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ORIGINAL PAPER

Estimated total amyloid burden from ^{18}F-florbetaben positron emission tomography predicts all-cause mortality in light-chain cardiac amyloidosis

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Aims

The positron emission tomography (PET) tracer ^{18}F-florbetaben is a promising diagnostic tool for light-chain cardiac amyloidosis (AL-CA). A greater cardiac uptake might signal more amyloid burden and a worse outcome. We aimed to assess the prognostic significance of ^{18}F-florbetaben uptake in AL-CA.

Methods and results

Consecutive patients with AL-CA underwent ^{18}F-florbetaben PET scans. Total amyloid burden (TAB; calculated as mean standardized uptake value multiplied by molecular volume) was assessed in the left and right ventricles (LV/RV) in early (5–15′) and late (50–60′) acquisitions. The endpoint was all-cause mortality. Forty patients (median age 69 years, 73% males, Mayo 2004 Stage III in 80%) underwent ^{18}F-florbetaben PET with a median time from tissue biopsy of 21 days (interquartile range, IQR 7–83). Late LV TAB, but not early LV TAB, correlated with N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity (hs)-troponin T. Over 13 months after the PET scan (IQR 5–21), 65% of patients died. A late LV TAB ≥273 cm^3 (cut-off derived from spline curve analysis) predicted 18 and 24 month all-cause mortality independently from baseline variables, including NT-proBNP, hs-troponin T, and Mayo 2004 stage. Late RV TAB ≥135 cm^3 independently predicted 18 and 24 month all-cause mortality. Patients with both late LV and RV TAB ≥ cut-offs had a shorter survival than those with only LV TAB ≥ cut-off and those with TAB in both ventricles < cut-offs (Log-rank 16.52, $P < 0.001$).

Conclusion

^{18}F-florbetaben PET imaging offers valuable prognostic information in AL-CA. Values of late TAB measured in the LV and RV are strong predictors of all-cause mortality.

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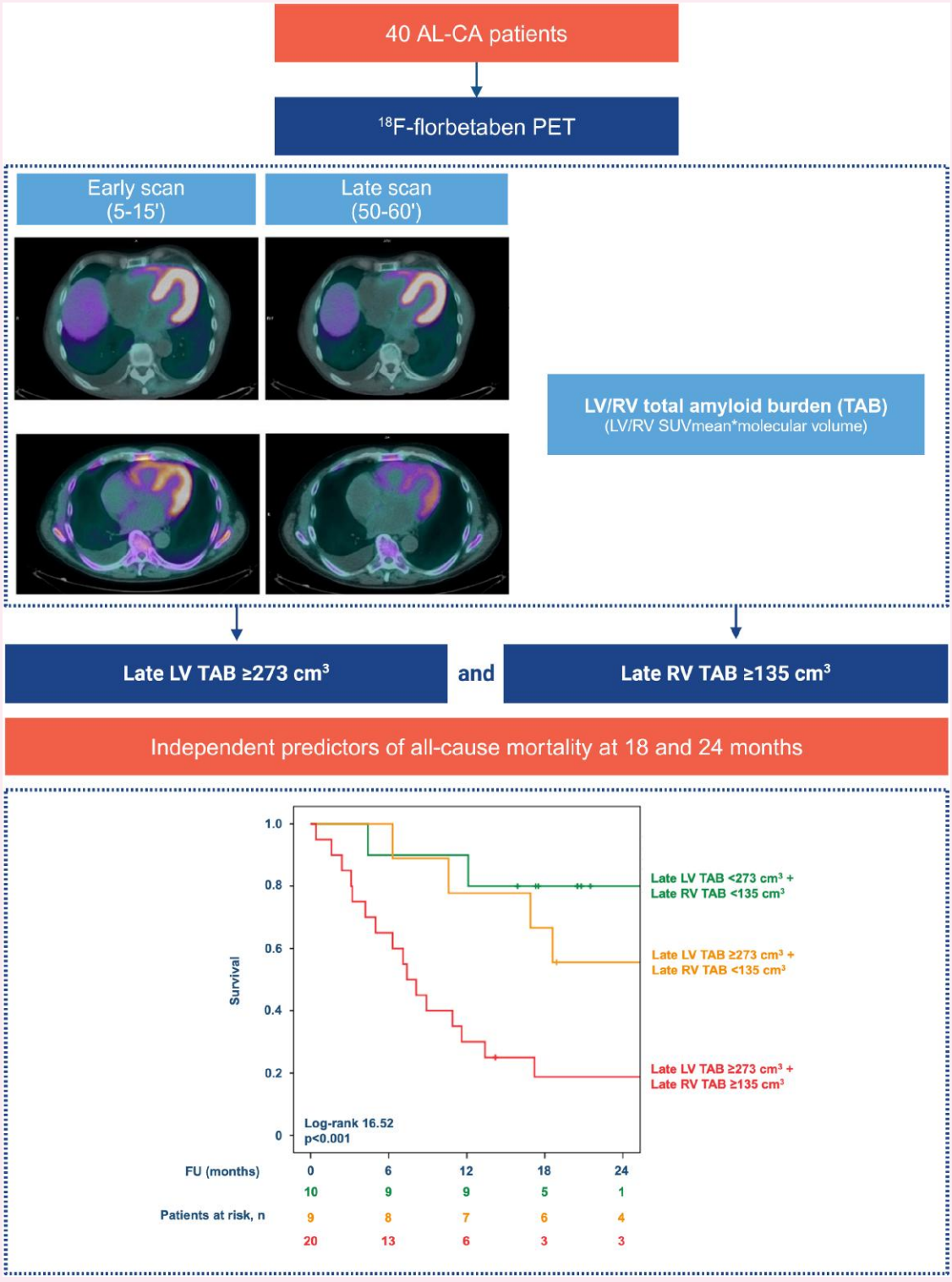
Graphical Abstract



