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Intravascular Hemolysis and the Spectrum of Tissue Injury Following Pulsed Field Ablation for Atrial Fibrillation: A Systematic Review of Clinical Markers, Catheter Designs, and Renal Outcomes

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Abstract

Pulsed field ablation (PFA) is a novel treatment option for atrial fibrillation (AF) that offers myocardial selectivity and tissue-specific ablation. However, its systemic effects, particularly intravascular hemolysis and potential downstream renal injury, remain incompletely characterized. This systematic review aimed to synthesize the available evidence regarding hemolysis biomarkers, renal outcomes, tissue injury, and the influence of PFA catheter design. A comprehensive literature search of PubMed, the Cochrane Library, Embase, and Scopus was conducted from inception through April 2026. Prospective, retrospective, cohort, registry-based, and cross-sectional studies evaluating systemic or renal effects following PFA for AF, including intravascular hemolysis and catheter-related outcomes, were eligible for inclusion. Outcomes of interest included hemolysis biomarkers (lactate dehydrogenase (LDH), haptoglobin, free plasma hemoglobin (fHb), and bilirubin), acute kidney injury (AKI), hemoglobinuria, and markers of tissue injury. The risk of bias in the included studies was assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. A quantitative meta-analysis was not feasible because of substantial clinical and methodological heterogeneity and the limited availability of comparable numerical data across studies. Therefore, the findings were synthesized narratively using a qualitative synthesis approach. Nine studies involving 18,439 patients were included in the qualitative synthesis. All studies demonstrated evidence of postprocedural intravascular hemolysis. LDH increased by 63-160 U/L ($p < 0.001$), while haptoglobin decreased by up to 1.22 g/L ($p < 0.001$). fHb increased approximately 5- to 12-fold, and bilirubin levels consistently increased following PFA. Biochemical AKI occurred in 3.2-7.0% of patients and demonstrated a dose-dependent association with PFA exposure, whereas clinically severe AKI was rare (0.03%). Hemoglobinuria was reported in up to 75% of dehydrated patients in the reported study; however, the available evidence is insufficient to determine whether adequate periprocedural hydration prevents hemoglobinuria or AKI. Neurological assessments and cerebral imaging revealed limited evidence of clinically overt neurological events or radiologically detected acute cerebral ischemic injury, whereas biomarkers of myocardial injury increased following the procedure. Pentaspline catheter systems were associated with greater degrees of hemolysis and renal injury than balloon-based, circular-array, and monopolar systems, suggesting that catheter design may substantially influence systemic outcomes. PFA is consistently associated with substantial but predictable intravascular hemolysis, while clinically severe renal complications remain uncommon. The magnitude of hemolysis and renal effects appears to be influenced by procedural dose, catheter design, and hydration status. Optimization of these procedural factors, particularly adequate hydration and catheter selection, may reduce systemic effects and improve the safety profile of PFA.

Categories: Cardiology, Internal Medicine
Keywords: atrial fibrillation, catheter designs, intravascular hemolysis, renal outcomes, spectrum

Introduction And Background

Atrial fibrillation (AF) remains the most prevalent sustained cardiac arrhythmia worldwide and is associated with substantial morbidity, including stroke, heart failure, and impaired quality of life. Traditionally, heat-based modalities such as radiofrequency ablation and cryoablation have been used, and catheter ablation has emerged as a key component of rhythm-control strategies. Alternative energy sources with better safety profiles are being developed because these methods are associated with collateral tissue damage, including esophageal injury, pulmonary vein stenosis, and thromboembolic complications [1,2].

Because of its tissue selectivity and lower risk of extracardiac harm, pulsed field ablation (PFA), a nonthermal approach based on irreversible electroporation, has become a viable option for AF ablation [3]. PFA has demonstrated favorable procedural efficiency and safety outcomes by preferentially targeting cardiac cells while protecting surrounding structures. However, tissue selectivity does not completely prevent exposure of circulating blood cells to the electrical field. During PFA delivery, high-voltage electrical pulses can permeate the blood pool surrounding the catheter and induce electroporation of circulating erythrocytes. The formation of transient or irreversible membrane pores may cause ion leakage, osmotic imbalance, and erythrocyte disruption, resulting in intravascular hemolysis. The resulting release of free hemoglobin into the circulation can exceed endogenous haptoglobin-mediated scavenging capacity and, particularly when hemolysis is substantial, may lead to hemoglobinuria and contribute to renal tubular injury through heme-mediated oxidative and cytotoxic mechanisms [2-6]. The extent of hemolysis may vary according to electrical field characteristics, the number of energy applications, catheter-tissue interaction, and catheter configuration [5,6]. Biochemical evidence of hemolysis can be detected using complementary laboratory markers: increased plasma-free hemoglobin reflects the direct release of hemoglobin from lysed erythrocytes; decreased haptoglobin reflects consumption of this hemoglobin-scavenging protein; increased lactate dehydrogenase (LDH) reflects erythrocyte destruction and cellular injury; and increased bilirubin, particularly the unconjugated fraction, may reflect subsequent hemoglobin catabolism [4,5]. Consequently, growing clinical evidence indicates that intravascular hemolysis is a reproducible biochemical phenomenon following PFA, characterized by decreases in haptoglobin and increases in plasma-free hemoglobin, LDH, and bilirubin [4,5].

Research on the clinical significance of PFA-induced hemolysis is ongoing. Although most studies report mild and transient hemolysis, concerns remain about its possible downstream effects, particularly acute kidney injury (AKI), which may result from oxidative stress and hemoglobin-mediated tubular toxicity [6]. Interestingly, recent meta-analyses indicate that although PFA is associated with considerably higher levels of hemolysis biomarkers than thermal ablation, this does not always translate into a higher incidence of clinically apparent AKI [7]. The importance of procedural optimization is further highlighted by recent findings showing that the degree of hemolysis may vary with catheter design, energy delivery parameters, and ablation platform [7].

Despite these emerging data, important gaps remain in the current literature. Existing studies have primarily evaluated hemolysis biomarkers and procedural safety in isolation. In contrast, the relationships between the magnitude of hemolysis and downstream renal, neurological, radiological, and myocardial effects remain incompletely characterized. In addition, evidence regarding the influence of catheter configuration, procedural dose, and hydration status on hemolysis and renal outcomes is fragmented and heterogeneous, and the available findings have not been comprehensively synthesized across different PFA platforms. Therefore, a systematic evaluation of these outcomes is warranted.

