	Prognostic recurrence cohort	Restrictive OR sensitivity set
Wang 2021 [45]	China	Single-centre observational cohort	Persistent AF undergoing radiofrequency catheter ablation	Radiofrequency catheter ablation	114/114	6	Recurrence-specific qualitative cohort	Systematic review only
Sun 2026 [46]	China	Single-centre observational cohort	Older patients with paroxysmal AF	Radiofrequency catheter ablation	205/205	12	Prognostic recurrence cohort	Restrictive OR sensitivity set
Kong 2025 [47]	China	Single-centre observational cohort	AF undergoing cryoablation	Cryoballoon ablation	210/200	6	Prognostic recurrence cohort	Restrictive OR sensitivity set
Wu 2025 [48]	China	Single-centre observational cohort	AF undergoing first radiofrequency catheter ablation	Radiofrequency catheter ablation	125/125	3	Prognostic recurrence cohort	Restrictive OR sensitivity set
Xu 2025 [49]	China	Single-centre observational cohort	Paroxysmal AF undergoing radiofrequency catheter ablation	Radiofrequency catheter ablation	155/155	12	Prognostic recurrence cohort	Restrictive OR sensitivity set
Lai 2023 [50]	China	Model-development cohort with training and validation samples	AF undergoing radiofrequency catheter ablation	Radiofrequency catheter ablation	389/359	12	Prognostic recurrence cohort	Qualitative evidence retained; not selected in restrictive model
Cui 2015 [51]	China	Longitudinal pre/post-ablation study	AF undergoing radiofrequency catheter ablation	Radiofrequency catheter ablation	30/—	3	Longitudinal peri-ablation expression study	Longitudinal only
Zhao 2015 [52]	China	Longitudinal pre/post-ablation profiling study	AF undergoing radiofrequency catheter ablation	Radiofrequency catheter ablation	30/—	3	Longitudinal peri-ablation expression study	Longitudinal only

Table 1. *Cont.*

Study	Country	Design	AF Population	Ablation	Enrolled/Analysed	Follow-Up, Mo	Evidence Role	Quantitative Status
Nan Jing 2015 [53]	China	Longitudinal pre/post-ablation study	AF undergoing radiofrequency catheter ablation	Radiofrequency catheter ablation	30/—	3	Longitudinal peri-ablation expression study	Longitudinal only
Xu 2016 [54]	China	Longitudinal intracardiac pre/post-ablation study	AF undergoing radiofrequency catheter ablation	Radiofrequency catheter ablation	30/—	3	Longitudinal peri-ablation expression study	Longitudinal only
Wang Yiran 2015 [55]	China	Longitudinal pre/post-ablation study	AF undergoing radiofrequency catheter ablation	Radiofrequency catheter ablation	30/—	3	Longitudinal peri-ablation expression study	Longitudinal only
Li Bing 2017 [56]	China	Longitudinal pre/post-ablation study	AF undergoing radiofrequency catheter ablation	Radiofrequency catheter ablation	60/—	1	Longitudinal peri-ablation expression study	Longitudinal only

Note: Across the 25 independent recurrence cohorts, 3309 participants were enrolled and 3205 were analyzed. Cohort totals are not the sample sizes of a single quantitative model: the restrictive OR and HR sensitivity analyses included 1162 and 364 participants, respectively. AF, atrial fibrillation; HR, hazard ratio; OR, odds ratio. Values and analytical roles are reproduced from the audited extraction dataset.GEO, Gene Expression Omnibus; RFA, radiofrequency ablation; RFCA, radiofrequency catheter ablation; RF, radiofrequency; PVI, pulmonary vein isolation; SVT, supraventricular tachycardia; qRT-PCR, quantitative reverse transcription polymerase chain reaction; ddPCR, droplet digital polymerase chain reaction.

Table 2. Effect estimates retained in the reviewer-prompted restrictive cross-biomarker sensitivity set.

