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► To cite this version:

Raphaël Decoin, Laura Butruille, Thomas Defrancq, Jordan Robert, Nicolas Destrait, et al.. High liver fibrosis scores in metabolic dysfunction-associated fatty liver disease patients are associated with adverse atrial remodeling and atrial fibrillation recurrence following catheter ablation. *Frontiers in Endocrinology*, 2022, 13, 10.3389/fendo.2022.957245 . hal-04353006

HAL Id: hal-04353006

<https://hal.science/hal-04353006>

Submitted on 19 Dec 2023

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1 **High liver fibrosis scores in MAFLD patients are**
2 **associated with adverse atrial remodeling and atrial**
3 **fibrillation recurrence following catheter ablation**

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16 **Keywords: MAFLD, Atrial fibrillation, Atrial remodeling, Catheter ablation, Liver fibrosis.**

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17 **Abstract**

18 Background: A number of epidemiological studies have suggested an association between Metabolic-
19 dysfunction Associated Fatty Liver Disease (MAFLD) and the incidence of atrial fibrillation (AF).
20 However, the pathogenesis leading to AF in the context of MAFLD remains unclear. We therefore
21 aimed at assessing the impact of MAFLD and liver fibrosis status on left atrium (LA) structure and
22 function.

23 Methods: Patients with a Fatty Liver Index (FLI) >60 and the presence of metabolic comorbidities
24 were classified MAFLD+ . In MAFLD+ patients, liver fibrosis severity was defined using the
25 NAFLD Fibrosis Score (NFS) as follows: MAFLD w/o fibrosis ($NFS \leq -1.455$); MAFLD w/
26 indeterminate fibrosis ($-1.455 < NFS < 0.675$); MAFLD w/ fibrosis ($NFS \geq 0.675$). In a first cohort of
27 patients undergoing AF ablation, the structural and functional impact on LA of MAFLD was
28 assessed by LA strain analysis and endocardial voltage mapping. Histopathological assessment of
29 atrial fibrosis was performed in a second cohort of patients undergoing cardiac surgery. Finally, the
30 impact of MAFLD on AF recurrence following catheter ablation was assessed.

31 Results: In the AF ablation cohort (NoMAFLD n=123; MAFLD w/o fibrosis n=37; MAFLD ind.
32 fibrosis n=75; MAFLD w/severe fibrosis n=10), MAFLD patients with high risk of F3-F4 liver
33 fibrosis presented more LA low voltage areas compared to patients without MAFLD (16.5[10.25; 28]
34 vs 5.0[1; 11] low voltage areas p=0.0115); impaired LA reservoir function assessed by peak left atrial
35 longitudinal strain (19.7±8% vs 8.9±0.89% p=0.0268); and increased LA volume (52.9±11.7ml/m²
36 vs 43.5±18.0ml/m² p=0.0168). Accordingly, among the MAFLD patients those with high risk of F3-
37 F4 liver fibrosis presented a higher rate of AF recurrence during follow-up (p=0.0179). In the cardiac
38 surgery cohort (NoMAFLD n=12; MAFLD w/o fibrosis n=5; MAFLD w/ fibrosis n=3), an increase
39 in histopathological atrial fibrosis was observed in MAFLD patients with high risk of F3-F4 liver
40 fibrosis(p=0.0206 vs NoMAFLD; p=0.0595 vs MAFLD w/o fibrosis).

41 Conclusion: In conclusion, we found that liver fibrosis scoring in MAFLD patients is associated with
42 adverse atrial remodeling and AF recurrences following catheter ablation. The impact of the
43 management of MAFLD on LA remodeling and AF ablation outcomes should be assessed in
44 dedicated studies.

45 1 Introduction

46 Non-Alcoholic Fatty Liver Disease (NAFLD) refers to a spectrum of liver diseases characterized by
47 excessive hepatic fat accumulation, associated or not with liver inflammation and fibrosis with the
48 exclusion of chronic alcohol consumption. Recently, a new concept of Metabolic-dysfunction
49 Associated Fatty Liver Disease (MAFLD) has been proposed to broaden the diagnostic criteria to
50 meet the needs of a population not previously included in clinical studies¹. As such, the MAFLD
51 definition includes alcohol consumption in the presence of at least 1 metabolic syndrome criterium^{2,3}.
52 Fatty liver diseases are the leading cause of chronic liver diseases in many western countries with a
53 worldwide estimated prevalence of approximately 25%⁴. Several studies reported an epidemiological
54 association between MAFLD and cardiovascular diseases, and pathophysiological mechanisms
55 linking these two clinical entities have been recently suggested⁵⁻⁷.

56 Although the liver-heart interaction is well described in the context of atherosclerosis⁸ and ventricular
57 remodeling⁹, only sparse data explored the association between atrial pathology and MAFLD⁹⁻¹¹. A
58 limited number of epidemiological studies have shown an independent association between MAFLD
59 and the incidence of atrial fibrillation (AF)¹²⁻¹⁴, however the pathogenesis leading to AF in the
60 context of MAFLD remains unclear.

61 AF pathogenesis encompasses a wide spectrum of mechanisms involving electrophysiological and
62 structural remodeling of the left atrium (LA)¹⁵. Furthermore, metabolic disorders have been
63 previously associated with LA remodeling (*e.g.* mitochondrial dysfunction in diabetic patients¹⁶⁻¹⁸,
64 enhanced LA fibrosis in high fat diet fed mice¹⁹), but did not emphasize the liver phenotype.
65 Therefore, data assessing the impact of MAFLD on LA remodeling are severely lacking. Moreover,
66 such insights might critically impact the management of patients presenting both AF and MAFLD,
67 especially when an invasive management of AF (*i.e.* using catheter ablation) is considered.

68 We hypothesized that MAFLD is associated with poor LA remodeling and might thus alter outcomes
69 associated with AF catheter ablation. To explore this hypothesis, we first assessed the impact of
70 MAFLD on LA the structure and function (as assessed by LA echocardiographic parameters,
71 endocardial electrophysiological mapping and histopathological assessment of LA fibrosis) using two
72 distinct cohorts of patients. Then, the impact of MAFLD on AF recurrence following catheter
73 ablation was assessed.