The purpose of this systematic review is to synthesize the available evidence regarding the extent of intravascular hemolysis following PFA, its potential renal and systemic consequences, and the influence of catheter technology and procedural factors on these outcomes, with particular emphasis on renal safety.

Review

Methods

Study Design and Registration

The PRISMA statement was followed in conducting this systematic review (CRD420261387507) [8].

Study Selection

Electronic databases, including PubMed, the Cochrane Library, Embase, and Scopus, were systematically searched from inception through April 30, 2026, to identify studies evaluating intravascular hemolysis, tissue injury, catheter design, and renal outcomes following PFA for AF. The search strategy combined terms related to PFA and AF (e.g., “pulsed field ablation”, “PFA”, and “atrial fibrillation”) with terms related to hemolysis biomarkers and clinical outcomes, including “hemolysis”, “lactate dehydrogenase”, “haptoglobin”, “free hemoglobin”, “bilirubin”, “hemoglobinuria”, “acute kidney injury”, “renal dysfunction”, “troponin”, “cardiac injury”, and “brain injury”, as well as catheter-specific terms such as “FARAWAVE”, “VOLT”, and “PulseSelect”, using relevant synonyms and Boolean operators. Studies reporting biochemical markers of hemolysis, AKI, hemoglobinuria, cardiac injury, brain injury, or other relevant clinical outcomes were considered. Complete database-specific search strategies are provided in Appendix A.

To ensure methodological rigor and minimize selection bias, the study selection process was conducted independently by two reviewers (SMU and GT). After duplicate records were identified and removed using Zotero, the titles and abstracts of all retrieved records were independently screened by two investigators (JA and NM) using Rayyan. Records considered potentially relevant or for which eligibility could not be determined from the title and abstract were retrieved for full-text assessment. Full-text articles were independently evaluated against the predefined inclusion and exclusion criteria. Any disagreements

between the investigators at either the title/abstract or full-text screening stage were resolved through discussion and consensus (FN); when consensus could not be reached, a third investigator was consulted for final adjudication. The screening process and reasons for exclusion at the full-text stage were documented to ensure transparency and reproducibility.

Eligibility Criteria

Studies were included if they met the following criteria: (1) a prospective, retrospective, cohort, registry-based, or cross-sectional study design; (2) enrollment of patients with AF undergoing PFA; (3) evaluation of PFA-related systemic, renal, hemolysis, neurological/radiological, or tissue injury outcomes; (4) reporting of at least one relevant outcome, including hemolysis biomarkers such as LDH, haptoglobin, plasma-free hemoglobin, or bilirubin; renal outcomes, including AKI or hemoglobinuria; or other markers of systemic or tissue injury; and (5) publication as a full-text, peer-reviewed article in English.

Studies were excluded if they (1) did not involve patients with AF undergoing PFA; (2) did not report outcomes relevant to hemolysis, renal injury, systemic effects, neurological/radiological outcomes, or tissue injury; (3) were case reports or case series; (4) were reviews, systematic reviews, meta-analyses, editorials, letters, commentaries, or conference abstracts/proceedings; (5) lacked accessible full-text information; or (6) were published in languages other than English (Table *1*).

Component	Description across the nine studies
Population (P)	Patients with symptomatic paroxysmal or persistent AF undergoing catheter ablation.
Intervention (I)	PFA using various platforms, including pentaspline (FARAPULSE), circular-array (PulseSelect, VARIPULSE), balloon-in-basket (VOLT), or lattice-tip (Affera) catheters.
Comparison (C)	Conventional radiofrequency ablation, head-to-head comparisons of different PFA catheter designs, different application doses (e.g., 8 vs. 16 pulses), or hydration protocols.
Outcomes (O)	Intravascular hemolysis: Changes in haptoglobin, LDH, total and indirect bilirubin, fHb, and red blood cell microparticles. Tissue injury: AKI and creatinine changes, myocardial injury (troponin, creatine kinase-MB), and neural injury (S100).
Study design (S)	Prospective and retrospective observational studies, quasi-randomized controlled trials, and large-scale multicenter registries.

TABLE 1: Inclusion criteria of included studies according to the PICOS framework.

AF, atrial fibrillation; AKI, acute kidney injury; fHb, free plasma hemoglobin; LDH, lactate dehydrogenase; PFA, pulsed field ablation

Extraction of Data

To ensure consistency and completeness, data extraction was carried out using a uniform, structured template. Study characteristics (author, year, and study design), population details (sample size and patient demographics), procedure parameters (type of PFA catheter and number of applications), and outcomes of interest were among the variables extracted. Hemolysis indicators, including LDH, haptoglobin, fHb, and bilirubin, were among the main outcomes. Secondary outcomes included the incidence of AKI; alterations in renal function (creatinine and estimated glomerular filtration rate (eGFR)); hemoglobinuria; cardiac injury markers (troponin and creatine kinase); neurological injury markers (S100 protein); and dose-response correlations between PFA treatments and hemolysis severity. Furthermore, catheter design features and their correlations with outcomes were systematically documented.

Quality Assessment of Included Studies

The methodological quality and risk of bias of the included studies were assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [9]. The assessment was conducted independently by two investigators (HB and TA) across the seven predefined domains: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result. Each domain was judged as having a low, moderate, serious, or critical risk of bias, or as having no information when the available evidence was insufficient to make a judgment. Disagreements between the investigators were resolved through discussion and consensus, with consultation of a third investigator (FKP) when necessary. The overall risk of bias for each study was determined based on the domain-level assessments according to the ROBINS-I framework.

Data Synthesis

Due to substantial clinical and methodological heterogeneity among the included studies, a quantitative meta-analysis was not performed. The included studies differed considerably in catheter platforms and configurations, procedural characteristics, definitions and assessment of hemolysis, biomarker measurement methods, timing of outcome assessment, and reporting of renal and other systemic outcomes. In addition, considerable variation was observed in the reporting of statistical measures, including means, medians, SDs, ranges, and interquartile ranges, as well as differences in measurement units and laboratory reporting methods across studies. These discrepancies limited the direct comparability and reliable quantitative pooling of the reported outcomes. Therefore, statistical pooling was considered inappropriate and potentially misleading. Instead, the findings were qualitatively and narratively synthesized, with results organized according to hemolysis biomarkers, renal outcomes, other systemic effects, and catheter- and procedure-related factors. Where appropriate, patterns and consistencies across studies were compared descriptively, while differences in study design, populations, statistical reporting, measurement units, and outcome assessment were considered when interpreting the findings.