^{18}F-florbetaben uptake and outcome in patients with light-chain cardiac amyloidosis (AL-CA). Total amyloid burden (TAB) was calculated as mean SUV multiplied by molecular volume. Left ventricular (LV) TAB ≥273 cm^3 and right ventricular (RV) TAB ≥135 cm^3 predicted 18 and 24 months all-cause mortality independently from N-terminal pro-B-type natriuretic peptide, high-sensitivity troponin T, and Mayo 2004 stage. Examples are shown from patients with high (upper panels) and low (lower panels) cardiac uptake. FU, follow-up.

Keywords florbetaben • positron emission tomography • AL amyloidosis • light-chain • prognosis

Introduction

Amyloidosis is a systemic disorder caused by the deposition of misfolded proteins in various organs, with the kidney, heart, and peripheral nervous system being most frequently affected.[1] Clinical presentation, treatment, and prognosis vary according to the specific amyloidogenic protein and organs involved.[1,2] In >95% of cases, cardiac involvement is due to either immunoglobulin light-chain (AL) or transthyretin (ATTR) amyloid.[1,2]

AL amyloidosis has an estimated prevalence of 51 cases per million.[3] It is caused by an abnormal proliferation of a plasma cell clone producing an excess of immunoglobulin light chains. These immunoglobulin chains misfold and aggregate, causing both direct tissue damage due to their cytotoxic properties and the formation of amyloid fibrils that deposit into target organs, disrupting morphology and function.[2] Cardiac involvement in systemic AL amyloidosis occurs in ∼50% of patients, and is a major determinant of outcome.[4] Accordingly, the proposed staging systems for AL amyloidosis incorporate plasma levels of cardiac biomarkers (N-terminal pro-B-type natriuretic peptide—NT-proBNP—and troponin T) as indicators of cardiac damage.[5] Accurate risk prediction in patients with AL amyloidosis and those with cardiac amyloidosis (CA) is crucial to select the best therapeutic strategy.[6]

^{18}F-florbetaben is a positron emission tomography (PET) tracer with a high affinity for β-amyloid plaques, which has also emerged as a possible diagnostic tool for AL-CA.[7–9] While cardiac uptake in an early phase (between 5 and 15 min from tracer injection) was similar between patients with AL- or ATTR-CA and those with other forms of left ventricular (LV) hypertrophy, late uptake (between 50 and 60 min) was found only in AL-CA.[9] Two Phase 3 multicentre studies are currently testing the diagnostic performance of ^{18}F-florbetaben PET in patients with suspected CA and a monoclonal gammopathy (NCT05184088, NCT06048601). Additionally, the intensity of cardiac tracer uptake might reflect the amount of AL amyloid in the heart, which in turn is associated with the severity of cardiac disease. In this study, we investigated for the first time whether the standardized uptake value (SUV), a measure of cardiac tracer uptake, holds prognostic significance in patients with AL-CA.

Methods

Patient population and study protocol

Consecutive patients with a definite diagnosis of AL-CA were screened during elective visits at a dedicated clinic of the Fondazione Toscana Gabriele Monasterio (FTGM) in Pisa, Italy. AL-CA was diagnosed according to the current diagnostic algorithm, which requires tissue biopsy (either peripheral or in a clinically affected organ) in patients with CA suspected and a monoclonal protein.[10] When immunohistochemistry was not conclusive, amyloid typing was sought through mass spectrometry or immunoelectron microscopy.[11] Patients with either a new diagnosis of AL-CA or a previous diagnosis of AL-CA were enrolled. An ^{18}F-florbetaben scan was proposed to all patients without hypersensitivity to the active substance or any excipients.[12] Due to the lack of data on the pharmacokinetics of ^{18}F-florbetaben in patients with renal or liver impairment, we excluded patients with estimated glomerular filtration rate <30 mL/min/1.73 m^2 or chronic liver disease (demonstrated by transaminases, gamma-glutamyl transpeptidase, or bilirubin levels >2 times above the reference limit).[12]

Within 1 week before the ^{18}F-florbetaben PET scan, patients underwent a transthoracic echocardiogram and measurement of cardiac biomarkers [NT-proBNP, high-sensitivity (hs)-troponin T] and plasma creatinine. The decision to perform a cardiac magnetic resonance (CMR) scan was left to the discretion of the cardiologist enrolling the patient. The study complied with the Declaration of Helsinki and was approved by the institution ethics committee and the Agenzia Italiana del Farmaco (EudraCT number 2017-001660-38). All patients provided written informed consent.