74 2 Materials and methods

75 *Study populations*

76 Catheter ablation cohort: Between March 2018 and April 2021, we retrospectively enrolled all
77 patients candidate for a first AF catheter ablation in the Lille University Hospital. As specified in the
78 2016 ESC Guidelines for the management of AF, patients were eligible to catheter ablation if they
79 had new onset or under-treated paroxysmal, or persistent AF²⁰. Patients with prior AF catheter
80 ablation or severe valvular heart disease were excluded. The protocol was approved by the local
81 ethics committee and patients gave informed consent.

82 POMI-AF (NCT03376165): The cohort study population consisted of consecutive patients (aged ≥ 18
83 years) undergoing cardiac surgery referred to the cardiovascular surgery department at the Lille
84 University Hospital (Lille, France) for aortic valve replacement or mitral valve repair (with or
85 without coronary artery bypass graft). Patients with another notable valvular disease, a medical
86 history of previous cardiac surgery, or congenital heart diseases were excluded. The ethics committee
87 of our institution approved the cohort protocol. Written informed consent was obtained from all
88 patients before inclusion in this cohort.

89 *Diagnosis of MAFLD and severity assessment*

90 As recommended by the current guidelines²¹ and taking into account other metabolic disorders listed
91 below (including alcohol consumption)¹, MAFLD was diagnosed using the Fatty Liver Index (FLI),
92 which was calculated using blood triglyceride levels, body mass index (calculated as the weight in
93 kilograms divided by the height in square meters), gamma-glutamyl transpeptidase (GGT) activity in
94 blood, and waist circumference (in centimeters) according to^{22,23} as follows: $0.953 \times \ln(\text{triglycerides, mg/dL}) + 0.139 \times \text{BMI, kg/m}^2 + 0.718 \times \ln(\text{GGT, U/L}) + 0.053 \times \text{waist circumference, cm} - 15.745$. Patients with an FLI score of 60 or higher with metabolic syndrome (waist circumference
97 $>94\text{cm}$ in men or >80 in women associated with at least two of the following parameters :
98 triglyceridemia $>1.5\text{g/L}$; HDL-c $<0.4\text{g/L}$ in men or $<0.5\text{g/L}$ in women ; fasting glycaemia $>1\text{g/L}$;
99 systolic arterial blood pressure $>130\text{mmHg}$ and/or diastolic blood pressure $>85\text{mmHg}$)²⁴ were
100 considered as having MAFLD. To assess the severity of hepatic fibrosis, we used the validated
101 NAFLD fibrosis score (NFS) in patients with positive diagnosis of MAFLD³. The NFS was assessed
102 as follows: $[-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{body mass index (kg/m}^2) + 1.13 \times \text{diabetes mellitus (if presence, given 1)} + 0.95 \times \text{AST (U/L) to ALT (U/L) ratio} - 0.013 \times \text{platelet count}$

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104 $(10^{-9}/L) - 0.66 \times \text{albumin (mg/L)}$]. According to the original validation work, patients with a NFS of
105 0.675 or higher were considered as positive for advanced liver fibrosis. Patients presenting a NAFLD
106 fibrosis score below -1.455 were considered as free from advanced liver fibrosis. A score between
107 0.675 and -1.455 was considered indeterminate^{25,26}. For each patient, insulin resistance was estimated
108 by HOMA-IR calculation ($[\text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mmol/L)}] / 22.5$).

AF ablation procedure and low voltage area exploration

110 All procedures were performed under local anesthesia and conscious sedation using intravenous
111 boluses of morphine. Left atrial reconstruction was performed using a CARTO3 (Biosense
112 Webster®) electroanatomic mapping system. Mapping of the pulmonary veins was performed with a
113 deflectable decapolar catheter (Lasso, Biosense Webster®). Ablation was performed using a 3.5-mm
114 irrigated ablation catheter with contact force sensing (ThermoCool Biosense Webster®). A third,
115 standard quadripolar catheter was used for reference and placed into the coronary sinus. For all
116 procedures, and according to current guidelines, a pulmonary vein isolation was performed in both
117 paroxysmal and persistent AF and cavotricuspid isthmus ablation in case of typical atrial flutter.
118 Additional lines (superior vena cava isolation, left atrial roof line, other left atrial endocardial line),
119 voltage mapping or re-cording of continuous fragmented atrial electrograms (CFAEs) to target
120 ablation were deployed to consultant conviction. For patients with left atrial voltage mapping, data
121 were collected at the beginning of the AF ablation procedure in sinus rhythm, using an
122 electroanatomic mapping (EAM) system (CARTO3, Biosense Webster) and a mapping catheter with
123 a 3.5-mm distal tip and a 2-mm inter-electrode spacing (NaviStar, Thermocool Smartouch, Biosense
124 Webster Inc). Adequate endocardial contact was confirmed by stable electrograms and increased
125 contact force values of ≥ 10 g. The left atrium was divided into nine regions, i.e., septum, superior,
126 posterior, inferior, and lateral walls, and the 4 PVs antrum (Supplementary S1). In each predefined
127 region, at least 12 voltage-mapping points were collected. A low-voltage zone (LVZ) was defined by
128 a region with bipolar voltage less than 0.5 mV in patients in SR at the time of point acquisition. Low
129 voltage area was calculated as the ratio: point displaying voltage $<0.5\text{mV}/\text{total point acquires}$.

Follow-up and recurrence assessment

131 All patients underwent a clinical follow-up (up to 3 years). First AF recurrence was established as
132 documented AF or atrial flutter on 12-lead electrocardiogram and/or episode $>30\text{s}$ during Holter
133 monitoring. Within the first year after ablation, our in-house protocol unfolds electrocardiograms

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134 when symptoms are reported, during outpatient visits in our tertiary hospital, or in the treating
135 cardiologist's office (at 3, 6 and 12 months). 24-h to 48-h Holter monitoring are also performed at 3
136 months and 6 months. The treating cardiologists then followed up with the patients, with the number
137 of outpatient visits at clinician discretion. A 90 days 'blinking period' was respected. Follow-up of
138 "MAFLD" vs "NoMAFLD" subgroups was censored at 1200 days, and follow-up of "MAFLD"
139 patients according to liver fibrosis risk was censored at 400 days because the sample size dropped to
140 only one patient.