Results

Study Selection

A total of 3,519 records were identified through database searches, including 1,198 from PubMed, 265 from Embase, 1,489 from Scopus, and 567 from the Cochrane Library. After 688 duplicate records were removed, 2,831 records remained for title and abstract screening. Of these, 453 records were excluded, leaving 2,378 reports sought for retrieval. Thirteen reports could not be retrieved; therefore, 2,365 reports were assessed for eligibility. Following full-text assessment, 2,356 reports were excluded because of an ineligible population (n = 1,199), an ineligible intervention (n = 467), or ineligible outcomes (n = 690). Ultimately, nine studies [10-18] were included in the systematic review. The complete study selection process is presented in the PRISMA flow diagram (Figure *1*).

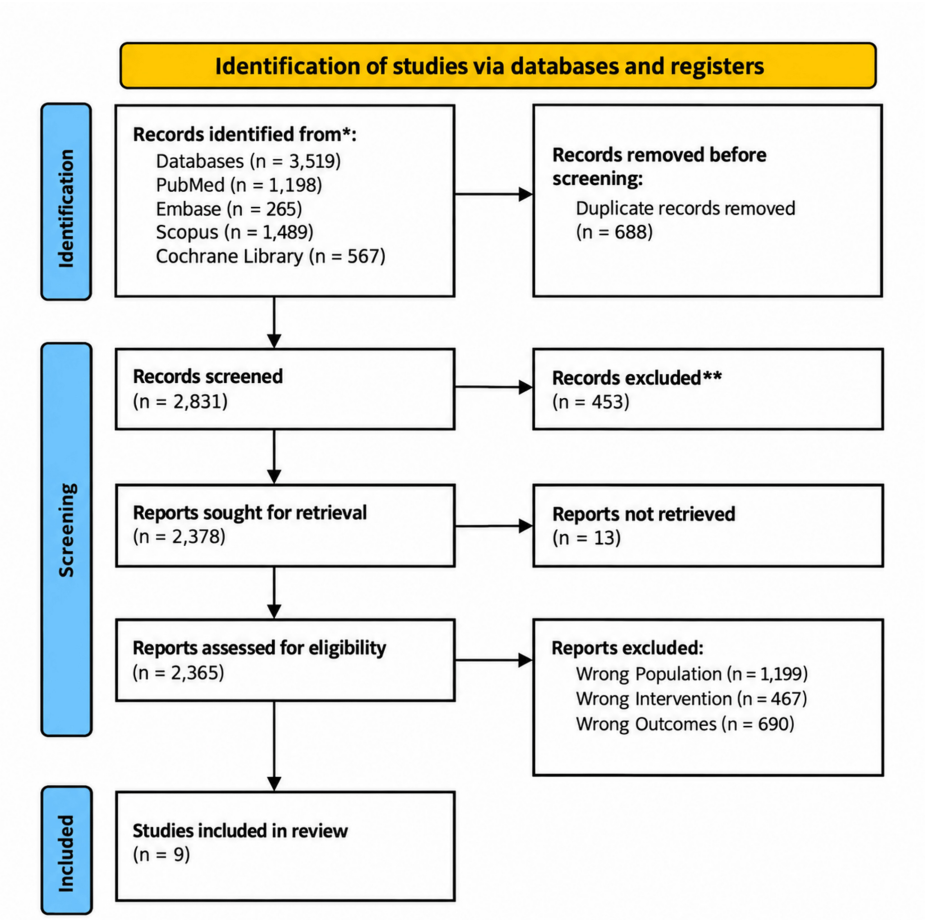

FIGURE 1: PRISMA flow diagram of included studies.

* Indicate the number of records identified from each database or register searched.

** Indicate the number of records excluded during screening.

Baseline Characteristics and Patient Demographics

The nine included studies comprised a total reported population of 18,439 patients undergoing PFA for AF. Study sample sizes ranged from 47 PFA-treated patients to 17,642 patients. The studies included prospective nonrandomized, prospective observational, prospective case-series, multicenter, retrospective observational, prospective real-world, and registry-based designs. The mean or median age of participants generally ranged from approximately 64 to 71 years, indicating a predominantly older population. Male participants accounted for approximately 38.3-75% of the study populations. Paroxysmal AF was the predominant AF phenotype, with reported proportions ranging from approximately 35% to 66.7%, while persistent AF accounted for a smaller proportion where reported. Baseline hypertension was common across studies, with reported prevalence ranging from approximately 44% to 88%, whereas diabetes mellitus was less frequent, ranging from approximately 6% to 21%. Some studies included mixed AF populations or reported ranges for baseline characteristics across different treatment groups. Detailed baseline characteristics of the included studies are presented in Table *2*.

Author (year)	Study design	Sample size (N)	Age (years)	Male (%)	AF type (paroxysmal/persistent)	Baseline comorbidities (HTN/DM)
Ekanem et al. (2024) [10]	Retrospective registry	17,642 (MANIFEST-17K)	64 (11-96)	65.30%	57.8% paroxysmal/35.2% persistent	NR
Venier et al. (2023) [11]	Prospective cohort	68	64.3 ± 10.5	75.00%	35.0% paroxysmal/29.0% persistent/35.0% LSP	HTN: 44.0%; DM: 12.0%
Gold et al. (2025) [12]	Prospective analysis	68 (40 Affera/14 Select/14 FARA)	65-70 (medians)	62.5-71.4%	47.5-71.4% paroxysmal	HTN: 64.3-85.7%; DM: 0-21.4%
Wenzel et al. (2026) [13]	Prospective, nonrandomized	81 (35 VOLT/46 FARAPULSE)	66.0-69.5 (medians)	47.8-60.0%	48.6-63.0% paroxysmal	HTN: 51.4-65.2%; DM: 6.5-17.1%
Popa et al. (2024) [14]	Multicenter analysis	215 (145 PFA/70 RFA)	65.7 ± 9.8	69.3% (71.7% in PFA)	49.8% paroxysmal/50.2% persistent	HTN: 55.8%; DM: 12.4-17.1%
Stojadinović et al. (2024) [15]	Prospective observational	60	68 (62-72)	72.00%	51.7% paroxysmal	HTN: 88.0%; DM: 10.0%
Osmancik et al. (2024) [16]	Prospective, nonrandomized	70 (47 PFA/23 RFA)	64.7 ± 10.2	53.0% (59.6% in PFA)	51.4% paroxysmal	HTN: 78.7%; DM: 19.1% (PFA arm)
Kuraoka et al. (2025) [17]	Retrospective observational	120 (39 FARA/66 Select/15 RF)	71.2 ± 10.3	61.7% (53.8-68.2% across PFA)	66.7% paroxysmal	HTN: 63.6-73.3%; DM: 17.9-26.7%
Martinez et al. (2026) [18]	Prospective real-world	115	70.6 ± 10.8	65.20%	Mixed (100% PVI + 94% extra-PV)	HTN: ~88.0%; DM: ~15.0%

TABLE 2: Baseline characteristics and patient demographics.