^{18}F-florbetaben PET scan

Patients underwent an ^{18}F-florbetaben PET scan with the Discovery VCT scanner (GE Healthcare, Milwaukee, WI, USA; $n = 24$) or the Siemens Biograph Vision 450 edge scanner (Siemens Healthcare, Erlangen, Germany; $n = 16$) with a three-dimensional acquisition protocol. A low-dose heart computed tomography scan was performed for attenuation correction, with an effective dose of 1 mSv. Patients received an intravenous infusion of either 300 MBq ($n = 22$) or 150 MBq ($n = 18$) of ^{18}F-florbetaben, followed by a saline flush of 10 mL. The first patients received the 300 MBq dose based on the protocol for brain amyloid scans; in subsequent patients, the dose was halved to reduce radiation exposure without affecting SUV values. The mean whole-body exposure due to the radiopharmaceutical was 2.9–5.8 mSv. Dynamic images were reconstructed from the list-mode scan, which was conducted for 60 min. Early and late static images were then reconstructed between 5 and 15 min and between 50 and 60 min after injection, respectively.

Static cardiac scans acquired at 5–15 and 50–60 min were examined on a dedicated workstation (SyngoVia, Siemens Healthineers) by experienced readers (A.G. and D.G.). On each scan, volumes of interest were selected in the LV and right ventricle (RV). The maximum SUV (SUVmax) and the average voxel intensity within the volume of interest (SUVmean) were determined. By using appropriate iso-contour thresholds for the volume of interest, it was possible to isolate tissue uptake in the RV wall while avoiding contamination from the blood pool. The molecular volume (MV) within each volume of interest was automatically derived as the sum of voxels with SUV values exceeding 50% of the SUVmax. The total amyloid burden (TAB) was estimated as SUVmean × MV.

Echocardiogram, CMR, and cardiac biomarkers

See Supplementary material for details.

Management and follow-up

Following the PET scan, all patients received contemporary state-of-the-art treatment[2,6,13] in the Hematological Department of the University Hospital of Pisa. Two patients were also enrolled in a clinical trial involving an antibody targeting AL fibrils (NCT04973137). Patients were followed in the outpatient clinic of the FTGM, with follow-up timing dictated by the need to assess cardiac response to treatment. The endpoint was all-cause mortality. Outcome data were retrieved in June 2024 from electronic health records and phone calls to patients, family members, or general practitioners. No patient was lost to follow-up. The follow-up began on the day of the ^{18}F-florbetaben PET scan.

Statistical analysis

Statistical analysis was performed using SPSS (version 29) and R (version 4.2.2). Categorical variables were reported as absolute numbers and percentages. Since all continuous variables were not normally distributed, they were reported as medians (interquartile range, IQR) and ln-transformed for further analyses. Categorical variables were compared through χ^2 analysis, and continuous variables through the Mann–Whitney *U* test for independent samples. The strength of correlations between variables was assessed through linear regression analysis and calculation of the Spearman's rho values. Cubic spline interpolation (with 4 degrees of freedom) was conducted to visually represent changes in the risk of the endpoint according to early and late TAB values. The inflection points of the spline curves, corresponding to the TAB values above which the risk increased more steeply, were identified as cut-offs. Kaplan–Meier survival analysis with the log-rank test was performed. The proportional hazard assumption was checked by examining the Schoenfeld residuals. As this assumption was not met, the prognostic value of PET indicators was tested at fixed time points (18 and 24 months) through univariable logistic regression analysis and then through multivariable models. Only 2 variables were

entered into multivariable models based on the number of events, in agreement with the rule stating that 1 predictive variable can be studied for every 10 events.[14] Baseline characteristics were then entered one at a time in the model as adjusting variables. Multicollinearity was excluded using the variance inflation factor (cut-off 5). *P*-values <0.05 were considered significant.

Results

Patient characteristics

Patients ($n = 40$) were more often males (75%), with a median age of 69 years (IQR 63–74). NT-proBNP and hs-troponin T values were 5099 ng/L (1554–13 256) and 77 ng/L (43–142), respectively, resulting in a Mayo 2004 Stage III in 80%. Patients had a New York Heart Association Class III or IV in 40%, and a median LV ejection fraction (LVEF) of 54% (49–61). Twenty-three patients (58%) underwent a CMR scan as part of their diagnostic workup, with a median time interval between PET and CMR scans of 14 days (8–36). The median extracellular volume (ECV) value was 55% (47–65%; *Table 1*).

The majority of patients (70%) underwent ^{18}F-florbetaben PET as part of their diagnostic workup and within 1 month after the tissue biopsy, while the other patients had been previously diagnosed with AL-CA. A comparison between patients with new or prior diagnoses of AL-CA did not reveal any significant differences, except for current or previous haematological therapy (see Supplementary data online, *Table S1*). Only 5 patients (13%) were receiving a haematological treatment at the time of the ^{18}F-florbetaben PET scan (bortezomib, cyclophosphamide, dexamethasone, $n = 1$; melphalan plus prednisone, $n = 1$; pomalidomide, $n = 3$). Eight patients (25%) had previously received a haematological treatment, including bone marrow transplantation in 2 (data not shown).