Study	microRNA	n	Matrix/Sampling	Follow-Up	Measure	Analysis Estimate (95% CI)	SE	Selection Under Restrictive Hierarchy
Šustr 2024 [34]	miR-206	48	Peripheral plasma; pre-ablation	6 months	OR	2.650 (1.200–8.590)	0.502121	Author-designated primary prognostic biomarker
Lage 2023 [31]	miR-451a	42	Left-atrial plasma; pre-ablation	24 months	OR	0.715 (0.560–0.910)	0.123856	Author-designated primary prognostic biomarker
Vardas 2026 [39]	miR-10b-5p	126	Peripheral plasma; pre-ablation	12 months	OR	0.060 (0.010–0.330)	0.891983	Author-designated primary validation estimate

Table 2. *Cont.*

Study	microRNA	n	Matrix/Sampling	Follow-Up	Measure	Analysis Estimate (95% CI)	SE	Selection Under Restrictive Hierarchy
Galenko 2019 [27]	miR-150	141	Peripheral plasma; pre-/peri-ablation	12 months	OR	0.980 (0.965–0.999)	0.008833	Unique compatible model-based estimate
Li 2024 [44]	miR-21-5p	120	Peripheral serum; six hours post-ablation	12 months	OR	1.371 (1.021–1.892)	0.157363	Author-designated primary prognostic biomarker
Sun 2026 [46]	miR-101-3p	205	Peripheral serum; pre-ablation	12 months	OR	0.443 (0.263–0.746)	0.265967	Author-designated primary prognostic biomarker
Kong 2025 [47]	miR-320a	200	Peripheral serum; timing not reported	6 months	OR	2.655 (1.496–4.710)	0.292580	Author-designated primary prognostic biomarker
Wu 2025 [48]	miR-21	125	Peripheral serum; on admission	3 months	OR	0.121 (0.045–0.324)	0.503601	Unique compatible model-based estimate; coding retained as published
Xu 2025 [49]	miR-30a-5p	155	Peripheral serum; pre-ablation	12 months	OR	3.526 (2.106–5.904)	0.262974	Author-designated primary prognostic biomarker
Pradhan 2023 [30]	miR-21-5p	175	Arterial serum; pre-ablation	12 months	HR	1.104 (0.398–3.063)	0.520596	Reported primary HR
Zhou 2018 [26]	miR-21	102	Peripheral serum; pre-ablation	12 months	HR	1.736 (1.301–2.316)	0.147122	Reported primary HR
Liu 2022 [29]	miRNA21	87	Left-atrial plasma; pre-ablation	6 months	HR	1.168 (1.044–1.307)	0.057316	Reported primary HR

Note: Estimates are retained exactly as reported. The microRNAs, matrices, sampling times, exposure units, and assay scales are not commensurate; numerical effects cannot be compared directly across rows and do not represent a common biological class effect. CI, confidence interval; HR, hazard ratio; OR, odds ratio; SE, standard error.

3.3. Risk of Bias

The risk of bias ranged from low or moderate to high across the 26 recurrence-specific reports. Representative concerns included incomplete reporting of preanalytical handling or normalization, limited adjustment for established clinical predictors, recurrence ascertainment based on intermittent rather than continuous monitoring, and selective or internally inconsistent model reporting. For example, some cohorts lacked a fully specified adjustment set, whereas others reported several biomarkers without a uniquely designated primary prognostic analysis. Eligibility was not based on these judgments (Supplementary Figure S3).

3.4. Candidate-Specific Molecular and Translational Map

Applying the post hoc framework uniformly identified six priorities for prospective validation: miR-21-5p, miR-150-5p, miR-29b-3p, miR-451a, miR-10b-5p, and miR-320a. These are research priorities rather than established biomarkers. Mature-arm-specific names are used in the synthesis; arm-unspecified labels from legacy studies are retained only where assay documentation did not permit mature-arm assignment. The candidate evidence, molecular interpretation, source/carrier uncertainty, and candidate-specific certainty are summarized in Tables 3, S7 and S11.

Table 3. Candidate-centered molecular and translational evidence map.

Candidate	Direct Recurrence Evidence	Molecular Context	Source/Carrier Status	Principal Limitation	Interpretive Status
miR-21-5p (legacy miR-21)	Multiple peripheral and intracardiac reports; direction varies by compartment, assay, and coding [26,29,30,36,44,48].	Fibroblast cross-talk and Spry1-supported profibrotic signaling [30,57].	Serum/plasma; atrial and extracellular-vesicle source unresolved.	Arm, matrix, compartment, platelet/hemolysis effects, and coding.	Prospective-validation priority; certainty very low.
miR-150-5p (legacy miR-150)	Recurrence-specific and longitudinal evidence, including adjusted estimates and post-ablation kinetics [22,38,42,50,56].	Experimental inhibition of fibroblast activation through c-Myb [58].	Circulating source and carrier unresolved; legacy labels are not arm confirmation.	Legacy labels, scale, normalization, and blood-cell/platelet contribution.	Prospective-validation priority; certainty very low.
miR-29b-3p (legacy miR-29b)	Several recurrence reports; one estimate had a non-computable confidence bound [35,41,50].	ECM/collagen regulation and experimentally supported PDGF-B signaling [59,60].	Serum/plasma may reflect systemic matrix turnover; atrial source unconfirmed.	Arm attribution, scale, attrition, and one zero confidence bound.	Prospective-validation priority; certainty very low.
miR-451a	Lower left-atrial abundance was associated with recurrence; a second cohort reported an adjusted inverse association [31,40].	Phenotype-level association with atrial scar; no validated atrial target pathway.	Erythrocyte-enriched and highly hemolysis-sensitive [61,62].	Hemolysis, sampling compartment, and small event counts.	Prospective-validation priority; certainty very low.