Data are presented as reported by the primary studies. Continuous variables are expressed as mean ± SD, median (range/IQR), or range of reported cohort values, whereas categorical variables are presented as percentages or ranges of percentages.

AF, atrial fibrillation; DM, diabetes mellitus; HTN, hypertension; LSP, long-standing persistent; NR, not reported; PFA, pulsed field ablation; PVI, pulmonary vein isolation; RF, radiofrequency; RFA, radiofrequency ablation

Risk of Bias Assessment Using ROBINS-I

The risk of bias in the nine included studies was assessed using the ROBINS-I tool across seven domains [9]. Overall, five studies [12,14-17] were judged to have a moderate overall risk of bias. Four studies [10,11,13,18] were judged to have a serious overall risk of bias. No study was classified as having a critical overall risk of bias.

Across the individual domains, bias in the selection of participants (D2), classification of interventions (D3), and selection of the reported result (D7) was consistently rated as low risk across all nine studies. Bias due to deviations from intended interventions (D4) was also predominantly rated as low risk, although moderate risk was identified in Ekanem et al. (2024) [10]. Bias due to missing data (D5) was rated as low risk in five studies [12,14-17] and as moderate risk in Ekanem et al. (2024) [10] and Venier et al. (2023) [11], whereas serious risk was identified in Wenzel et al. (2026) [13] and Martinez et al. (2026) [18]. Bias in the measurement of outcomes (D6) was considered low risk in all studies except Ekanem et al. (2024) [10], which was judged to have a serious risk of bias. Bias due to confounding (D1) represented an important source of concern, with moderate risk identified in Gold et al. (2025) [12], Wenzel et al. (2025) [13], Popa et al. (2024) [14], Stojadinović et al. (2024) [15], Osmancik et al. (2024) [16], Kuraoka et al. (2025) [17], and Martinez et al. (2026) [18] and serious risk identified in Ekanem et al. (2024) [10] and Venier et al. (2023) [11]. The detailed domain-level assessments and overall ROBINS-I judgments are presented in Figures *2*, *3*.

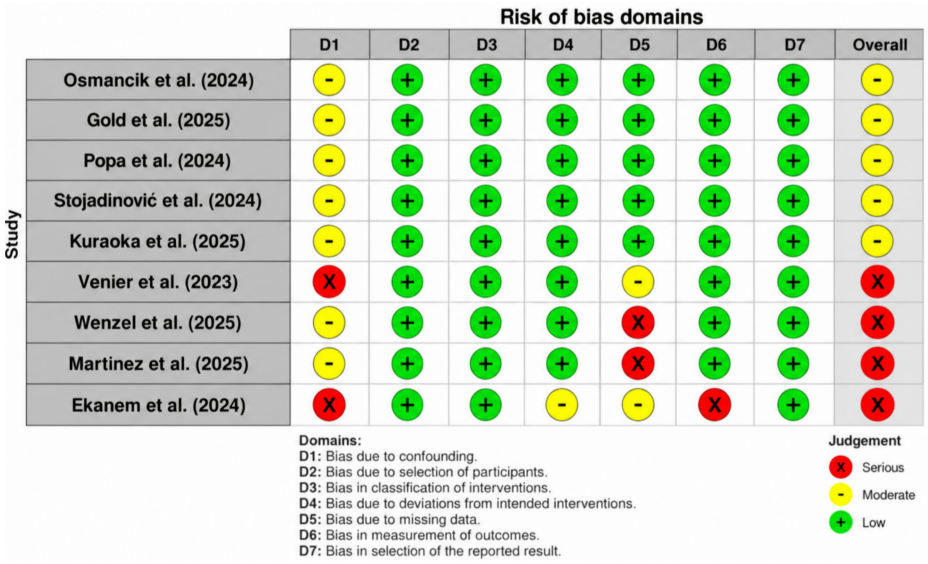

FIGURE 2: Traffic light plot of ROBINS-I quality assessment across included studies.

Traffic light plot illustrating the domain-specific and overall risk-of-bias assessments of the included nonrandomized studies using the ROBINS-I tool. D1: bias due to confounding; D2: bias due to selection of participants; D3: bias in classification of interventions; D4: bias due to deviations from intended interventions; D5: bias due to missing data; D6: bias in measurement of outcomes; D7: bias in selection of the reported result. Green indicates a low risk of bias, yellow indicates a moderate risk of bias, and red indicates a serious risk of bias.

ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions

[10-18]

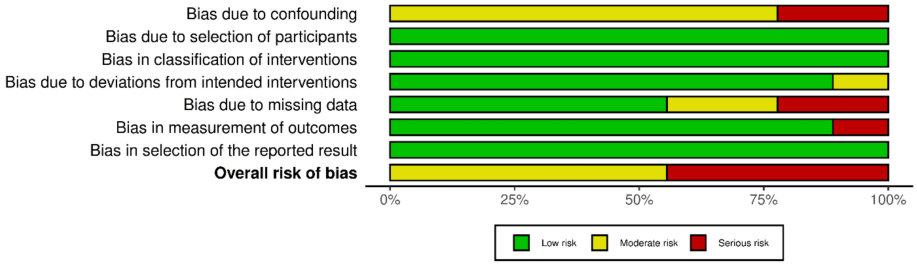

FIGURE 3: ROBINS-I summary plot showing the proportion of risk-of-bias judgments across domains.

Summary plot showing the proportion of studies categorized as having a low, moderate, or serious risk of bias across each ROBINS-I domain and in the overall assessment of the included nonrandomized studies. Green represents a low risk of bias, yellow represents a moderate risk of bias, and red represents a serious risk of bias.

ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions

Primary Outcomes

The outcomes are summarized in Table *3*.