Histological analysis

142 Atrial biopsies were recovered during the cardiac operation in POMI-AF patients. Biopsies were then
143 processed for paraffine embedding. Paraffin-embedded sections were stained with Sirius Red (RAL
144 ref.363440-0005) and images were captured using a ZEISS Axio Scan.Z1 slide scanner. Collagen
145 surface assessment was performed using ImageJ software (version 2.1.0/1.53C for Windows) on the
146 entire image surface, except for the epicardium. The area corresponding to collagen was divided to
147 the total area of the quantified surface to obtain the ratio of fibrosis.

Statistics

149 Continuous variables were tested for normality with Shapiro test, and were represented as mean±SD
150 in case of normality or median [IQR] otherwise. Continuous variables with no Gaussian distribution
151 are given as median (IQR). Categorical variables were given as percentages of individuals. Bivariate
152 comparisons were performed using the t test for normally distributed continuous variables or the
153 Mann-Whitney U test for variables not normally distributed. Bivariate comparisons of categorical
154 variables were done with the χ^2 test. When expected counts were lower to 5, Fisher's exact test was
155 used. Event-free survival was estimated by the Kaplan–Meier method. First, the association between
156 baseline characteristics and outcome was investigated in MAFLD and non-MAFLD patients
157 separately. The association between liver fibrosis and AF recurrence was then investigated according
158 to the 3 groups defined by the MAFLD fibrosis score (no or mild fibrosis, indeterminate score and
159 severe fibrosis or cirrhosis). The baseline characteristics between the 3 groups were compared by
160 one-way ANOVA for normally distributed variables or the Kruskal Wallis test for not normally
161 distributed variables. Second, the association between liver fibrosis and AF recurrence was
162 investigated after adjustment confounders [namely subtype of AF, age, left atrial size, BMI, sex] in
163 separate multivariate proportional hazards Cox models. A two-tailed P-value <0.05 was considered

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164 statistically significant. All analyses were done using MedCalc v16.4 (Olstead, Belgium). Visual
165 rendering of the graphics were done using GraphPad Prism version 9.0.0 for Windows (GraphPad
166 Software, San Diego, California USA).

167 **3 Results**

168 *MAFLD classifications and baseline characteristics.*

169 291 patients referred to our center for a first AF ablation were included from march 2017 to
170 december 2021. After excluding patients with missing components of non-invasive hepatic fatty liver
171 or fibrosis scores, and/or no available follow-up for AF recurrence, 245 were available for analysis.
172 Using the FLI cut-off of 60²⁷, 123 patients were classified as free from MAFLD (“NoMAFLD”
173 group) and 122 as having MAFLD (MAFLD group). Comparing “NoMAFLD” to “MAFLD” (**Table**
174 **1**), no differences were observed regarding age (60±10 vs 58±10 years). However, cardiovascular
175 comorbidities were more prevalent in the MAFLD group, such as hypertension (29% vs 55%
176 p=0.0001) or heart failure (20% vs 30% p=0.083). Half of procedures were performed for
177 paroxysmal AF. Interestingly, MAFLD patients displayed LA dilatation with an increased area (23
178 [19; 26]cm² vs 28[24; 31]cm², p<0.0001).

179 In the MAFLD group, the NFS was used to dichotomize patients at risk for severe liver fibrosis
180 (n=10; “MAFLD w/ fibrosis”), patients with an undetermined risk for liver fibrosis (n=75; “MAFLD
181 indetermin. fibrosis”), and patients not at risk for liver fibrosis (n=37; “MAFLD w/o fibrosis”). The full
182 flow chart is provided in **Figure S2**. Baseline characteristics of the three resulting groups are shown
183 in **Table 2**. Patients in the “MAFLD w/ fibrosis” group were older (52±11 for “MAFLD w/o
184 fibrosis” vs 60±8 for “MAFLD indetermin. Fibrosis” vs 67±4years for “MAFLD w/ fibrosis” p<0.001)
185 and had higher HOMA-IR (1.99 [1.45; 2.60] for “MAFLD w/o fibrosis” vs 2.65 [1.89; 3.58] for
186 “MAFLD indetermin. Fibrosis” vs 3.44 [1.65; 4.43] for “MAFLD w/ fibrosis” p=0.029). Thus, the NFS
187 identified a subgroup of patients exhibiting a poor metabolic profile.

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188 *Left atrial structural and functional remodeling according to NAFLD Fibrosis Score (NFS)*

189 Structural and function atrial remodeling were explored in this cohort using 3D-voltage mapping and
190 LA echographic parameters. A total of 183 patients were explored in sinus rhythm with 3D-voltage
191 mapping. Of note, the median left atrial low voltage area was 0% [0; 10]. Therefore, most patients
192 presented no or a limited low voltage area. However, the “MAFLD w/ severe fibrosis” patients
193 presented an increase in extra-veinous low voltage area sections (**Figure 1A**), in total low voltage
194 area sections (**Figure 1B**) compared to the three other groups (*e.g.* total low voltage area sections:
195 “NoMAFLD”=5 [1; 11] vs “MAFLD w/ severe fibrosis”=16.5 [10.25; 28] p=0.0115). The two
196 remaining MAFLD subgroups (“MAFLD indetermin. fibrosis” and “MAFLD w/o fibrosis”) did not
197 display any significant difference regarding low voltage area compared to “noMAFLD” patients.
198 Since low voltage zones have been associated to local fibrosis²⁸ which may impact LA
199 hemodynamics, we explored the LA reservoir and contractile function assessed by four chamber LA
200 2D-speckle tracking in patients presenting sinus rhythm prior to AF ablation.