Table 3. *Cont.*

Candidate	Direct Recurrence Evidence	Molecular Context	Source/Carrier Status	Principal Limitation	Interpretive Status
miR-10b-5p	Two-phase discovery and separately recruited internal validation; lower expression was associated with recurrence [39].	FOXO, p53, senescence, and circadian enrichment analyses were performed in silico [39].	Atrial cellular source, carrier fraction, and tissue concordance unresolved.	Single center, discovery multiplicity, mixed technologies, no target validation.	Prospective-validation priority; certainty very low.
miR-320a (also reported as miR-320a-3p)	Adjusted estimates in two cohorts with different matrices, labels, sampling, and model reporting [40,47].	Remodeling-associated extracellular signal; atrial target unvalidated [63].	Serum/plasma; extracellular-vesicle enrichment not established.	Matrix/arm differences, unclear timing, model inconsistency.	Prospective-validation priority; certainty very low.

Note: The pale blue header shading distinguishes column headings and has no analytical meaning. ECM, extracellular matrix.

3.5. Secondary Exploratory Quantitative Synthesis

Nine independent cohorts ($n = 1162$) contributed fixed-time ORs and three cohorts ($n = 364$) contributed HRs under the reviewer-prompted restrictive hierarchy. Six OR cohorts that had been selected only through the earlier title/abstract-order rule were not retained in this sensitivity model; their qualitative and candidate-specific evidence remains in the review. Figure 2 presents the selected study-level estimates without a pooled diamond.