Outcome	Studies (author, year)	Main findings
LDH	Wenzel et al. (2025) [13]; Popa et al. (2024) [14]; Stojadinović et al. (2024) [15]; Osmancik et al. (2024) [16]; Kuraoka et al. (2025) [17]; Gold et al. (2025) [12]	LDH increased following PFA. Reported changes included +99 U/L (Wenzel) [13], +160.5 U/L (Popa) [14], 3.1 to 6.8 μkat/L (Stojadinović) [15], +1.97 mmol/L (Osmancik) [16], +84.8 U/L (Kuraoka) [17], and +63 U/L (Gold) [12].
Haptoglobin	Wenzel et al. (2025) [13]; Venier et al. (2023) [11]; Popa et al. (2024) [14]; Osmancik et al. (2024) [16]; Kuraoka et al. (2025) [17]; Gold et al. (2025) [12]	Haptoglobin decreased after PFA. Changes included -28 mg/dL (Wenzel) [13], 1.40 to 0.18 g/L (Venier) [11], 1.2 ± 0.4 to 0.5 ± 0.4 g/L (Popa) [14], 1.20 to 0.44 g/L (Osmancik) [16], 0.990 ± 0.471 to 0.385 ± 0.267 g/L (Kuraoka) [17], and -0.09 g/L (Gold) [12] (not statistically significant, p = 0.153).
Plasma-fHb	Popa et al. (2024) [14]; Venier et al. (2023) [11]; Osmancik et al. (2024) [16]; Stojadinović et al. (2024) [15]; Kuraoka et al. (2025) [17]	Marked increases in fHb were reported: 70.6 ± 23.7 to 592.8 ± 330.6 mg/L (Popa) [14], 40 to 493 mg/L (Stojadinović) [15], 403 ± 443 to 623 ± 341 mg/L (Kuraoka) [17], 70.8 to 846.6 Nr/μL, and a peak of 0.04 g/L (Venier) [11].
Bilirubin	Wenzel et al. (2025) [13]; Popa et al. (2024) [14]; Osmancik et al. (2024) [16]; Kuraoka et al. (2025) [17]; Gold et al. (2025) [12]	Increased bilirubin was reported following PFA, supporting biochemical evidence of intravascular hemolysis.
Hemoglobinuria	Popa et al. (2024) [14]; Venier et al. (2023) [11]; Osmancik et al. (2024) [16]	Hemoglobinuria was reported in 36.4% of patients in Popa et al. [14] and 27% in Venier et al. [11]. Hydration was associated with lower hemoglobinuria frequency in the reported comparison (75% vs. 0%).
AKI	Ekanem et al. (2024) [10]; Wenzel et al. (2025) [13]; Popa et al. (2024) [14]; Venier et al. (2023) [11]; Martinez et al. (2026) [18]	Clinically significant AKI was uncommon but reported. Ekanem et al. [10] reported dialysis-requiring AKI in 0.03% (5/17,642) of patients. Martinez et al. [18] reported 7.0% (8/115). Popa et al. [14] reported 3.2%. Venier et al. [11] reported two cases of severe AKI. Wenzel et al. [13] reported a modest decline in renal function.
Creatinine/renal dose-response	Popa et al. (2024) [14]; Martinez et al. (2026) [18]	Popa et al. [14] reported a +27 μmol/L creatinine increase in patients with baseline renal impairment (p = 0.010). Martinez et al. [18] demonstrated a dose-dependent creatinine increase beyond 38 PFA applications, with estimated AKI probability exceeding 95% after approximately 255 applications.
Dose-response relationship	Popa et al. (2024) [14]; Stojadinović et al. (2024) [15]; Venier et al. (2023) [11]; Osmancik et al. (2024) [16]; Kuraoka et al. (2025) [17]; Martinez et al. (2026) [18]	Greater PFA exposure was associated with greater hemolysis/renal biomarker changes. Reported correlations included r = 0.81 (Stojadinović) [15] and r = 0.62 between PFA exposure and fHb (Popa) [14]. Venier et al. [11] reported r = -0.411 for the evaluated relationship. Martinez et al. [18] demonstrated a dose-dependent renal effect.
Hemoglobin decline	Venier et al. (2023) [11]; Kuraoka et al. (2025) [17]; Gold et al. (2025) [12]	A postprocedural decline in hemoglobin was reported in these studies, consistent with procedural hemolysis.
Troponin	Gold et al. (2025) [12]	Troponin increased following PFA as a marker of myocardial injury.
Creatine kinase (CK)	Gold et al. (2025) [12]	CK increased following PFA.
S100/neurological injury marker	Gold et al. (2025) [12]	S100 remained unchanged (0.056 ± 0.026 to 0.056 ± 0.034, p = 0.854), indicating no significant biochemical evidence of neural injury in the reported analysis.
Clinical/radiological neurological outcomes	Gold et al. (2025) [12]	No clinically overt neurological events or significant radiologically detected acute cerebral ischemic injury were reported in the evaluated study.

TABLE 3: Summary outcomes for included studies.

AKI, acute kidney injury; CK, creatine kinase; fHb, free hemoglobin; LDH, lactate dehydrogenase; PFA, pulsed field ablation

Biochemical markers of intravascular hemolysis following PFA: PFA consistently resulted in significant

intravascular hemolysis across the included studies, as evidenced by concordant changes in LDH, haptoglobin, fHb, and bilirubin. Six studies reported LDH levels with paired baseline and postprocedural values. Popa et al. (2024) [14] reported an increase from 192.2 ± 51.6 to 352.7 ± 115.7 U/L (Δ +160.5; $p < 0.001$), while Kuraoka et al. (2025) [17] observed a rise from 183.2 ± 47.1 to 268.0 ± 49.1 U/L (Δ +84.8; $p < 0.001$) in the FARAPULSE cohort. Gold et al. (2025) [12] demonstrated an increase from 194 ± 35 to 257 ± 57.2 U/L (Δ +63; $p < 0.001$). Similarly, Osmancik et al. (2024) [16] reported an increase from 2.70 to 4.67 µkat/L (Δ +1.97; $p < 0.001$), Wenzel et al. (2025) [13] reported a median increase of +99 U/L (IQR 76-121; $p < 0.001$) in the pentaspline cohort, and Stojadinović et al. (2024) [15] observed an increase from 3.1 to 6.8 µkat/L ($p < 0.0001$). Overall, postprocedural LDH elevations indicated a consistent 1.5- to 2-fold increase following PFA.