201 The LA reservoir function, as assessed by the mean peak left atrial longitudinal strain (PALS), was
202 significantly reduced in the “MAFLD w/ severe fibrosis” group compared to the “NoMAFLD” group
203 (**Figure 1C**, 19.7±8% vs 8.9±0.89% p=0.0268). Furthermore, a trend toward a decrease of the peak
204 atrial contraction strain (PACS) was also observed in the “MAFLD w/ severe fibrosis” compared to
205 “NoMAFLD” group (**Figure 1D**, 10.0±5.1% vs 4.1±5.2% p=0.0628). Taken together, these data
206 indicated an altered LA compliance and a trend toward a depressed contractility of the LA in
207 patients presenting “MAFLD w/ severe fibrosis”. Accordingly, an increased LA volume was
208 observed with the LA volume indexed (LAVI) (**Figure 1E**, 43.5±18ml/m² in “NoMAFLD” vs
209 52.9ml/m² in “MAFLD w/ severe fibrosis”, p=0.0168) and 50.4% of the “NoMAFLD” group vs 90%
210 in the “MAFLD w/ severe fibrosis group” presenting severe LA dilatation (p=0.0196).
211 Representative examples of atrial function and voltage according to MAFLD fibrosis status are
212 provided in **Figure 1F**. Taken together, these data suggest that increased NFS in a MAFLD
213 population detected more pronounced LA remodeling in patients which resulted in altered
214 electrophysiological and hemodynamic properties.

215 *Histological assessment of atrial remodeling*

216 The above data suggest an increase in atrial fibrosis in patients presenting MAFLD with severe liver
217 fibrosis. We therefore explored the presence of atrial fibrosis according to MAFLD status in atrial

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218 biopsies collected in a second cohort of patients undergoing cardiac surgery (POMI-AF
219 NCT03376165). In this cohort, a total of 20 patients underwent right atrial appendage biopsies during
220 cardiac surgery and were classified according to the same FLI and NFS cut-off levels. Their baseline
221 characteristics are summarized in **Table S1**. The histological analysis (using Sirius-Red coloration)
222 of the 20 biopsies revealed atrial fibrosis patches (**Figure 2**). Of note, the fibrosis patches originated
223 from capillary vessels, as frequently observed in the fibrotic process. After a semi-automatic
224 quantification, patients in the “MAFLD w/ severe fibrosis” had an on average 2.78 fold increase in
225 atrial fibrosis compared to “NoMAFLD” patients ($p=0.0206$). Accordingly, these patients tend to
226 display higher LA areas (**Table S1**, 24 [22.5-29.5] vs 41 [24-45] cm², $p=0.0847$). Thus, in line with
227 the AF ablation cohort, an increased NFS among MAFLD patients is associated with more severe
228 structural atrial remodeling.

229 *AF ablation recurrence according to MAFLD and liver fibrosis status*

230 Since atrial remodeling might critically impact the outcomes of AF ablation, we assessed the impact
231 of MAFLD status on AF recurrence following ablation in the AF ablation cohort. In 201 out of 245
232 patients, a lone pulmonary vein isolation (PVI) was performed. For the remaining 46 patients,
233 additional lesions were performed and included roof lines for 19 patients, cavo-tricuspid isthmus
234 lines for 19 patients, box isolation for 6 patients and other lines for 15 patients. Of note, at the end of
235 the procedure, PVI was achieved in 100% of the patients.

236 After a median follow-up of 418 days [197; 868], AF recurrence occurred in 42.8% of the patients.
237 No significant difference in AF recurrence was observed according to MAFLD status alone (54% in
238 MAFLD patients vs 41% in noMAFLD patients at 1200 days; log-rank: $p= 0.3093$. **Figure 3A**). The
239 impact of liver fibrosis on AF recurrence was then assessed in the 3 MAFLD groups (“MAFLD w/o
240 fibrosis”; “MAFLD indetermin. fibrosis”; “MAFLD w/ severe fibrosis”). AF-free survival curves,
241 following a first intervention, up to 400 days are shown in **Figure 3B**. During follow-up, the
242 “MAFLD w/ severe fibrosis” patients presented a higher rate of AF recurrence (77%) than patients
243 with indetermin. fibrosis (32.5%) or without hepatic fibrosis (17.5%) according to NFS (log-rank for
244 trend $p= 0.0179$; “MAFLD w/o fibrosis” vs “MAFLD w/ severe fibrosis” HR=5.345 IC95% [1.335-
245 21.40]) (**Figure 3B**). Furthermore, the non-adjusted cox regression model (**Table 3A**) identified NFS
246 as predictive of AF recurrence ($p=0.0184$). After adjustment on LA area and AF subtype (known
247 non-covariable risk factors), the NFS remained significantly predictive of AF recurrence (**Table 3B**).

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248 In addition to the incidence of AF recurrence, the characteristics of AF recurrence according to
249 MAFLD status were further explored. During the follow-up, 103 patients presented AF recurrences.
250 Of note, 48 of this recurrence occurred as paroxysmal AF, 41 as persistent AF and 14 as permanent
251 AF. Moreover, the “MAFLD w/ severe fibrosis” group presented more frequently AF recurrence as
252 permanent AF subtype. Conversely, recurrences as paroxysmal AF were gradually less frequent in
253 the “MAFLD w/ severe fibrosis” group (**Figure 3C**, Chi^2 : $p=0.0004$). Accordingly, MAFLD patients
254 with severe liver fibrosis were less likely to undergo a second AF ablation (=redo) after recurrence,
255 in comparison to MAFLD patient without severe liver fibrosis (Chi^2 -for-trend: $p=0.051$, **Figure**
256 **S3A**).

257 To gain insight into the mechanisms leading to AF recurrence in “MAFLD w/ severe fibrosis”
258 patients, the electrophysiological findings observed during redo procedures were further explored.
259 During follow-up, 25 redo procedures were performed. During redo procedures, venous
260 reconnections were observed in 84% of patients. Interestingly, patients presenting AF recurrence
261 without venous reconnection tended to have higher NFS compared to patients presenting venous
262 reconnection. (**Figure 3D**).

263 Taken together, these data suggest that patients presenting MAFLD and severe liver fibrosis exhibit a
264 higher risk for AF recurrence after ablation. Furthermore, these recurrences are more likely
265 associated to a higher AF burden.

266 4 Discussion

267 Cardiac remodeling, AF and metabolic disorders are closely intertwined. Furthermore, MAFLD has
268 been recently suggested as a potential actor in AF pathogenesis of patients exhibiting metabolic
269 syndrome¹⁰.