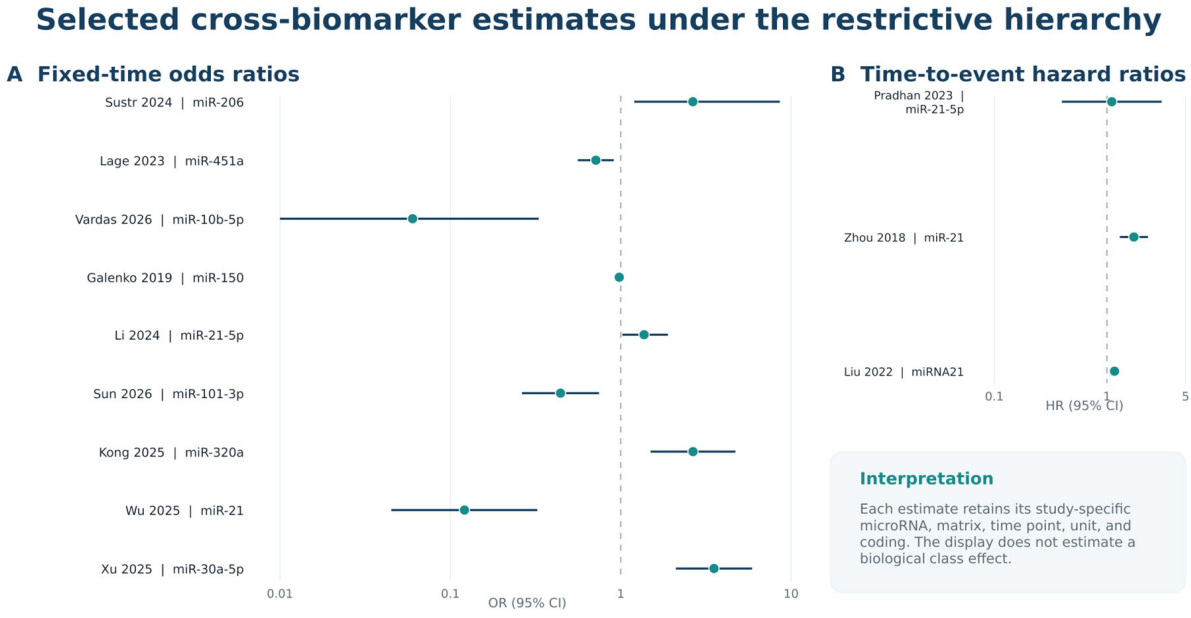


Figure 2. Study-level estimates retained under the reviewer-prompted restrictive hierarchy. Panel (**A**) displays nine fixed-time ORs and panel (**B**) displays three reported HRs. No pooled diamond is shown because the molecules and their assay scales are non-commensurate; the figure does not estimate a biological class effect. Teal circles indicate point estimates, horizontal dark blue lines indicate 95% confidence intervals, and vertical dashed lines indicate the null value of 1. Axes use logarithmic scales. Sources: Šustr et al. [34], Lage et al. [31], Vardas et al. [39], Galenko et al. [27], Li et al. [44], Sun et al. [46], Kong et al. [47], Wu et al. [48], Xu et al. [49], Pradhan et al. [30], Zhou et al. [26], and Liu et al. [29].

The estimates varied in direction and magnitude across different microRNAs, matrices, compartments, sampling times, and assay scales. Because these exposures are not biologi-

cally or analytically commensurate, the main text does not interpret an average class effect. Secondary random-effects model estimates and leave-one-out checks are reported only as sensitivity analyses in Supplementary Table S8 and Supplementary Figures S1 and S2.

3.6. Candidate-Specific Certainty of Evidence

Candidate-specific certainty was very low for each of the six prioritized microRNAs. The reasons differed by candidate but included risk of bias, limited independent replication, inconsistent matrices or compartments, mature-arm and assay uncertainty, small samples, imprecise estimates, and suspected selective reporting. Mechanistic plausibility did not upgrade certainty for clinical prognosis, and no candidate had enough independent studies for a meaningful funnel-plot or asymmetry test (Supplementary Table S11).

4. Discussion

The main finding is a candidate-specific molecular map rather than a pooled microRNA class effect. miR-21-5p and miR-150-5p have the strongest recurrence-specific support; miR-29b-3p, miR-451a, and miR-10b-5p link clinical signals to extracellular matrix-, scar-, or senescence-related biology; and miR-320a has model-based evidence of recurrence but limited mechanistic specificity. These markers form a prospective validation set rather than established clinical tests, and the molecular map is an evidence-organization framework rather than a clinical ranking.

Pooling different microRNAs cannot establish the prognostic value of any individual candidate. Opposite associations across biologically distinct molecules can average toward the null, and a random-effects model does not correct non-commensurate exposure units, compartments, or sampling times. Accordingly, the revision removes the outcome-informed adverse-profile fold, omits pooled class-effect estimates from the Abstract and primary Results, and relegates the restrictive OR and HR summaries to the Supplementary Material as sensitivity analyses. Their prediction intervals were 0.04–16.69 for the OR model and 0.04–46.36 for the HR model. Both intervals cross 1 widely, indicating substantial uncertainty about the direction and magnitude of association in a new population. The Chinese-language amendment expanded the eligible evidence base, while explicit cohort linkage prevented overlapping publications from receiving duplicate quantitative weight.

4.1. Molecular Interpretation: Signal, Source, and Mechanism

Three interpretive layers must remain separate. First, measured abundance depends on matrix, processing, normalization, and exposure coding. Second, the circulating carrier and cellular source may include extracellular vesicles, protein-bound RNA, platelets, erythrocytes, leukocytes, injured cardiomyocytes, fibroblasts, or altered clearance. Exosomes can transfer functional microRNAs between cells [64], but most recurrence cohorts quantify total circulating RNA and do not isolate a carrier fraction. Third, a validated target pathway in experimental tissue does not prove that the corresponding blood measurement is a causal mediator. This separation is central to the molecular synthesis in Figure 3.

The strongest mechanistic convergence concerns fibrosis. miR-21 participates in cardiomyocyte–fibroblast cross-talk and experimental atrial profibrotic signaling involving Spry1, yet arterial, venous, peripheral, and left-atrial findings are discordant [26,29,30,36,44,48,57]. miR-29b is an antifibrotic regulator of extracellular-matrix programs; experimental overexpression of miR-29b-3p in a rat model reduced atrial fibrosis, collagen I, and alpha-smooth muscle actin (α-SMA), increased connexin 43 (Cx43), and directly suppressed PDGF-B [59,60]. miR-150 inhibits cardiac-fibroblast activation through c-Myb [58], but clinical evidence includes arm-unspecified labels and non-commensurate concentration scales. These mechanisms support plausibility, not transportable prediction.