Haptoglobin depletion further confirmed intravascular hemolysis, with paired baseline and postprocedural data reported across studies. Popa et al. (2024) [14] demonstrated a decrease from 1.2 ± 0.4 to 0.5 ± 0.4 g/L (Δ -0.7; $p < 0.001$), while Osmancik et al. (2024) [16] reported a reduction from 1.20 to 0.44 g/L (Δ -0.76; $p < 0.001$). Kuraoka et al. (2025) [17] observed a decrease from 0.990 ± 0.471 to 0.385 ± 0.267 g/L (Δ -0.605; $p < 0.001$), and Venier et al. (2023) [11] reported a decline from 1.40 to 0.18 g/L (Δ -1.22; $p < 0.0001$). Wenzel et al. (2025) [13] reported a median decrease of -28 mg/dL (IQR -39 to -18; $p < 0.001$), whereas Gold et al. (2025) [12] showed a nonsignificant change (116 ± 51.1 to 107 ± 46.4 mg/dL; Δ -0.09 g/L; $p = 0.153$).

fHb and red blood cell microparticles (RBCµ) demonstrated marked postablation elevations. Popa et al. (2024) [14] reported an fHb increase from 70.6 ± 23.7 to 592.8 ± 330.6 mg/L ($p < 0.001$), Stojadinović et al. (2024) [15] reported an increase from 40 to 493 mg/L (IQR 327-848; $p < 0.0001$), and Kuraoka et al. (2025) [17] reported an increase from 403 ± 443 to 623 ± 341 mg/L ($p < 0.001$). Venier et al. (2023) [11] reported a postprocedural peak fHb value of 0.04 g/L. In addition, Osmancik et al. (2024) [16] measured erythrocyte fragmentation directly using flow cytometry, demonstrating a 12-fold increase in RBCµ, from 70.8 to 846.6 Nr/µL ($p < 0.001$). Across studies, clinically significant thresholds (>200 mg/L) for cell-fHb were exceeded in the majority of patients.

Bilirubin elevation was also consistently observed. Popa et al. (2024) [14] reported an increase from 9.6 ± 4.7 to 21.3 ± 11.3 µmol/L (Δ +11.7; $p < 0.001$). Osmancik et al. (2024) [16] reported an increase in indirect bilirubin from 10.3 to 14.1 µmol/L (Δ +3.8; $p < 0.001$), Wenzel et al. (2025) [13] reported a median increase of +5.2 µmol/L ($p < 0.001$), Kuraoka et al. (2025) [17] reported an increase in total bilirubin from 0.668 ± 0.336 to 1.33 ± 0.571 mg/dL ($p < 0.001$), and Gold et al. (2025) [12] reported an increase in total bilirubin from 0.69 ± 0.45 to 0.97 ± 0.54 mg/dL ($p < 0.001$).

Secondary Outcomes

AKI: AKI following PFA was uncommon but variably reported across the included studies. Ekanem et al. (2024) [10] reported a 0.03% incidence of dialysis-requiring AKI (5/17,642) in the largest cohort. Smaller cohorts reported higher rates of AKI, including 7.0% (8/115) in Martinez et al. (2026) [18], 3.2% in Popa et al. (2024) [14], and 2.1% (1/47) in Osmancik et al. (2024) [16]. Popa et al. (2024) [14] further demonstrated a significant association between hemolysis and renal dysfunction, with a mean increase in serum creatinine of 27.0 µmol/L among patients with baseline renal impairment ($p = 0.010$). Martinez et al. (2026) [18] identified a dose-dependent increase in serum creatinine beyond 38 PFA applications, with the estimated probability of AKI exceeding 95% after approximately 255 applications. Wenzel et al. (2025) [13] reported a modest but significant decline in renal function following pentaspline PFA, while Venier et al. (2023) [11] described two cases of severe AKI associated with a high lesion burden (>100 applications). In contrast, Kuraoka et al. (2025) [17], Gold et al. (2025) [12], and Stojadinović et al. (2024) [15] reported no AKI events.

Hemoglobinuria: Hemoglobinuria was variably reported across the included studies but was associated with the degree of intravascular hemolysis. Popa et al. (2024) [14] reported macroscopic hemoglobinuria in 36.4% of patients following PFA, while Venier et al. (2023) [11] observed an incidence of 27%. Across these cohorts, hemoglobinuria occurred alongside marked reductions in haptoglobin and increases in cell fHb and LDH.

Dose-response relationship: A consistent dose-response relationship between the number of PFA applications and the severity of hemolysis was demonstrated across multiple studies. Stojadinović et al. (2024) [15] reported a strong linear correlation between peak fHb and the total number of PFA applications ($r = 0.81$, $p < 0.001$), with >74 applications accurately predicting major hemolysis (fHb >500 mg/L; area under the curve = 0.934; sensitivity, 89%; specificity, 87%). Popa et al. (2024) [14] also reported a dose-dependent association between PFA exposure and hemolysis. Venier et al. (2023) [11] reported correlations between PFA applications and LDH ($r = 0.601$) and haptoglobin ($r = -0.411$). Osmancik et al. (2024) [16] demonstrated associations between PFA exposure and RBC microparticles ($r = 0.31$) and LDH ($r = 0.40$), while Kuraoka et al. (2025) [17] reported a correlation between PFA applications and fHb in the FARAPULSE cohort ($r = 0.540$). Furthermore, Martinez et al. (2026) [18] identified a threshold of 38 PFA applications, beyond which serum creatinine exhibited a dose-dependent increase of approximately 0.003-0.004 mg/dL per additional application.

Hemoglobin decline: Postprocedural decreases in hemoglobin were observed across several PFA cohorts. Kuraoka et al. (2025) [17] reported a mean hemoglobin reduction of -1.7 g/dL (from 13.7 ± 1.66 to 12.0 ± 1.54

g/dL; p < 0.001) in the FARAPULSE pentaspline cohort, while Venier et al. (2023) [11] observed a decline from 14.5 to 12.9 g/dL (Δ -1.6 g/dL; p = 0.0001). Gold et al. (2025) [12] and Stojadinović et al. (2024) [15] also reported statistically significant postprocedural decreases (p = 0.003 and p < 0.001, respectively). In Wenzel et al. (2025) [13], hemoglobin decreased in the balloon-in-basket cohort (Δ -0.71 ± 1.13 g/dL; p = 0.002), whereas hemoglobin remained unchanged in the pentaspline cohort (Δ +0.12 ± 0.98 g/dL; p = 0.415). Overall, the reported hemoglobin decreases were not associated with transfusion-requiring hemolytic anemia in the included studies.