270 In this study, we showed that (i) the presence of MAFLD is associated with adverse atrial remodeling
271 as assessed by echocardiographic, electrophysiological and histopathological analysis. More
272 precisely, we showed a structural remodeling as indicated by the increase in LA volume, impaired
273 LA reservoir function and increased low voltage areas in MAFLD patients at risk of liver fibrosis.
274 Accordingly, atrial fibrosis was increased in MAFLD patients at risk of liver fibrosis. (ii) The liver
275 fibrosis scoring in MAFLD patient was predictive of AF recurrence after ablation. (iii) In case of AF
276 recurrence, MAFLD patients with high liver fibrosis score presented a higher AF burden.

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277 Atrial remodeling

278 Atrial remodeling can be characterized by any complex of structural, architectural, contractile or
279 electrophysiological changes affecting the atria with the potential to produce clinically-relevant
280 manifestations²⁹. Such hallmarks of LA remodeling process were recently defined by the concept of
281 atrial cardiomyopathy¹⁵. Beyond its pathophysiological value, accumulating works highlight the
282 clinical relevance of LA remodeling in order to manage AF and non-AF patients^{30,31}.

283 It is now well recognize that metabolic disorders critically affect the course of patients presenting AF
284 in terms of AF incidence³², stroke risk³³, and rhythm management³⁴. Therefore, understanding LA
285 remodeling in the context of metabolic disorders represents a major opportunity to improve
286 metabolic patient's care. However, the mechanisms leading to LA remodeling in the context of
287 metabolic disorders remain incompletely understood.

288 Although metabolic disorders were first believed to directly induce LA remodeling and AF³⁵, recent
289 data highlighted the potential role of MAFLD as a candidate involved in the pathogenesis of AF in
290 patients presenting metabolic disorders. Such a mechanism was first suggested by epidemiological
291 studies associating NAFLD and the incidence of AF. Targher et al. published two studies involving
292 type 2 diabetes patients who had an independent association between NAFLD and AF development
293 (adjusted OR: 5.88; 95% CI: 2.72 to 12.7 and 6.38; 95% CI: 1.7 to 24.2)^{13,36}. Similarly, Käräjämäki et
294 al. published a prospective cohort study of 958 hypertensive patients, which demonstrated an
295 independent association between NAFLD and AF (adjusted OR: 1.88; 95% CI: 1.03 to 3.45)³⁷.

296 Despite, these established epidemiological observations, mechanistic approaches are severely
297 lacking. Recently, a study published by Suffee *et al.* using a High Fat Diet mouse model showed a
298 vulnerability to AF linked to a shorter action potential duration caused by enhanced K-ATP current
299 in context of obesity¹⁹. Although interesting, such studies did not emphasize the liver phenotype so
300 far.

301 A precise assessment of LA remodeling in MAFLD patients was not performed so far to the best of
302 our knowledge. Of note, assessing LA remodeling in patients require a multidimensional approach to
303 qualify hemodynamic, histopathological and electrophysiological parameters of atria.

304 In the AF ablation cohort, the hemodynamic assessment of LA was performed using
305 echocardiographic speckle-tracking, which was previously correlated with LA hemodynamic

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306 profile³⁸. Importantly, we observed a reduced reservoir and contractile function in patient with a high
307 probability of liver fibrosis (“MAFLD w/ fibrosis”). Such hemodynamic alteration might critically
308 impact patient’s outcomes since impaired PALS was previously associated with increased risk for
309 AF, stroke, and heart failure³⁹.

310 The electrophysiological remodeling was also observed with an increase in bipolar low voltage areas
311 in patients presenting MAFLD at high risk of liver fibrosis. Low-voltage areas act as arrhythmogenic
312 substrates, promoting more persistent AF by slowing electrical conduction and sustaining fibrillatory
313 conduction⁴⁰⁻⁴². Furthermore, low voltage areas were identified as predictors of AF recurrence
314 following AF ablation and associated with an increased risk for stroke⁴³. Therefore, the increased
315 prevalence of low voltage area in MAFLD patients might severely impact outcomes following
316 ablation.

317 In our study, the presence of atrial fibrosis in patients with MAFLD was specifically assessed using
318 histopathological assessment of right atrial appendages biopsies. Interestingly, we found that atrial
319 fibrosis was particularly increased in patients presenting MAFLD with high liver fibrosis scoring.
320 Atrial fibrosis is a dominant factor for the development of AF⁴⁴, and is promoted by several clinical
321 conditions such as heart failure or hypertension⁴⁵ and AF itself⁴⁶.

322 Taken together our data suggest a fibrotic-mediated LA remodeling according to MAFLD and liver
323 fibrosis classification. However, the mechanisms leading to such fibrotic process need to be clarified.
324 Atrial and liver fibrosis mechanisms share some similar pathogenic mechanisms, upstream to
325 fibroblast activation within the myocardium or its counterpart, the hepatic stellate cell (HSC), in the
326 liver. These cells, as activated myofibroblast, contributes to the majority of collagen formation^{47,48}. In
327 the liver, recruited or resident macrophages are known to trigger HSC activation through TGF β ⁴⁹.
328 Similarly in the heart, macrophages are thought to be a major actor in fibroblast activation⁵⁰. Thus, if
329 we consider MAFLD as a systemic low grade inflammation, fibrosis development may be due to
330 prior immune cell activation within the heart. Moreover, in our study, short term MAFLD (*i.e.* with
331 low liver fibrosis probability) is not associated with atrial fibrosis, making the early metabolic
332 dysfunction hypothesis alone insufficient in our population.

333 The visceral adipose tissue was also suggested as a major actor in atrial remodelling. More
334 particularly, epicardial adipose tissue volume has been associated with AF incidence and ablation
335 outcome⁵¹⁻⁵⁴. Previous studies also suggested the potential role of adipokines in myocardial

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336 remodelling. In a cohort of 94 patients, the circulating adiponectin level was inversely correlated with
337 indexed left ventricular mass⁵⁵. In line, a positive correlation was observed between indexed left
338 atrial volume and E/e' ratio with serum adiponectin levels⁵⁶. These clinical findings are also
339 supported by translational studies suggesting the importance of adipokines on atrial myocardium^{57,58}.
340 Patients presenting MAFLD with liver fibrosis display major alterations in adipokines profile such as
341 lower adiponectin⁵⁹ levels or increased leptin levels⁶⁰, in comparison to patients without morbid
342 obesity. Therefore, an adipose tissue-mediated atrial remodelling could also be considered in the
343 context of MAFLD.