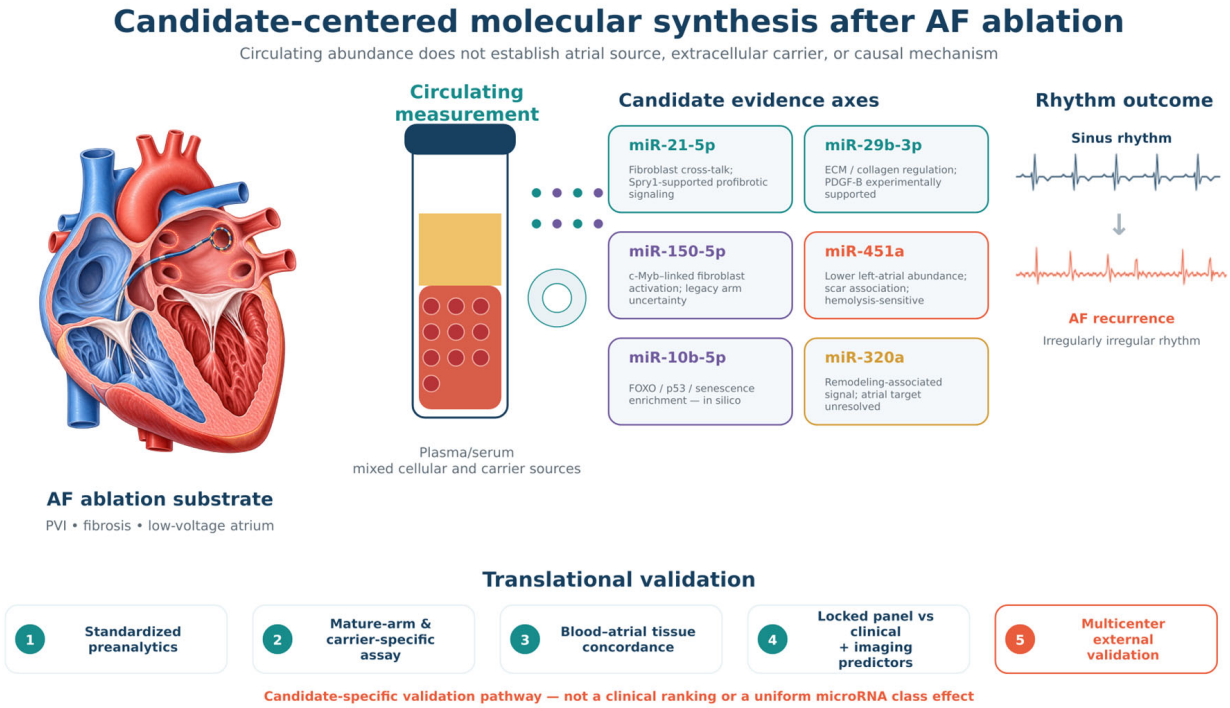


Figure 3. Candidate-centered molecular synthesis and translational validation pathway. The six priorities are organized by their best-supported experimental, computational, or phenotype-level axis while preserving uncertainty about cellular source and extracellular carrier. The electrocardiographic sequence distinguishes regular sinus rhythm from irregularly irregular AF recurrence. The lower sequence shows the analytical and clinical gates required before implementation. Candidate-box colors group the displayed evidence axes: teal, experimental profibrotic or extracellular-matrix signaling; purple, c-Myb-linked biology or computational pathway enrichment; coral, scar association and hemolysis sensitivity; and gold, a remodeling-associated signal with an unresolved atrial target. These colors do not denote certainty or clinical rank. The colored dots and carrier symbol are schematic and do not establish a cell or carrier of origin. Blue and coral electrocardiographic traces illustrate sinus rhythm and AF recurrence, respectively; the five numbered circles indicate sequential validation steps. PVI, pulmonary vein isolation; ECM, extracellular matrix.

