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Independent Prognostic Utility of ^{11}C-Pittsburgh Compound B Positron Emission Tomography in Light-Chain Cardiac Amyloidosis Patients

Short running title: ^{11}C-PiB PET in AL Cardiac Amyloidosis

You-Jung Choi,[1] Youngil Koh,[2] Hyun-Jung Lee,[1] In-Chang Hwang,[3] Jun-Bean Park,[1,4] Yeonyee E. Yoon,[3,4] Hack-Lyoung Kim,[4,5] Hyung-Kwan Kim,[1,4] Yong-Jin Kim,[1,4] Goo-Yeong Cho,[3,4] Dae-Won Sohn,[1,4] Jin-Chul Paeng,[6] Seung-Pyo Lee[1,4]

[1]Division of Cardiology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; [2]Division of Hemato-oncology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; [3]Department of Internal Medicine and Cardiovascular Center, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, South Korea; [4]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea; [5]Division of Cardiology, Department of Internal Medicine, Boramae Medical Center, Seoul National University College of Medicine, Seoul, South Korea; [6]Department of Nuclear Medicine, Seoul National University Hospital and Seoul National University College of Medicine, Seoul, South Korea.

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Address for correspondence:

Seung-Pyo Lee, MD, PhD

Professor, Department of Internal Medicine, Seoul National University Hospital

101 Daehak-ro, Jongno-gu, Seoul, 03080, South Korea

Telephone: +82-2-2072-1980, Fax: +82-2-2072-2578

E-mail: sproll1@snu.ac.kr

Address for first author:

You-Jung Choi, MD

Clinical fellow, Department of Internal Medicine, Seoul National University Hospital

101 Daehak-ro, Jongno-gu, Seoul, 03080, South Korea

E-mail: flyiing48@gmail.com

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Abstract

^{11}C-Pittsburgh compound B positron emission tomography/computed tomography (^{11}C-PiB PET/CT) visualizes the amount of myocardial amyloid deposit and can be used to prognosticate patients with light-chain (AL) cardiac amyloidosis (CA). However, whether ^{11}C-PiB PET/CT has any independent additional prognostic value beyond the commonly used biomarkers remains unknown. **Methods:** This was a prospective cohort of 58 consecutive patients with ALCA who underwent ^{11}C-PiB PET/CT. Patients were stratified into 2 groups based on a visual assessment on whether there was a myocardial ^{11}C-PiB uptake or not on PET/CT. The primary endpoint was 1-year overall mortality. The independent prognostic utility of ^{11}C-PiB PET/CT was analyzed using net reclassification improvement and integrated discrimination improvement. **Results**: Among the 58 patients enrolled, 35 patients had a positive myocardial ^{11}C-PiB uptake on PET/CT. Patients with a positive myocardial ^{11}C-PiB PET uptake had a worse 1-year overall survival rate than those with a negative uptake (81.8% vs. 45.5%, *P*=0.003 by log-rank test). In the multivariate analysis, a positive myocardial ^{11}C-PiB uptake on PET/CT was an independent predictor of 1-year mortality (adjusted hazard ratio 3.382, 95% confidence interval 1.011–11.316, *P*=0.048). In each subgroup analysis of patients with troponin I ≥0.1 ng/mL, N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥1,800 pg/mL, and the difference between free light chains (dFLC) ≥180 mg/mL, the three commonly used biomarkers and its thresholds for staging in AL amyloidosis, Kaplan-Meier curves showed that the patients with a positive myocardial ^{11}C-PiB uptake on PET/CT had a worse prognosis than those with a negative myocardial ^{11}C-PiB uptake, respectively. Additionally, when the result of ^{11}C-PiB PET/CT was added to these three biomarkers, the performance of 1-year mortality prediction significantly improved by net reclassification improvement (^{11}C-PiB PET/CT

added to troponin I, 0.861; NT-proBNP, 0.914; dFLC, 0.987) and by integrated discrimination improvement (0.200, 0.156, and 0.108, respectively). **Conclusion:** ^{11}C-PiB PET/CT is a strong independent predictor of 1-year overall mortality and provides incremental prognostic benefits beyond the three commonly used biomarkers of AL amyloidosis staging. Considering the recent developments of numerous amyloid-targeting molecular imaging agents, further investigations are warranted on whether PET/CT should be included in the risk stratification for patients with ALCA.

Keywords: ^{11}C-Pittsburgh compound B positron emission tomography; cardiac amyloidosis; mortality; risk stratification.