344 Atrial fibrillation recurrence

345 In our study, the impact of MAFLD on AF recurrence was assessed. We first report an incidence of
346 AF recurrence of 42.8% at 418 days of median follow-up. Such AF recurrence incidence is consistent
347 with previous AF ablation studies including similar proportions of persistent and paroxysmal AF : in
348 the open-label multicenter clinical trial CABANA⁶¹ (n=1108), AF recurrence was observed in 49.9%
349 of the patient, of which 16% had persistent or long-standing persistent AF while we found 13.6% in
350 our study.

351 The impact of metabolic disorders on AF ablation outcomes has been previously demonstrated. In the
352 LEGACY trial⁶², 355 overweight patients with non-permanent AF were classified according to body
353 weight loss (median follow up $\sim 48 \pm 18$ months). Weight loss of 10% or more accomplished to
354 increase by a factor 6 probability of arrhythmia-free survival (adjusted OR: 6; 95% CI: 3.4 to 10.3).
355 Accordingly, a recent study showed a similar impact of weight loss of 10% or more on AF recurrence
356 after ablation among MAFLD patient (Log-rank = 27.90; $p < 0.0001$)⁶³. This latter article by
357 Donnellan *et al.*⁶³ also suggested that MAFLD mediates the effect of metabolic disorders on AF
358 ablation outcomes. In this study, the authors found a higher rate of AF recurrence (56% vs 21% at 60
359 month) using liver imaging to diagnose steatosis presence in MAFLD. Interestingly, we did not
360 found this effect comparing MAFLD patient to “NoMAFLD” patient using a clinico-biological score
361 (*i.e.* FLI), suggesting that this effect is indeed driven by liver steatosis, and not by one of the
362 components of the score such as the BMI. Using the NFS to stratify patient according to probability
363 of liver fibrosis, Donnellan *et al.* reported a higher arrhythmia recurrence with high probability of liver
364 fibrosis (82%) compared to patients whose risk of fibrosis is excluded (31%) (Log rank=11.70;
365 $p=0.003$.) Our data are therefore in accordance with those from of Donnellan *et al.* in a different
366 population of MAFLD patients.

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367 For the first time, we provide insights regarding characterization of AF recurrence after AF ablation
368 in MAFLD patients. Interestingly, we observed that MAFLD patients presented a higher AF burden
369 when recurrence occurred as shown by the increased proportion of permanent AF following AF
370 recurrence. This clinical observation may be secondary to the atrial remodeling observe in these
371 patient leading to long lasting AF episodes. Therefore, poor metabolic profile associated with high
372 risk of liver fibrosis could be considered as a risk marker of atrial remodeling and poor related
373 clinical outcomes.

374 Future perspectives

375 The association between MAFLD and atrial remodelling raises several questions regarding
376 management of patients scheduled for AF ablation. On the one hand, the impact of intensive
377 management of the metabolic syndrome prior to AF ablation is likely beneficial to reduce recurrence
378 risk, and may even justify postponing the procedure. On the other hand, a personalized AF ablation
379 strategy in MAFLD patients with severe liver fibrosis could be considered, with a more extensive
380 approach (e.g additional lines and/or combined approach with vein of Marshall ethanol infusion),
381 especially in the setting of persistent AF. Therefore, further clinical studies assessing the impact of
382 AF ablation strategies after MAFLD scoring are needed to address these questions.

383 Study limitations

384 In both cohorts, patients were classified under the MAFLD spectrum, thus including mild to
385 moderate alcohol consumption and other cardio-metabolic pathologies. Using this classification it is
386 more difficult to attribute the observation specifically to the liver, but the data is certainly more
387 relevant to clinical practice with patients suffering of metabolic syndrome¹. Liver status was
388 determined using two non-invasive biological scores (FLI & NFS) in accordance to the first steps of
389 NAFLD diagnosis recommendation²¹, given that liver imaging (elastography or MRI) are not in
390 common practice among cardiologists, liver biopsies are not a possibility in such cohorts, and to be
391 consistent with previous liver fibrosis classification²². This classification results in a “at risk”
392 classification of patient, without being able to affirm the real liver status. Moreover, it results in a
393 grey area (“indeterminate fibrosis”) for the majority of patients. The BMI was not included in our
394 Cox model since this variable was included in the FLI and NFS formula. Therefore, further studies
395 assessing the impact of liver fibrosis on AF ablation using alternative liver fibrosis assessment tools
396 (e.g. transient elastography) to better integrate such confounder. Moreover, we had few patients in

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397 the most severely affected group in both cohorts, resulting in a lack of statistical power. Nevertheless,
398 due to the low number of “MAFLD w/ fibrosis” patients indicated for invasive intervention, a much
399 larger cohort would be needed. The impact of the duration of MAFLD was not integrated in the
400 current analysis. Given the complex dynamic process involving metabolic disorders and fibrotic
401 processes, further studies will be of interest to specifically investigate the impact of MAFLD duration
402 on LA remodeling. Similarly, duration of AF history was not available in our cohort as it would
403 require intensive cardiac monitoring. Nevertheless, the AF subtypes still significantly correlate with
404 the overall AF burden as shown in previous studies⁶⁴. Finally, the screening of AF recurrence was not
405 based on a predefined intensive screening strategy but on routine clinical practice. Therefore, this
406 could result in a significant rate of non-detected AF recurrences, however counterbalanced by the
407 relative long-term follow-up of the cohort reducing the probability of non-detected AF recurrences.

408 Conclusion

409 Patients presenting MAFLD at risk for liver fibrosis exhibit an increased LA remodeling with
410 impaired hemodynamic, electrophysiological and histopathological properties. These patients also
411 exhibit a higher risk for AF recurrence following catheter ablation. The impact of the management of
412 MAFLD on LA remodeling and AF ablation outcomes should be assessed in dedicated studies.

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413 **5 Conflict of Interest**

414 The authors declare that the research was conducted in the absence of any commercial or financial
415 relationships that could be construed as a potential conflict of interest.