The other candidates illustrate distinct translational hazards. Lower left-atrial miR-451a abundance was associated with recurrence, whereas greater scar burden was positively associated with recurrence; a second cohort reported an adjusted inverse association [31,40]. Erythrocyte enrichment makes objective control of hemolysis indispensable [61,62], and no atrial target pathway has been confirmed in recurrence cohorts. For miR-10b-5p, FOXO, p53, cellular senescence, and circadian pathways were identified through in silico enrichment of validated targets; the study did not demonstrate a causal mechanism [39]. Circulating extracellular miR-320a-3p has been associated with paroxysmal AF [63], and two recurrence cohorts reported adjusted estimates of miR-320a [40,47], but matrices, mature-arm labels, sampling details, and model reporting differed. None of these signals establishes extracellular-vesicle transport or concordance with atrial tissue.

4.2. Analytical Validity and Sampling Time

Analytical validity is the first translational gate. Serum versus plasma, anticoagulant, processing delay, platelet activation, hemolysis, extraction efficiency, normalization, and freeze–thaw history can materially alter abundance [61,62,65,66]. A lower concentration can denote risk for one marker, while a higher ΔCq denotes lower expression for another; neither is equivalent to outcome-informed folding toward an adverse profile. Future studies should prespecify collection and processing, document hemolysis and platelet depletion;

use validated reference or spike-in strategies; report assay linearity, limits, and precision; and state whether total, protein-bound, or extracellular vesicle-enriched RNA is measured.

Sampling time is a biological design variable rather than a convenience. Baseline concentrations may reflect pre-existing atrial substrate, immediate peri-procedural measurements may capture injury or inflammation, and later changes may accompany reverse remodeling. The nine contextual longitudinal publications describe dynamic peri-ablation expression but cannot support recurrence prognosis without adjusted, recurrence-specific effects. Baseline prognostic and pharmacodynamic sampling should therefore be analyzed as separate questions.

4.3. Clinical Validation Pathway

Clinical utility remains unestablished. Association and prediction are distinct, and few studies reported calibration, optimism correction, decision curves [67], or incremental performance beyond clinical and imaging variables. Future incremental-value analyses should compare prespecified microRNA models against established clinical and imaging predictors, use separate model-development and external-validation cohorts, and avoid data-driven re-selection of biomarkers or cut points. A multicenter program should assay the six candidates individually and as a locked panel; blind laboratories to outcomes; standardize rhythm surveillance; and evaluate calibration, discrimination, reclassification, and decision curves across AF phenotypes and ablation technologies. Nested tissue, left-atrial/peripheral, and carrier-fraction substudies would determine whether prediction and molecular source are concordant.

4.4. Strengths and Limitations

Strengths include eligibility criteria independent of study results or quality, separation of publications from linked programs, prevention of duplicate weighting, source-based risk-of-bias judgments, and reproducible code. Limitations include incomplete bibliographic identities for part of the historical full-text exclusion log, probable rather than confirmed overlap within the five-report Beijing program, candidate prioritization developed post hoc, substantial clinical heterogeneity, non-commensurate assay units, internal inconsistencies in several reports, and limited candidate-specific replication. The reviewer-prompted quantitative hierarchy is also post hoc and cannot remove conceptual non-commensurability. These limitations support candidate mapping as the primary approach and quantitative pooling only as a supplementary sensitivity analysis.

5. Conclusions

Candidate-specific mapping identified miR-21-5p, miR-150-5p, miR-29b-3p, miR-451a, miR-10b-5p, and miR-320a as priorities for hypothesis-driven prospective validation after AF ablation. Their certainty is very low, and their molecular contexts, biological sources, matrices, and assay scales differ. The available evidence does not establish a common direction, a uniform circulating-microRNA class effect, or clinical utility. Translation requires standardized preanalytics, mature-arm and carrier-specific assays, prespecified models, independent multicenter validation, and demonstration of incremental value beyond established clinical and imaging predictors.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biom16111590/s1. Supplementary Methods S1–S5 describe the search update, evidence layers and cohort linkage, effect selection, statistical sensitivity analyses, and candidate-specific certainty assessment. Table S1 presents the search strategies; Tables S2A and S2B provide the PRISMA 2020 and abstract checklists; Table S3 presents the translational evidence-mapping framework; Table S4 documents contextual reports and full-text exclusions; Tables S5 and S6 describe candidate

prioritization and phenotype-oriented interpretation; Table S7 presents the candidate-specific evidence map; Table S8 reports the restrictive sensitivity models; Table S9 documents the Wanfang update; Table S10 provides the effect-selection audit; and Table S11 provides candidate-specific GRADE profiles. Figures S1–S3 show the exploratory models, leave-one-out analyses, and QUIPS judgments. Sources cited in Table S4 are included in the main reference list [15,23,24,51–56,68–93].

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