Introduction

Amyloidosis is a rare group of disorders caused by the accumulation of proteinaceous fibrils in certain organs that compromises their structure and function (*1*). Cardiac amyloidosis (CA) refers to the myocardial deposition of amyloid fibrils, of which the immunoglobulin light chain (AL) and transthyretin are the most common types (*2*). Cardiac involvement is the major determinant of prognosis in AL amyloidosis patients and therefore, accurate evaluation of the degree of involvement is crucial for prognostication (*3*).

Endomyocardial biopsy is commonly used for the evaluation of CA, where the presence of AL proteins can be evaluated, together with its degree of deposition (*4*). However, it involves invasive removal of the myocardial tissue and does not provide information on disease activity nor the hemodynamic consequences. In contrast, biomarkers such as serum cardiac troponins and N-terminal pro-B-type natriuretic peptide (NT-proBNP)/BNP, which are associated with the hemodynamic burden to the heart, are used for cardiac staging, albeit not specific for CA (*5*-*7*). The absolute difference between the involved and uninvolved free light chains (dFLC), as a parameter for hematologic disease burden, is also incorporated into the staging system and improves the risk stratification of AL amyloidosis patients (*8*). Additionally, imaging markers such as left ventricular (LV) strain on speckle tracking echocardiography and the gadolinium enhancement pattern on cardiovascular magnetic resonance (CMR) are helpful for the prognostication of AL amyloidosis patients (*9*-*14*).

To date, advances in nuclear imaging have allowed a more specific, non-invasive approach to the diagnosis and prognostication of CA (*15*). We and others have shown that ^{11}C-Pittsburgh compound B (PiB) positron emission tomography (PET)/computed tomography (CT) may be used

for the diagnosis of ALCA by reflecting the amount of myocardial amyloid deposit and that it is associated with patient prognosis (*16-18*). However, for a new imaging test to be clinically useful, it should be verified whether it has any independent additional prognostic values beyond the commonly used conventional prognosticators. In this study, we aimed to determine whether ^{11}C-PiB PET/CT could provide an independent incremental prognostic value over the serum biomarkers in patients with ALCA.

Materials and Methods

Study Population

This is a prospective cohort study of patients with ALCA diagnosed at Seoul National University Hospital between 2012 and 2019. Cardiac involvement of AL amyloidosis was diagnosed with confirmation of monoclonal gammopathy in the peripheral blood and lineage-restricted expansion of plasma cells in the bone marrow, together with either a positive endomyocardial biopsy or by cardiac imaging-based diagnosis with histological confirmation of amyloid infiltration by non-cardiac biopsies (*19-21*).

1. Average LV wall thickness ≥12mm on echocardiography with no identifiable cause.
2. Unexplained low voltage QRS amplitude <0.5mV in the limb leads of the 12-lead electrocardiogram.
3. Typical features of CA on CMR, including diffuse late gadolinium enhancement and myocardial extracellular volume expansion.

The endomyocardial biopsy was performed in a standard manner (*22*). Deposition of amyloid in the myocardium was confirmed with a positive amyloid P staining by immunohistochemistry, as well as apple-green birefringence by Congo-red staining (*23*).

The study complies with the declaration of Helsinki and has been approved by the Institutional Review Boards. All subjects signed an informed consent form.

^{11}C-PiB PET/CT Protocol and Image Interpretation

^{11}C-PiB PET/CT was performed using a dedicated PET/CT machine (Biograph 40, Siemens Medical Solution, Knoxville, TN). After low-dose CT scanning, ^{11}C-PiB (555 MBq) was injected

intravenously and 30 minutes after the tracer injection, a 3-dimensional PET/CT scan was performed at 3 minutes per bed position with a spatial resolution of 4.2 mm. The detailed protocol of ^{11}C-PiB PET/CT has been published elsewhere (*16*). Images were displayed on transaxial, coronal, and sagittal planes of 5 mm slice thickness. As the purpose of this study was not to analyze the diagnostic accuracy of ^{11}C-PiB PET/CT for ALCA but to demonstrate the clinical utility of ^{11}C-PiB PET/CT in ALCA and taking into consideration of our previous results of static ^{11}C-PiB PET/CT reflecting the myocardial amyloid load (*17*), we used the visual estimation of the static PET/CT image to divide the study population into either a positive versus negative myocardial ^{11}C-PiB uptake group (Figure 1) instead of using the quantified best cut-off standardized uptake value as in our previous study(*16,17*). The ^{11}C-PiB PET/CT was considered positive when the myocardial ^{11}C-PiB uptake was visually discernible from the blood pool (i.e., left ventricular cavity) (Supplemental Figure 1). The individual images and interpretations of ^{11}C-PiB PET/CT for the entire participants are listed in Supplemental Figure 2. All images were interpreted by a single expert blinded to all other findings of subjects and in ambiguous cases, another independent observer participated in the visual analysis.