Metrics of ^{18}F-florbetaben uptake in the left ventricle

All patients displayed ^{18}F-florbetaben uptake both in the early (5–15 min) and late (50–60 min) acquisitions. ^{18}F-florbetaben uptake in the LV was quantified using different metrics: SUVmean, SUVmax, MV, and TAB. The only significant difference between these metrics in early and late scans was observed for LV TAB, whose median value was 34% lower in the late acquisition (579 vs. 871 cm^3, $P < 0.001$; *Table 2*).

We then searched for correlations between metrics of uptake in the LV from early and late scans. Late LV TAB displayed significant correlations with all measures of LV uptake from the early and late scans except for early LV MV (*Table 3*). Moreover, late LV TAB correlated with NT-proBNP and hs-troponin T ($P = 0.002$ and $P = 0.007$, respectively), whereas all metrics from the early scan did not correlate with cardiac biomarkers, and late SUVmean did not correlate with NT-proBNP (*Figure 1* and Supplementary data online, *Table S2*).

Metrics of ^{18}F-florbetaben uptake in the RV

SUVmean, SUVmax, MV, and TAB were then evaluated in the RV. In this case, there was no significant difference between early and late metrics (see Supplementary data online, *Table S3*). Late RV TAB correlated with all metrics of RV uptake from the early and late scans (see Supplementary data online, *Table S4*), as well as cardiac biomarkers and tricuspid annular plane systolic excursion (TAPSE; see Supplementary data online, *Table S5*).

Table 1 Patient characteristics at the time of ^{18}F-florbetaben PET scan

	Whole cohort $n = 40$
Clinical features	
Men, *n* (%)	30 (75)
Age (years)	69 (63–74)
Current haematological therapy, *n* (%)	5 (13)
Previous haematological therapy, *n* (%)	8 (20)
BMI (kg/m^2)	24 (21–26)
NYHA III and IV, *n* (%)	16 (40)
AF, *n* (%)	5 (13)
Laboratory values	
eGFR (mL/min/1.73 m^2)	73 (54–87)
NT-proBNP (ng/L)	5099 (1554–13 256)
hs-troponin T (ng/L)	77 (43–142)
Mayo 2004 Stage I/II/III, *n* (%)	0/8/32 (0/20/80)
Echocardiogram	
LVEF (%)	54 (49–61)
GLS (%)[a]	−11 (−13 to −8)
LVMI (g/m^2)	133 (115–162)
E/*e*′	20 (15–24)
TAPSE (mm)	16 (14–21)
sPAP (mmHg)	43 (33–50)
CMR[b]	
ECV (%)	55 (47–65)
Cardiological therapy	
Beta-blockers, *n* (%)	30 (75)
ACEi/ARBs/ARNI, *n* (%)	18 (45)
MRA, *n* (%)	23 (58)

ACEi/ARB/ARNI, angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitor; AF, atrial fibrillation; BMI, body mass index; CMR, cardiac magnetic resonance; ECV, extracellular volume; eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; GLS, global longitudinal strain; LVEF, left ventricle ejection fraction; LVMI, left ventricular mass index; MM, multiple myeloma; MRA, mineralocorticoid receptor antagonist; New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.
[a]Global longitudinal strain could be measured in 36 patients (90%).
[b]Performed in 23 patients (58%).

Table 2 Metrics of tracer uptake in the LV from the early and late scans

	Early scan	Late scan	*P*-value
SUVmean LV	4.8 (3.8–7.0)	4.0 (2.5–6.0)	0.121
SUVmax LV	7.6 (6.1–11.7)	7.1 (4.1–10.4)	0.168
MV LV (cm^3)	187 (132–228)	141 (99–215)	0.052
TAB LV (cm^3)	871 (644–1391)	579 (241–1095)	**<0.001**

P-values for the comparison between early and late scans are provided. The significant *P*-value is reported in bold.
MV, molecular volume; SUV, standardized uptake value.

Table 3 **Correlations between metrics of uptake in the LV from early and late scans**

	Early SUVmean LV	Early SUVmax LV	Early MV LV (cm^3)	Early TAB LV (cm^3)	Late SUVmean LV	Late SUVmax LV	Late MV LV (cm^3)	Late TAB LV (cm^3)
Early SUVmean LV	—	**$P < 0.001$** beta = 0.946	$P = 0.960$	**$P < 0.001$** beta = 0.789	**$P < 0.001$** beta = 0.830	**$P < 0.001$** beta = 0.799	$P = 0.872$	**$P < 0.001$** beta = 0.560
Early SUVmax LV	**$P < 0.001$** beta = 0.946	—	$P = 0.973$	**$P < 0.001$** beta = 0.745	**$P < 0.001$** beta = 0.771	**$P < 0.001$** beta = 0.769	$P = 0.630$	**$P = 0.007$** beta = 0.475
Early MV LV (cm^3)	$P = 0.960$	$P = 0.973$	**—**	**$P < 0.001$** beta = 0.622	$P = 0.500$	$P = 0.434$	**$P = 0.002$** beta = 0.530	$P = 0.171$
Early TAB LV (cm^3)	**$P < 0.001$** beta = 0.789	**$P < 0.001$** beta = 0.745	**$P < 0.001$** beta = 0.622	—	**$P < 0.001$** beta = 0.580	**$P = 0.002$** beta = 0.536	$P = 0.099$	**$P < 0.001$** beta = 0.594
Late SUVmean LV	**$P < 0.001$** beta = 0.830	**$P < 0.001$** beta = 0.771	$P = 0.500$	**$P < 0.001$** beta = 0.580	—	**$P < 0.001$** beta = 0.948	$P = 0.182$	**$P < 0.001$** beta = 0.755
Late SUVmax LV	**$P < 0.001$** beta = 0.799	**$P < 0.001$** beta = 0.769	$P = 0.434$	**$P = 0.002$** beta = 0.536	**$P < 0.001$** beta = 0.948	—	$P = 0.230$	**$P < 0.001$** beta = 0.709
Late MV LV (cm^3)	$P = 0.872$	$P = 0.630$	**$P = 0.002$** beta = 0.530	$P = 0.099$	$P = 0.182$	$P = 0.230$	—	**$P < 0.001$** beta = 0.805
Late TAB LV (cm^3)	**$P < 0.001$** beta = 0.560	**$P = 0.007$** beta = 0.475	$P = 0.171$	**$P < 0.001$** beta = 0.594	**$P < 0.001$** beta = 0.755	**$P < 0.001$** beta = 0.709	**$P < 0.001$** beta = 0.805	—

