A Multidomain Atrial Damage Index for Atrial Fibrillation Recurrence

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Abstract

Atrial fibrillation (AF) recurrence after catheter ablation is associated with heterogeneous atrial remodeling that may not be adequately captured by single-domain predictors. We propose a Multidomain Atrial Damage Index (MADI) integrating electrical substrate (median bipolar voltage), geometric remodeling (left atrial volume), metabolic status (diabetes mellitus), and AF type (paroxysmal/persistent) into a composite 0–8 score.

In a retrospective cohort of 143 patients, MADI stratified patients into three stages with recurrence rates of 28% in Stage 1 (14/50), 32% in Stage 2 (22/68), and 68% in Stage 3 (17/25). Overall discriminative performance was modest (ROC-AUC=0.646 [95% CI 0.55–0.74]; OR=1.29 [95% CI 1.08–1.52]). Joint electrical-geometric phenotype analysis identified E4+G1, characterized by advanced electrical remodeling and intermediate geometric dilation, as the subgroup with the highest observed recurrence (71%, 5/7).

These findings suggest that multidomain integration provides an interpretable proof-of-concept framework for characterizing heterogeneous atrial remodeling and identifying potentially vulnerable substrate phenotypes. Its predictive value remains limited and requires validation in larger prospective cohorts.

1. Introduction

Atrial fibrillation (AF) recurrence after catheter ablation remains frequent, affecting approximately 20–50% of patients at one year despite advances in ablation strategies. This may partly reflect incomplete characterization of the complex and heterogeneous atrial substrate [1]. Current risk stratification approaches have important limitations: left atrial size provides incremental rather than definitive predictive value [2], electroanatomical voltage mapping is associated with recurrence but remains insufficient as a standalone predictor [3], and artificial intelligence/radiomics approaches, while promising, still show limited generalizability and clinical implementation [4]. Overall, AF recurrence appears to be influenced by multiple interacting domains that are typically evaluated separately in clinical practice.

In this context, we propose the Multidomain Atrial Damage Index (MADI), a composite scoring system integrating electrical substrate, geometric remodeling, metabolic status, and AF type into a unified framework. Rather than being designed primarily as a high-performance predictive model, MADI is intended as an interpretable proof-of-concept phenotyping framework for identifying distinct substrate profiles that may respond differently to therapy. The resulting score (range 0–8) stratifies patients into three stages (Stage 1: $\leq$2, Stage 2: 3–5, Stage 3: $\geq$6). We evaluated the association between MADI and AF recurrence in a retrospective cohort of 143 patients undergoing high-density electroanatomical mapping.

2. Methods

2.1. Study Population and Data Acquisition

This retrospective study included 143 patients from Clinica Universidad de Navarra undergoing first-time catheter ablation for paroxysmal or persistent atrial fibrillation between 2016 and 2021. High-density electroanatomical mapping was performed using the Rhythmia system, generating >10,000 bipolar mapping points per patient. Left atrial geometry was assessed using pre-procedural CT imaging. Clinical follow-up at 12 months was used to determine AF recurrence. Baseline characteristics were: paroxysmal AF 62%, persistent AF 38%, mean left atrial

volume 111±30 cm^3, and diabetes mellitus prevalence 11%.

2.2. MADI Computation

The MADI integrates electrical, geometric, metabolic, and temporal domains. The electrical score (E=0–4) was defined from quintiles of patient-level median bipolar voltage, with lower voltage indicating greater electrical remodeling. The geometric score (G=0–2) was based on tertiles of CT-derived left atrial volume. Metabolic (M=0/1) and temporal (T=0/1) domains represented diabetes mellitus and AF type, respectively (Table 1). The composite score was MADI=E+G+M+T, ranging from 0 to 8 and defining Stage 1 ($\leq$2), Stage 2 (3–5), and Stage 3 ($\geq$6).

2.3. Statistical Analysis

Statistical analysis was performed in MATLAB. Associations between variables were evaluated using point-biserial correlation and chi-square testing. Logistic regression models were used to estimate odds ratios (OR) for recurrence. Receiver operating characteristic (ROC) curves and area under the curve (AUC) with 95% confidence intervals (CI) were computed. A five-fold stratified cross-validation scheme was used to preserve class distribution across folds. As a sensitivity analysis, class imbalance in recurrence outcomes (37.1%) was evaluated strictly within training folds using a SMOTE approach.

3. Results

3.1. Stage Stratification and Baseline Characteristics

The MADI score stratified the cohort into three stages: Stage 1 (n=50, 35.0%), Stage 2 (n=68, 47.6%), and Stage 3 (n=25, 17.5%). Baseline characteristics and domain distributions are summarized in Table 2. Stage progression was associated with increasing clinical severity, with rising persistent AF and diabetes mellitus prevalence (Table 2). Each stage also presented distinct dominant electrogeometric phenotypes, shifting from isolated mild remodeling in Stage 1 (e.g., E0+G0, E1+G1) to combined multidomain alterations in Stages 2–3 (e.g., E1+G2, E4+G2).