Catheter design and hemolysis: Catheter design and energy-delivery characteristics were associated with differences in the severity of intravascular hemolysis and renal outcomes. Wenzel et al. (2025) [13] demonstrated greater biochemical evidence of hemolysis with pentaspline devices than with balloon-in-basket systems, characterized by a significantly greater LDH increase (+99 vs. +59 U/L; p < 0.001), greater haptoglobin reduction (-28 vs. -6 mg/dL; p < 0.001), and a greater decline in renal function (eGFR Δ -4.5 vs. -1.0 mL/min; p = 0.002). Kuraoka et al. (2025) [17] observed smaller changes in hemolytic biomarkers with circular-array systems (PulseSelect) than with pentaspline catheters (FARAPULSE), as evidenced by a significantly smaller reduction in the postprocedural-to-preprocedural haptoglobin ratio (0.556 vs. 0.405; p = 0.0027) and a lower LDH elevation (ratio, 1.36 vs. 1.51; p = 0.010). Furthermore, Gold et al. (2025) [12] reported significantly less haptoglobin depletion with monopolar, monophasic lattice-tip systems (Affera) than with the single-shot bipolar platforms PulseSelect and FARAPULSE. The mean haptoglobin changes were -13.8 ± 18.5 mg/dL for Affera, -36.8 ± 35.9 mg/dL for PulseSelect, and -60.7 ± 26.3 mg/dL for FARAPULSE (p < 0.001).

Discussion

Summary of Findings

This systematic review shows that PFA for AF is consistently associated with a reproducible pattern of intravascular hemolysis, characterized by significant haptoglobin depletion and elevated levels of LDH, fHb, and bilirubin. These biochemical alterations were observed across all included studies and demonstrated a distinct dose-response relationship with the number of PFA applications. Following the procedure, LDH increased by approximately 1.5- to 2-fold, haptoglobin levels decreased significantly, and fHb increased by up to 12-fold in some groups. Although subclinical renal impairment was more common in patients with a high lesion burden or dehydration, clinically severe AKI remained uncommon (0.03%) despite this biochemical burden. Crucially, catheter design had a major impact on the degree of hemolysis; pentaspline systems showed greater systemic effects than balloon-in-basket, circular-array, or monopolar lattice-tip systems. Hemoglobinuria and renal injury were observed despite periprocedural hydration, and the available evidence does not establish a definitive preventive effect of hydration.

Comparison With Existing Literature

We found that myocardial selectivity and procedural safety were the main focuses of early experimental and clinical research on PFA. The nonthermal mechanism described by Koruth et al. (2019) [19] demonstrated that pulsed electric fields can induce irreversible cardiac electroporation while sparing adjacent tissues. Early perceptions of biological selectivity were reinforced by the favorable safety profiles and low systemic toxicity reported in early clinical trials, including the IMPULSE and PEFCAT studies [20,21].

Furthermore, emerging clinical data have increasingly challenged the assumption that hemolysis following PFA is purely subclinical. The MANIFEST-PF registry [10], one of the largest real-world datasets, reported a high frequency of biochemical evidence of hemolysis following PFA. Consistent with these findings, our review suggests that hemolysis may represent a consistent and reproducible biological response to PFA, with a multimarker pattern characterized by LDH elevation, haptoglobin depletion, free hemoglobin release, and bilirubin elevation across the included studies. However, given the small number of studies and the predominantly observational nature of the available evidence, these findings should be interpreted cautiously, and further prospective studies are warranted to confirm the consistency, clinical significance, and determinants of hemolysis following PFA.

Additionally, these findings are supported by mechanistic experimental investigations. Erythrocytes are vulnerable to electroporation at energy thresholds similar to, or lower than, those of cardiac tissue under specific experimental conditions [20,22]. Similarly, experimental studies have demonstrated that high-density pulsed fields can cause red blood cell membrane disruption in a dose-dependent manner, providing a biological basis for the hemolytic patterns observed in clinical settings [1,23]. These findings are consistent with the dose-response association observed in our review between hemolysis severity and the number of PFA applications. Moreover, the device-specific variability observed in this review is consistent with earlier research in electrophysiology.

Pentaspline systems deliver larger, less focused electric fields than balloon-in-basket and lattice-tip systems, potentially increasing exposure of nontarget tissue, according to comparative investigations [24]. Similarly, differences in field dispersion and lesion homogeneity have been reported among catheter

platforms. The greater hemolytic burden observed with FARAWAVE pentaspline systems than with PulseSelect or Affera platforms in our analysis may be related to differences in electric field distribution and lesion characteristics; however, this remains a hypothesis that cannot be established from the available comparative data [23]. Further prospective and mechanistic studies directly comparing catheter platforms are needed to determine whether differences in electric field characteristics contribute to the observed variation in hemolytic burden.

Our findings regarding renal outcomes are also consistent with established nephrological evidence concerning pigment-induced nephropathy. Free hemoglobin can contribute to oxidative tubular injury, nitric oxide depletion, and renal vasoconstriction, while hemoglobinuria may contribute to acute tubular injury [25]. These mechanisms provide a plausible biological explanation for the cases of AKI and the dose-dependent increases in creatinine observed in patients undergoing higher-burden PFA procedures. However, the available clinical evidence does not establish a direct causal relationship between PFA-associated hemolysis and renal injury.

Earlier electrophysiological studies reported limited renal consequences; however, differences in biochemical monitoring and lesion burden may have influenced the detection of subclinical renal effects. Although hydration is biologically plausible as a renal-protective strategy in the setting of hemolysis, the available evidence from the included PFA studies is insufficient to establish a definitive preventive effect. Hemoglobinuria and AKI were still reported despite periprocedural hydration, and the available observational data do not permit a reliable assessment of whether hydration reduces the incidence or severity of these complications. Further prospective studies with standardized hydration protocols and appropriate comparison groups are needed to clarify its potential protective role.

Overall, recent clinical data and our synthesis suggest that PFA is associated with a consistent and measurable systemic hemolytic response, with potential downstream renal implications. However, clinically significant renal sequelae appear to be uncommon, and the contribution of periprocedural hydration and other renal-protective measures to this finding remains uncertain. Thus, rather than indicating an absence of systemic effects, the available evidence supports a paradigm of controlled but measurable hemolytic stress following PFA, while its clinical significance and long-term renal implications remain to be established.