All variables were ln-transformed. Significant *P* values are reported in bold.
MV, molecular volume; SUV, standardized uptake value; TAB, total amyloid burden.

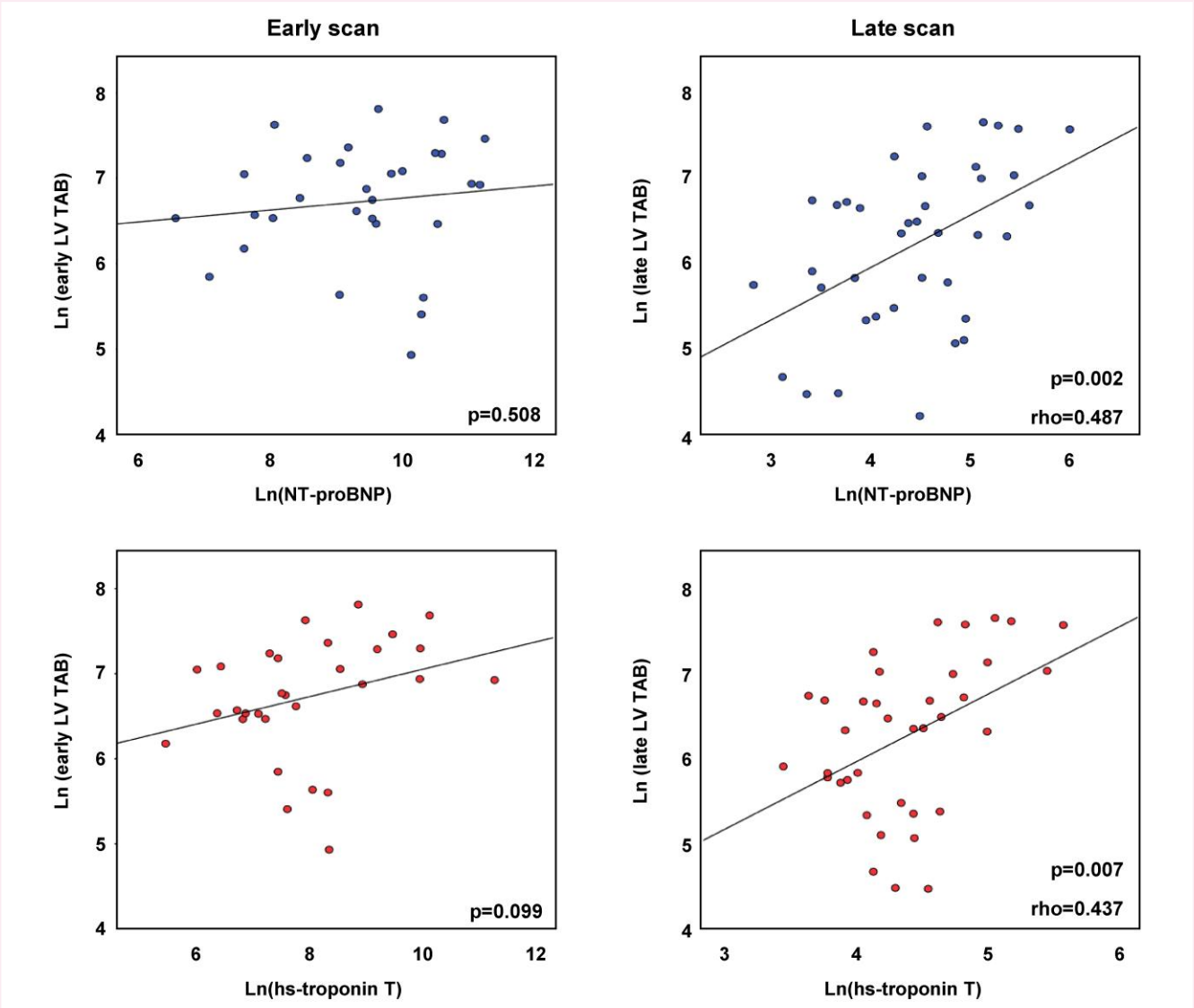


Figure 1 Correlations between LV TAB from early and late scans and cardiac biomarkers. Linear regression analysis. All variables were ln-transformed. hs, high-sensitivity; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

PET findings and outcomes

Twenty-six patients (65%) died over 13 months (5–21) after the PET scan. Follow-up duration was equal to 14 months (4–21) in patients with a new diagnosis vs. 15 months (9–28) in those with a previous diagnosis ($P = 0.373$). There was also no difference in the percentage of patients dying during follow-up ($n = 16$, 57%, vs. $n = 10$, 83%; $P = 0.112$).