Concomitantly, stage progression was accompanied by a marked decrease in median bipolar voltage (2.10±0.99 mV in Stage 1 to 0.26±0.18 mV in Stage 3) and an increase in left atrial volume (91.5±20.1 to 140.4±27.5 cm^3), as illustrated in Figures 1C and 1D, respectively.

3.2. Stage-Dependent Recurrence Pattern

AF recurrence rates showed a stage-dependent increase, most pronounced in Stage 3: Stage 1 (14/50, 28% [95% CI 16–40%]), Stage 2 (22/68, 32% [95% CI 21–43%]), and Stage 3 (17/25, 68% [95% CI 50–86%]). This pattern is visualized in Figure 1A and indicates a marked escalation in recurrence risk at the highest level of combined remodeling burden. The increase in recurrence from Stage 1 to Stage 2 was modest and did not reach statistical significance (28% vs. 32%), whereas Stage 3 showed a substantially higher recurrence rate, suggesting a stage-associated increase in recurrence driven primarily by patients with the highest multidomain remodeling burden. The difference between Stages 2 and 3 was statistically significant (χ^2=9.54, p=0.002; Fisher's exact p=0.004).

3.3. Predictive Performance and Phenotype Analysis

Logistic regression yielded an odds ratio for recurrence of 1.29 (95% CI 1.08–1.52), with an AUC of 0.646 (95% CI 0.55–0.74); the optimal operating point (MADI $\approx$ 5.5) aligned conceptually with the Stage 2/Stage 3 transition (sensitivity 32%, specificity 91%). Five-fold cross-validation yielded an AUC of 0.64 $\pm$ 0.07 (range 0.52–0.69) after SMOTE-based correction for class imbalance within each training fold; this is broadly consistent with the main-analysis AUC of 0.646, despite fold-to-fold variability attributable to the limited sample size, confirming results were not primarily driven by class imbalance. Joint electrical-geometric phenotype analysis identified combinations with particularly high observed recurrence: the E4+G1 phenotype (advanced electrical remodeling combined with intermediate geometric dilation, n=7) showed the highest recurrence among the electrical-geometric combinations (71%, 5/7), compared with 64% (9/14) in E4+G2. This exploratory, small-subgroup finding highlights the potential of MADI to identify vulnerable combined phenotypes obscured by single-domain analysis (Figure 1B).

4. Discussion

This study proposes a Multidomain Atrial Damage Index integrating electrical, structural, metabolic, and temporal descriptors into a single interpretable score for phenotyping catheter ablation patients. The main finding, a stage-dependent increase in recurrence that became markedly more pronounced in Stage 3 (Stage 2 vs. Stage 3, χ^2=9.54, p=0.002), indicates a strong association between the highest multidomain remodeling burden and AF recurrence. Despite reaching statistical significance within this cohort, the result should still be interpreted

Table 1. MADI Domain Discretization

Domain	Score	Criteria
Electrical	E = 0-4	Median bipolar voltage quintiles (mV):
		$>$ 1.764, 1.052–1.764, 0.627–1.052, 0.310–0.627, $\leq$ 0.310
Geometric	G = 0–2	LA volume tertiles (cm³):
		$<$94.3, 94.3–119.2, $>$119.2
Metabolic	M = 0/1	Diabetes mellitus (No/Yes)
Temporal	T = 0/1	AF type (Paroxysmal/Persistent)
MADI	0–8	Stage 1: $\leq$2; Stage 2: 3–5; Stage 3: $\geq$6

Table 2. MADI Stage Characteristics

Parameter	Stage 1 (n=50)	Stage 2 (n=68)	Stage 3 (n=25)
Recurrence rate (%)	28	32	68
MADI score (mean $\pm$ SD)	1.10 ± 0.86	4.07 ± 0.76	6.72 ± 0.68
LA volume (cm^3)	91.5 ± 20.1	114.9 ± 26.8	140.4 ± 27.5
Median bipolar voltage (mV)	2.1 ± 0.99	0.70 ± 0.43	0.26 ± 0.18
Diabetes mellitus (%)	4	9	32
Persistent AF (%)	10	43	84

cautiously given the relatively small Stage 3 sample size and the single-center retrospective design; larger, prospectively validated cohorts are needed to confirm whether this gradient holds and to determine its true magnitude. Previous studies have individually linked structural remodeling [2], electrical abnormalities [3], and machine learning [4] to AF recurrence, but standalone predictors often show limited interpretability and generalizability. MADI should thus be interpreted as a proof-of-concept phenotyping framework rather than a high-performance predictive model, valuable mainly for identifying substrate phenotypes that may respond differently to ablation therapies. The E4+G1 combination (71% recurrence, n=7) identified a subgroup with advanced electrical alteration and intermediate structural remodeling and a particularly high observed recurrence rate, although this small-subgroup finding remains exploratory. As MADI is additive, this observation illustrates the potential value of considering electrical and structural remodeling jointly rather than as isolated predictors.