Strengths and Limitations

This systematic review has several strengths. It is one of the most comprehensive assessments of PFA-associated systemic effects, comprising a large pooled sample of more than 18,000 patients. To enhance generalizability, we combined data from prospective cohort studies and large registries. We also evaluated multiple complementary biomarkers of hemolysis, renal injury, and cardiac stress to provide a multifaceted assessment of systemic tissue injury. Importantly, we performed a comparative evaluation of catheter platforms, providing early insights into potential device-specific biological effects.

Several limitations must be acknowledged. Given the predominantly observational design of the included studies, the findings may be subject to selection and reporting biases. The distribution of the overall study population also varied substantially across outcomes: clinical safety outcomes, particularly severe AKI, were heavily informed by the large MANIFEST-PF registry, whereas detailed biochemical hemolysis data were derived from a considerably smaller and more concentrated patient population from studies specifically evaluating hemolytic biomarkers. Direct comparability across studies was also limited by substantial variation in the definitions of hemolysis, criteria used to define AKI, biomarker measurement methods and units, and the timing of biomarker measurements. Quantitative meta-analysis was not performed because of substantial clinical and methodological heterogeneity, differences in statistical reporting, and incomplete datasets for some outcomes. Several studies did not provide complete data across all outcomes, further limiting direct comparison and quantitative synthesis. Additionally, comparisons between catheter platforms were based on indirect observational comparisons rather than randomized head-to-head trials and should therefore not be interpreted as establishing causal differences between devices. Finally, the long-term clinical significance of PFA-associated hemolysis remains uncertain because of limited data on long-term renal and systemic outcomes. These limitations should be considered when interpreting the magnitude and clinical implications of the observed associations.

Future Implications

Future studies should prioritize the systematic assessment of intravascular hemolysis and its potential renal consequences following PFA, particularly in patients undergoing procedures involving a high number of ablation applications. Standardized monitoring of hemolysis biomarkers, renal function, and hemoglobinuria would help clarify the relationship between the magnitude of hemolysis and clinically significant kidney injury. Further prospective studies and randomized head-to-head comparisons are needed to determine whether differences in catheter design and energy-delivery characteristics influence hemolytic burden and renal outcomes. Further prospective studies using standardized periprocedural hydration protocols and appropriate comparison groups are needed to clarify whether hydration is associated with a

reduction in hemoglobinuria or AKI following PFA. Mechanistic investigations examining erythrocyte susceptibility to electroporation and the relationship between energy delivery and tissue injury may further inform strategies to minimize systemic effects while preserving procedural efficacy and safety.

Conclusions

PFA for AF is associated with measurable biochemical evidence of intravascular hemolysis, including increases in LDH and fHb and reductions in haptoglobin. The available evidence suggests a possible dose-dependent relationship between procedural intensity and the magnitude of hemolysis, while catheter configuration and lesion burden may also influence these responses. Although clinically significant renal injury appears to be uncommon, the relationship between PFA-associated hemolysis and AKI remains uncertain. Periprocedural hydration may have a potential protective role; however, current evidence is insufficient to establish that hydration prevents hemoglobinuria or renal complications. Given the small number of predominantly observational studies, substantial methodological heterogeneity, and limited long-term outcome data, these findings should be interpreted cautiously. Further large, prospective studies are needed to clarify the clinical significance of PFA-associated hemolysis, evaluate catheter-specific differences, establish the relationship between hemolysis and renal injury, and determine whether hydration and other preventive strategies can reduce systemic complications.

Appendices

Appendix A

PubMed (n = 1,198)	Embase (n = 265)	Scopus (n = 1,489)	Cochrane Library (n = 567)
Search: ("Pulsed Field Ablation"[tiab] OR "PFA"[tiab] OR "Irreversible Electroporation"[Mesh] OR "Irreversible Electroporation"[tiab] OR "Electroporation"[Mesh]) AND ("Atrial Fibrillation"[Mesh] OR "Atrial Fibrillation" [tiab] OR "AF"[tiab]) AND ("Hemolysis"[Mesh] OR "Intravascular Hemolysis"[tiab] OR "Hemolysis"[tiab] OR "Lactate Dehydrogenase"[Mesh] OR "LDH"[tiab] OR "Haptoglobins" [Mesh] OR "Haptoglobin"[tiab] OR "Free Hemoglobin"[tiab] OR "Plasma Hemoglobin"[tiab] OR "Bilirubin" [Mesh] OR "Bilirubin"[tiab]) AND ("Acute Kidney Injury" [Mesh] OR "Renal Injury"[tiab] OR "Kidney Injury"[tiab] OR "Creatinine"[tiab] OR "Renal Function"[tiab]) AND ("Catheter"[tiab] OR "Catheter Design"[tiab] OR "Pentaspline"[tiab] OR "Lattice-tip"[tiab] OR "Balloon-in-basket"[tiab] OR "Farapulse"[tiab] OR "PulseSelect"[tiab] OR "Affera"[tiab])	('atrial fibrillation'/exp OR 'atrial fibrillation':ti,ab OR af:ti,ab) AND ('pulsed field ablation':ti,ab OR pfa:ti,ab OR 'irreversible electroporation'/exp OR 'irreversible electroporation':ti,ab OR electroporation:ti,ab) AND ('hemolysis'/exp OR hemolysis:ti,ab OR haemolysis:ti,ab OR 'intravascular hemolysis':ti,ab OR 'lactate dehydrogenase':ti,ab OR ldh:ti,ab OR haptoglobin:ti,ab OR 'free hemoglobin':ti,ab OR 'plasma hemoglobin':ti,ab OR bilirubin:ti,ab OR 'acute kidney injury'/exp OR 'acute kidney injury':ti,ab OR 'renal injury':ti,ab OR 'kidney injury':ti,ab OR creatinine:ti,ab OR 'renal function':ti,ab)	(TITLE-ABS- KEY ("atrial fibrillation" OR "AF") AND TITLE-ABS-KEY ("pulsed field ablation" OR "PFA" OR "irreversible electroporation" OR "electroporation"))	#1 "atrial fibrillation" OR AF #2 MeSH descriptor: [Atrial Fibrillation] explode all trees #3 #1 OR #2 #4 "pulsed field ablation" OR PFA #5 "irreversible electroporation" #6 MeSH descriptor: [Electroporation] explode all trees #7 #4 OR #5 OR #6 #8 #3 AND #7

TABLE 4: Search strategies.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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