Given the significant decrease in LV TAB values from the early to late scan and the previous evidence of a specific tracer uptake only in the late scan,[9] as well as the correlations between late LV and RV TAB and other metrics of uptake and cardiac biomarkers, we focused on the prognostic value of late LV and RV TAB. The relationship between late TAB values and all-cause mortality was visually represented through spline curves, and the inflection points of the curves (above which the risk increased more steeply) were derived (*Figure 2*). The inflection points corresponded to late LV TAB = 273 cm^3 and late RV TAB = 135 cm^3. Late LV TAB ≥273 cm^3 predicted all-cause mortality at 18 and 24 months independently from most baseline variables, evaluated one at a time, including age, sex, New York Heart Association Class III or IV, NT-proBNP, hs-troponin T, and Mayo 2004 stage (*Table 4*). Similarly, late RV TAB ≥135 cm^3 predicted all-cause mortality at 18 months independently of all baseline variables except for ECV (see Supplementary data online, *Table S6*).

All patients with a late RV TAB ≥135 cm^3 also had a late LV TAB ≥209 cm^3. Patients with both late LV and RV TAB values ≥cut-offs had the shortest survival free from all-cause mortality (*Figure 3*). This was confirmed also in the subgroup with new diagnoses (Log-rank 18.1, $P < 0.001$).

Discussion

In this study, we provide the first comprehensive evaluation of LV and RV uptake of ^{18}F-florbetaben in patients with AL-CA. We introduce a novel metric of tracer uptake, e.g. TAB, and we investigated its correlates and prognostic value. We provide cut-offs for late LV and RV TAB that refine risk prediction of all-cause mortality (*Graphical Abstract*),

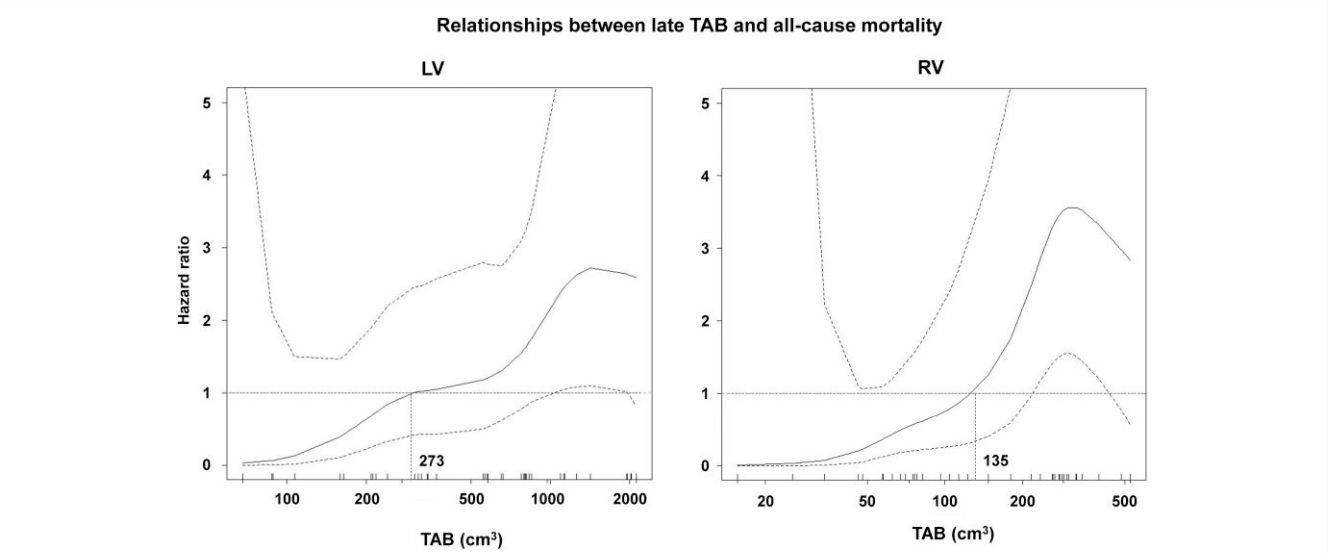


Figure 2 TAB: relationships with all-cause mortality. Spline curve analysis showing patient outcomes according to left ventricular TAB values. These values were calculated on early (left) and late scans (right). The TAB values corresponding to the inflection points of the curves (above which the risk increases more steeply) are reported.