416 **6 Author Contributions**

417 Patient inclusion and follow-up : (T.D., J.R., C.K., F.B., A.V., D.K.) ; Echography : (A.C., S.A.,
418 S.S.) ; biochemical assay : (P.M.) ; study design : (R.D., B.S., D.M., S.N., L.B., E.W., Z.G., D.D.) ;
419 wrote and/or revised manuscript : (R.D., B.S., D.M., S.N.).

420 **7 Funding**

421 This work was supported by the French National Agency programs PreciDIAB grant (ANR 18-
422 IBHU-0001), the European Genomic Institute for Diabetes (EGID, ANR-10-LABX-0046) and
423 PreciNASH (ANR-16-RHUS-0006). BS was a recipient of an ERC Advanced Grant (no. 694717).

424 **8 Acknowledgments**

425 We thank the BICeL-(UMS2014-US41) cell imaging platform for the access to the equipment and
426 for the technical advice provided.

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614

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615 **Table 1 : baseline characteristics According to MAFLD status**

Criteria	NOMAFLD (N = 123)	MAFLD (N=122)	P	616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657	616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657
	FLI<60	FLI≥0			
Age (years)	60.3±10.2	58.1±9.9	0.08		
Women, n (%)	56 (46%)	29 (23%)	0.0004		
BMI (kg/m ²)	24.7±3.0	31.4±4.5	<0.0001		
Chronic alcohol consumption, n (%)	9 (7%)	22 (18%)	0.023		
Waist circumference (cm)	91.3±9.6	112.0±12.1	<0.0001		
Hypertension, n (%)	36 (29%)	68 (55%)	0.0001		
Diabetes mellitus, n (%)	15 (12%)	27 (22%)	0.06		
CHA ₂ DS ₂ Vasc	1 [1;3]	2 [1;3]	0.409		
Paroxysmal AF, n (%)	72 (59%)	51 (41%)	0.004		
Persistent AF, n (%)	51 (41%)	69 (56%)			
PVI alone, n (%)	100 (83%)	92 (79%)	0.53		
PVI + lines, n (%)	21 (17%)	25 (21%)			
AAD at discharge	22 (17.9%)	34 (27.8%)	0.078		
Flecainide	12 (55%)	13 (38%)			
Sotalol	4 (18%)	4 (12%)			
Amiodarone	6 (27%)	17 (50%)			
History of heart failure, n (%)	24 (20%)	37 (30%)	0.08		
LVEF – normal range, n (%)	58 (48%)	38 (31%)	0.0075		
LVEF – mildly anormal range, n (%)	60 (50%)	76 (61%)			
LVEF – anormal range, n (%)	3 (2%)	10 (8%)			
Left atrium area (cm ²)	23 [19;26]	28 [24;31]	<0.0001		
Fasting glucose (mg/dl)	98±15	108±18	<0.0001		
HOMA IR	1.34 [0.89;2.06]	2.45 [1.65;3.45]	<0.0001		
Triglycerides (g/l)	90 [72;116]	137 [106;182]	<0.0001		
ASAT (UI/l)	23 [18;26]	24 [18;30]	0.027		
ALAT (UI/l)	20 [16;26]	27 [21;37]	<0.0001		
Gamma GT (UI/l)	24 [18;34]	47 [32;86]	<0.0001		
Albumin (g/l)	38 [36;42]	39 [36;42]	0.906		
Nt pro BNP (ng/l)	209 [97;487]	294 [115;659]	0.198		

658 linear trends (AF subtype ; PVI±other lines ; LVEF) chi-squared for trend. Abbreviations: MAFLD=
659 Metabolic-dysfunction Associated Fatty Liver Disease ; BMI=Body Mass Index ; AF=Atrial
660 Fibrillation ; PVI=Pulmonary Vein(s) Isolation ; AAD=Anti-Arrhythmic Drug ; LVEF=Left
661 Ventricular Ejection Fraction ; FLI=Fatty Liver Index. Norms: chronic alcohol consumption >40 g

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662 *per day in men, and >20 g per day in women*⁶⁵; *LVEF normal range* $\geq 50\%$; *mildly anormal rang*
663 *41-49% ; anormal range* $\leq 40\%$ ⁶⁶.

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664 **Table 2 : baseline characteristics of adults with MAFLD diagnosis classified according to liver**
 665 **fibrosis risk using the NAFLD Fibrosis Score (NFS)**

Criteria	No or mild fibrosis (n=37)	Indeterminate (n=75)	Severe fibrosis (n=10)	P
	FLI>60 NFS<-1.455	FLI>60 -1.455<NFS<0.675	FLI>60 NFS>0.675	
Age (years)	52±11	60±8	67±4	<0.001 (# Ø)
Women, n (%)	10 (26%)	15 (19%)	4 (40%)	0.319
BMI (kg/m ²)	30.0±3.6	32.1±4.6	31.5±6.1	0.056
Chronic alcohol, n (%)	4 (10.5%)	14 (18.4%)	4 (40%)	0.092
Waist circumference (cm)	108±11	114±12	108±11	0.042 (#)
Hypertension, n (%)	15 (40%)	44 (58%)	9 (90%)	0.012 (Ø)
Diabetes mellitus, n (%)	3 (8%)	19 (25%)	5 (50%)	0.009 (Ø)
CHA ₂ DS ₂ Vasc	1 [0;2]	2 [1;3]	4 [3;4]	<0.001 (Ø)
Paroxysmal AF, n (%)	23 (60%)	25 (33%)	3 (30%)	0.115
Persistent AF, n (%)	14 (37%)	48 (63%)	7 (70%)	
PVI alone, n (%)	26 (74%)	60 (83%)	6 (60%)	0.182
PVI + lines, n (%)	9 (26%)	12 (17%)	4 (40%)	
AAD at discharge	11 (29.7%)	21 (27.6%)	2 (20%)	0.5919
Flecainide	7 (64%)	6 (29%)	0 (0%)	0.034 (#)
Sotalol	1 (9%)	3 (14%)	0 (0%)	
Amiodarone	3 (27%)	12 (57%)	2 (100%)	
History of heart failure, n (%)	7 (18%)	29 (38%)	1 (10%)	0.078
LVEF – normal range, n (%)	32 (84%)	51 (67%)	8 (80%)	
LVEF – mildly anormal range, n (%)	6 (16%)	11 (15%)	1 (10%)	
LVEF – anormal range, n (%)	0 (0%)	14 (18%)	1 (10%)	0.005 (# Ø)
Fasting glucose (mg/dl)	101±8	110±20	119±27	
HOMA IR	1.99 [1.45;2.60]	2.65 [1.89;3.58]	3.44 [1.65;4.43]	
Triglycerides (g/l)	135 [111;167]	144 [107;197]	109 [101;177]	0.221
ASAT (UI/l)	25 [19;30]	24 [18;30]	27 [18;34]	0.662
ALAT (UI/l)	30 [23;43]	27 [19;35]	24 [15;33]	0.052
Gamma GT (UI/l)	49 [33;80]	45 [30;85]	63 [42;153]	0.220
Albumin (g/l)	40 [37;42]	39 [36;41]	35 [32;39]	0.023 (Ø)
Nt pro BNP (ng/l)	205 [58;595]	313 [138;659]	472 [232;1257]	0.164