5. Limitations

This study has several limitations. It is a single-center retrospective analysis (n=143) with a relatively short follow-up (12 months) and requires external validation in larger, multi-center prospective cohorts. The MADI framework also relies on simplified representations of complex biology: electrical remodeling is summarized as a single global median voltage value that does not capture regional heterogeneity, while metabolic and temporal domains are modeled as binary variables. The magnitude of the stage-dependent recurrence pattern and the E4+G1 subgroup finding should be considered exploratory given the small Stage 3 and subgroup sample sizes, respectively. The electrical quintile and geometric tertile thresholds were derived from the same cohort used for performance evaluation and were not re-estimated within cross-validation folds. This may introduce modest optimism in performance estimates. Finally, procedural and operator-dependent factors (e.g., lesion contiguity, contact force) were not included and may act as unmeasured confounders.

6. Conclusions

The MADI framework integrates electrical, structural, metabolic, and temporal descriptors into an interpretable proof-of-concept staging system for AF phenotyping. Although its overall discriminative performance was modest (AUC 0.646), patients with the highest multidomain remodeling burden showed substantially greater AF recurrence. These findings require validation in larger prospective cohorts before clinical application.

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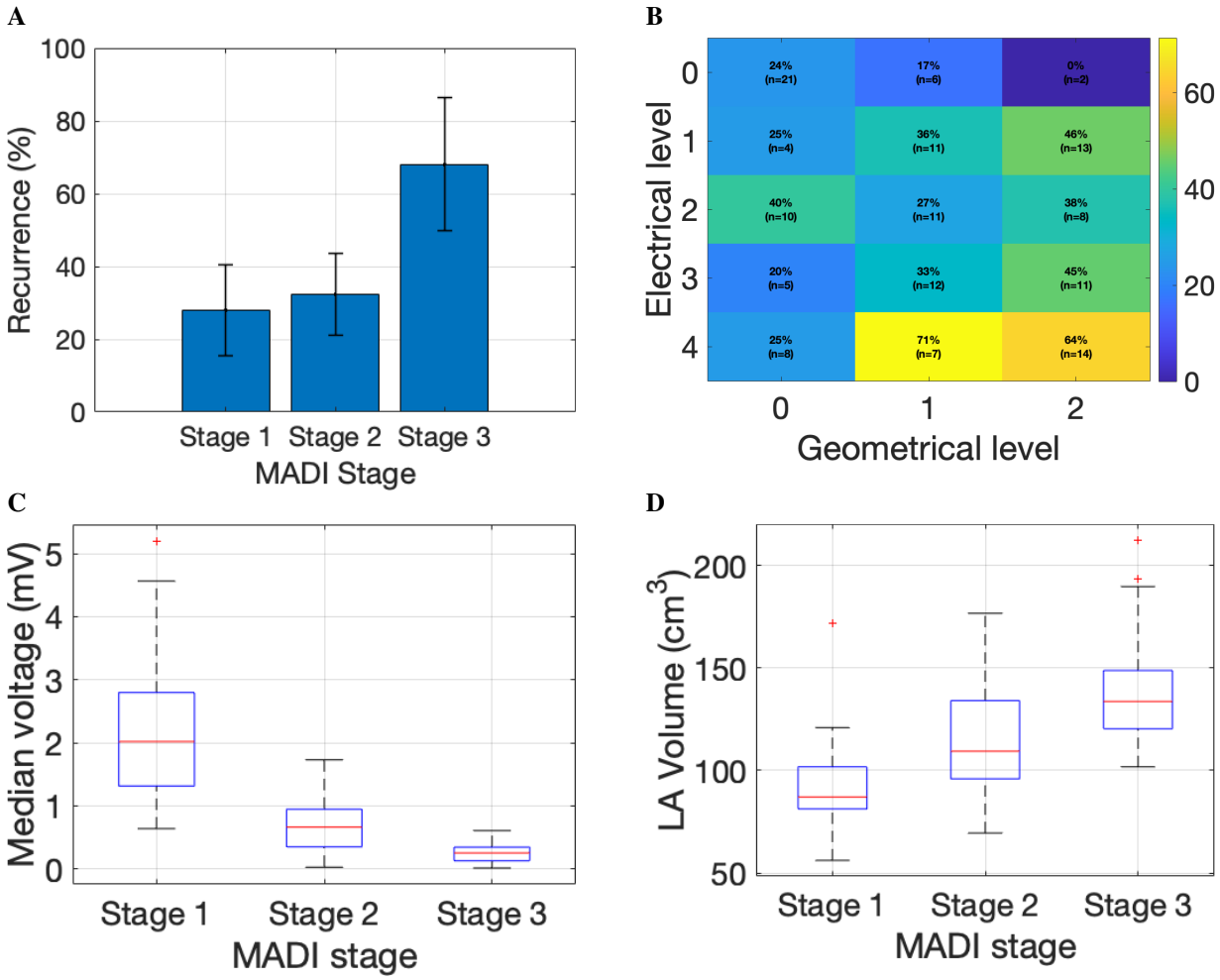

Figure 1. MADI phenotypic analysis. (A) Stage-dependent increase in AF recurrence, most pronounced in Stage 3 (error bars: 95% CI). (B) Electrical-geometric phenotype analysis identified E4+G1 as the phenotype with the highest observed recurrence. (C) Progressive decline in median bipolar voltage and (D) corresponding increase in left atrial volume across the three clinical stages.

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