Table 4 Independent prognostic value of LV late TAB ≥ 273 cm³

	All-cause mortality, 18 months		All-cause mortality, 24 months	
	P-value	OR (95% CI)	*P*-value	OR (95% CI)
Late LV TAB ≥273 cm³ +				
Men	0.022	7.91 (1.35–46.42)	0.015	8.97 (1.53–42.64)
Age	0.021	7.72 (1.35–44.05)	0.014	8.98 (1.56–51.50)
Current haematological therapy	0.052	—	0.035	11.31 (1.19–107.65)
Previous haematological therapy	0.032	12.32 (1.23–122.94)	0.019	16.07 (1.57–164.32)
BMI	0.013	9.91 (1.62–60.69)	0.008	12.45 (1.96–79.17)
NYHA III and IV	0.038	6.45 (1.11–37.50)	0.022	7.87 (1.35–46.05)
AF	0.022	7.56 (1.34–42.60)	0.014	8.87 (1.56–50.52)
eGFR	0.039	7.54 (1.11–51.34)	0.039	7.53 (1.1–51.34)
NT-proBNP	0.031	7.18 (1.20–43.08)	0.018	8.64 (1.44–51.82)
hs-troponin T	0.024	8.20 (1.31–51.20)	0.015	9.94 (1.56–63.26)
Mayo 2004 Stages I/II/III	0.017	9.33 (1.50–58.20)	0.009	11.90 (1.85–76.53)
LVEF	0.054	—	0.054	—
GLS	0.028	7.17 (1.23–41.67)	0.020	8.27 (1.40–48.86)
LVMI	0.026	7.52 (1.28–44.16)	0.026	7.52 (1.28–44.16)
E/*e*′	0.027	7.34 (1.25–43.11)	0.027	7.34 (1.25–43.11)
TAPSE	0.051	—	0.051	—
sPAP	0.012	13.25 (1.77–98.89)	0.012	13.25 (1.77–98.89)
ECV	0.124	—	0.066	—
Beta-blockers	0.014	9.14 (1.56–53.62)	0.023	7.64 (1.33–43.85)
ACEi/ARBs/ARNI	0.022	7.79 (1.35–45.17)	0.014	8.93 (1.55–51.36)
MRA	0.047	6.23 (1.02–38.00)	0.032	7.61 (1.19–48.66)

Models for multivariable logistic regression included late TAB ≥273 cm³ and another variable at the time. *P*, odds ratio (OR) and 95% confidence interval (CI) values refer to late SUVmean ≥3.3. Continuous variables were ln-transformed. ACEi/ARB/ARNI, angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitor. AF, atrial fibrillation; BMI, body mass index; CMR, cardiac magnetic resonance; ECV, extracellular volume; eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; GLS, global longitudinal strain; LVEF, left ventricle ejection fraction; LVMI, left ventricular mass index; MM, multiple myeloma; MRA, mineralocorticoid receptor antagonist; New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

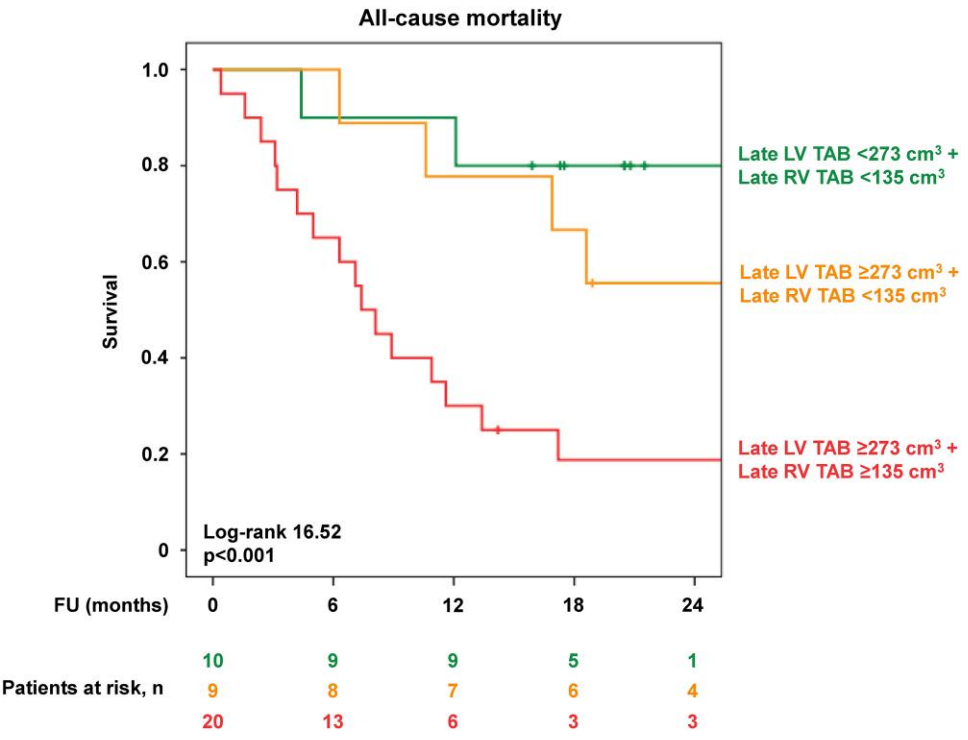


Figure 3 TAB in the LV and RV and survival. See text for details. FU, follow-up.

and which retain prognostic value even in the subset of patients with newly diagnosed AL-CA.