666 Statistics: for continuous variables with normal distribution = Student's t-test ; for continuous
 667 variables without normal distribution = Mann-Whitney U test ; for frequencies = chi-squared test ;
 668 for frequencies with linear trends (AF subtype ; PVI±other lines ; LVEF) chi-squared for trend.
 669 Abbreviations: MAFLD= Metabolic-dysfunction Associated Fatty Liver Disease ; BMI=Body Mass

Left atrial remodeling and MAFLD

670 *Index ; AF=Atrial Fibrillation ; PVI=Pulmonary Vein(s) Isolation ; AAD=Anti-Arrhythmic Drug ;*
671 *LVEF=Left Ventricular Ejection Fraction ; FLI=Fatty Liver Index. Norms: chronic alcohol*
672 *consumption >40 g per day in men, and >20 g per day in women ⁶⁵ ; LVEF normal range $\geq 50\%$;*
673 *mildly anormal rang 41-49% ; anormal range $\leq 40\%$ ⁶⁶. Symbols: #=significant No or mild fibrosis vs*
674 *Indeterminate \emptyset =significant No or mild fibrosis vs severe fibrosis.*

Left atrial remodeling and MAFLD

675 **Figure 1 : left atrial structural and electrical remodeling parameters.** Number of low voltage
 676 area extra-
 677 venous
 678 (A) or
 679 total (B) ;
 680 peak atrial
 681 longitudin
 682 al strain
 683 (C) and
 684 peak atrial
 685 contractio
 686 n strain
 687 (D) ; left
 688 atrial
 689 volume

690 indexed to body surface area (E) ; Representative echography, strain values and bipolar voltage maps
 691 (low voltage cut-off: 0.5mV) (F). NoMAFLD: FLI<60 ; MAFLD w/o fibrosis : FLI>60 &
 692 NFS<1.455 ; MAFLD ind. fibrosis : FLI>60 & -1.455<NFS<0.675 ; MAFLD w/ severe fibrosis :
 693 FLI>60 & NFS>0.675. Kruskal-Wallis test followed by Dunn's *post hoc* test. *p<0.05 ; **p<0.01 ;
 694 ***p<0.001. Abbreviations: MAFLD= *Metabolic-dysfunction Associated Fatty Liver Disease* ;
 695 LA=Left atria ; PALS= *Peak atrial longitudinal strain* ; PACS=*peak atrial contraction strain* ;
 696 LAVI=Left atrial volume index.

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700 **Figure 2 : Histological analysis of atrial fibrosis in patient biopsies.** Representative images of
 701 atrial fibrosis in NoMAFLD patient (A) ; MAFLD w/o fibrosis (B) ; MAFLD w/ severe fibrosis (C).
 702 Red arrows indicates fibrotic foci. Semi-automatic quantification : ratio between positive fibrotic area
 703 and total selected area (D). NoMAFLD: FLI<60 ; MAFLD w/o fibrosis : FLI>60 & NFS<1.455 ;
 704 MAFLD w/ severe fibrosis : FLI>60 & NFS>0.675. Kruskal-Wallis test followed by Dunn's *post hoc*
 705 test. *p<0.05. Abbreviations: MAFLD= *Metabolic-dysfunction Associated Fatty Liver Disease*

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709 **Figure 3 : AF recurrence burden according to liver status.** Atrial fibrillation recurrence after first
 710 ablation according to the MAFLD status (A) and liver fibrosis status in MAFLD patients (B). Atrial
 711 fibrillation recurrence subtype (NoMAFLD n=47 ; MAFLD w/o fibrosis n=16 ; MAFLD ind. fibrosis
 712 n=33 ; MAFLD w/ severe fibrosis n=7) (C) and recurrence mechanism according to the NAFLD
 713 Fibrosis Score (D). NoMAFLD: FLI<60 ; MAFLD w/o fibrosis : FLI>60 & NFS<1.455 ; MAFLD
 714 ind. fibrosis : FLI>60 & -1.455<NFS<0.675 ; MAFLD w/ severe fibrosis : FLI>60 & NFS>0.675.
 715 Survival analysis: log-rank (Mantel-Cox) if two groups (A & C) or log-rank for trend if more than
 716 two groups (B & D) ; Chi² for trend (E) ; Mann-Whitney test (F). Median±interquartile range (F).
 717 Abbreviations: MAFLD= *Metabolic-dysfunction Associated Fatty Liver Disease*; NAFLD=*Non*
 718 *Alcoholic Fatty Liver Disease* ; PPV=*Positive Predictive Value*; NPV=*Negative Predictive Value*.

Left atrial remodeling and MAFLD

A) Unadjusted	NFS (continuous)	0.0184	1.35 (0.15)	-	721
B) Adjusted	NFS (continuous)	0.023	1.37 (0.16)	-	722 723
	LAA (cm ²)	0.212	0.04 (0.03)	-	723
	Atrial fibrillation subtype	0.061	-	1.59 [0.98-2.58]	727 728
	Sex	0.657	-	0.83 [0.37-1.85]	731

Table 3:
Cox regression analysis of AF recurrence after ablation.

Abbreviations:
NFS=NAFLD fibrosis

732 score ; LAA=Left atrial area ; NAFLD=Non Alcoholic Fatty Liver Disease