Our results broadly align with the report of a prognostic value of PET tracers developed for Aβ amyloid in patients with suspected or known AL-CA. Specifically, Clerc et al. reported that ^{18}F-florbetapir could identify RV involvement in systemic AL and predict major adverse cardiac events,[15] and two other studies reported a prognostic value of ^{11}C-Pittsburgh Compound B in patients with AL-CA.[16,17] In this study, we focused on ^{18}F-florbetaben and patients with a diagnosis of AL-CA. We also introduced the novel parameter TAB, calculated as SUVmean multiplied by the MV and equivalent to a measure of tumour extent in ^{18}F-fluorodeoxyglucose PET, total lesion glycolysis. We report that TAB is a strong predictor of all-cause mortality in patients with AL-CA.

A significant aspect of our study was the comparison between early and late uptake of ^{18}F-florbetaben. Early uptake was measured between 5 and 15 min post-injection, while late uptake was measured between 50 and 60 min post-injection. All patients displayed ^{18}F-florbetaben uptake in both early and late phases, confirming our previous findings about the myocardial kinetics of this tracer in AL-CA.[9] Accordingly, we found no significant differences between early and late acquisitions in terms of mean and maximal SUV values and MV in both the LV and RV. Nonetheless, the median estimated TAB was 34% lower in the late acquisition compared with the early acquisition. This reduction suggests that late uptake may provide a more accurate reflection of the amyloid burden due to the washout of non-specific tracer uptake over time.

The early LV TAB showed significant correlations with current haematological therapy and LV mass index but not with cardiac biomarkers such as NT-proBNP or hs-troponin T. Conversely, the late LV TAB was not correlated with current haematological therapy or LV mass index, but showed significant correlations with NT-proBNP values and hs-troponin T. These differences indicate that late LV TAB may be more reflective of ongoing cardiomyocyte damage rather than just the structural alterations captured in the early scan.

The prognostic value of TAB was a key finding in our study. TAB, particularly when measured in the late phase, emerged as a significant predictor of all-cause mortality. Specifically, late LV TAB ≥273 cm^3 was identified as a strong prognostic marker, discriminating patient survival effectively in Kaplan–Meier analyses. Furthermore, it predicted all-cause mortality at 12, 18, and 24 months independently of most baseline variables, including age, sex, New York Heart Association Class III or IV, NT-proBNP, hs-troponin T, and Mayo 2004 stage. The strong prognostic value of TAB, particularly in the late phase, can be attributed to its ability to integrate both the extent of amyloid deposition and its impact on myocardial function. Unlike SUVmean alone, which provides a measure of tracer uptake intensity, the TAB combines this with the volume of affected myocardium, offering a more comprehensive assessment of disease severity.

RV TAB was another significant predictor of outcome. Both early RV TAB ≥209 cm^3 and late RV TAB ≥135 cm^3 were associated with all-cause mortality. Among these, late RV TAB ≥135 cm^3 emerged as a particularly strong univariable predictor of mortality. This parameter predicted all-cause mortality at 12 and 18 months independently of all baseline variables except for ECV. Patients with both late LV and RV TABs above their respective cut-offs had the shortest survival free from all-cause mortality, highlighting the critical importance of evaluating RV amyloid burden in these patients.

Our study has several limitations. It was a single-centre study with a small cohort size and a small number of events, preventing us from entering more than two variables in the same prognostic model. Additionally, the timing between the diagnosis of AL-CA and the PET scan was heterogeneous, but the majority of patients (70%) underwent ^{18}F-florbetaben PET within 1 month after the tissue biopsy. A comparison between these patients and those with an interval between tissue biopsy and PET longer than 1 month did not reveal any significant differences, except for current or previous haematological therapy. Some patients were on haematological therapy or had received therapy

before the PET scan, which could be a confounding factor affecting PET tracer uptake. Since a dynamic acquisition was not performed, it was not possible to derive the retention index value. Two scanners were used, which differ significantly in terms of spatial resolution (6 vs. 3 mm). However, the values of the parameters used for the quantitative analysis of the images obtained with the two different instruments are comparable. The use of different radiopharmaceutical activities does not result in significant variations in SUV and TAB values because these values are, by definition, normalized for the radiopharmaceutical activity administered. Finally, the idea that TAB corresponds to the 'total amyloid burden' is speculative in the sense that the relationship with the amount of tissue amyloid has never been demonstrated through tissue histology. Additionally, no significant correlations between late LV TAB and echo parameters emerged except for TAPSE and a trend towards worse GLS values in patients with more amyloid. On the other hand, we found quite strong correlations with cardiac biomarkers, which are established indicators of the severity of ongoing cardiac damage and are powerful predictors of outcome in AL-CA.[5] Finally, the proposed prognostic cut-offs should be validated in larger, multicentre cohorts, which would also allow for the exploration of potential confounding effects of ongoing or prior therapies.

Conclusion

^{18}F-florbetaben PET imaging offers valuable prognostic information in patients with AL-CA, particularly late-phase imaging. Values of TAB, calculated in the LV and RV on a late scan, are significant predictors of all-cause mortality. These findings support the use of ^{18}F-florbetaben PET as an additive tool for risk stratification in AL-CA.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

The data underlying this article will be shared on reasonable request with the corresponding author.

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