Echocardiography and Biomarker Measurement

Two-dimensional echocardiography was performed within 2 weeks of PET/CT according to the contemporary guidelines (*24*). We measured early diastolic transmitral inflow velocity (E velocity) and early diastolic mitral annular velocity (e' velocity) at the septal annulus by Doppler echocardiography to calculate the E/e' ratio.

We collected data on the serum biomarkers retrospectively, based on the review of the

electronic medical records. Serum free light chain assay was performed at the initial diagnosis of amyloidosis and the dFLC was calculated with these results. Serum NT-proBNP and troponin I were measured within 1 month from ^{11}C-PiB PET/CT. Subgroups analysis was done in patients with serum biomarker values higher than the threshold values for each biomarker used in the revised Mayo staging system: troponin I ≥0.1 ng/mL, NT-proBNP ≥1,800 pg/mL, and dFLC ≥180 mg/mL (*8*).

Outcome Ascertainment

The outcome of the study was all-cause death, confirmed either by review of medical records or by reviewing the official nationwide data on death certification provided by the National Statistical Office of Korea. Patients were censored when they underwent heart transplantation. Each patient was followed from the date of the ^{11}C-PiB PET/CT scan to either the date of death or up to 1 year.

Statistical Analysis

Continuous variables are described as mean±standard deviation and/or median [interquartile range (IQR)], and the categorical variables are summarized as frequencies (percentages). We compared the continuous variables with Student's t-test or Mann-Whitney U-test after testing for normality with Shapiro-Wilk test, and the categorical variables between the two groups with either the Chi-square test or Fisher's exact test.

We used the Kaplan-Meier estimate to describe and compare the survival curves between groups with the log-rank test. The proportional hazards assumption was checked using a statistical

test based on the Schoenfeld residuals and their plots. Hazard ratios (HRs) with a 95% confidence interval (CI) were determined using the Cox proportional hazards regression. Covariates with a *p*-value <0.05 on univariate Cox analysis were included in the multivariable model. Time zero was defined as the time of the ^{11}C-PiB PET/CT scan. To determine the incremental predictive value of ^{11}C-PiB PET/CT in addition to the three conventional serum biomarkers (troponin I, NT-proBNP, and dFLC), the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) were computed in regards to 1-year overall mortality (*25*).

All analyses used a two-sided *p*-value (*P*), and *p*-value <0.05 was considered statistically significant. Statistical analyses were performed with the IBM SPSS statistics version 25.0 (IBM Corp, Armonk, NY) or R programming version 4.0.5 (http://www.R-project.org; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

Among the 62 patients diagnosed with CA who underwent ^{11}C-PiB PET/CT, 58 patients were included in the final analysis, excluding those with non-AL type CA (N=4). Among the 58 patients, 53 were histologically diagnosed with CA by endomyocardial biopsy, and the remaining 5 were diagnosed based on findings strongly suggestive of CA in at least two noninvasive modalities, such as echocardiography, CMR or electrocardiogram. The average age was 64.0±9.1 years and 43% were male. There were 35 patients with a positive ^{11}C-PiB PET/CT. Comparison of the baseline demographic and clinical data according to the myocardial ^{11}C-PiB PET uptake are outlined in Table 1.

The average age was numerically higher in patients with a positive ^{11}C-PiB PET/CT than those with a negative ^{11}C-PiB PET/CT (65.5±9.8 years vs. 61.7±7.6 years, *P*=0.121). The systolic blood pressure was lower in patients with a positive ^{11}C-PiB PET/CT (median 104.0 mmHg [IQR 92.5–114.0 mmHg] vs. 111.0 mmHg [104.5–122.5 mmHg], *P*=0.034). During the 1-year follow-up, patients with a negative ^{11}C-PiB PET/CT received more autologous peripheral blood stem cell transplantation (PBSCT) (30.4% vs 8.6%, *P*=0.040). As for the echocardiography data, there was no significant difference between the two groups, except for E velocity (*P*=0.021), e' velocity (*P*=0.043), and E/e' ratio (*P*=0.004).

Outcome Comparison according to the ^{11}C-PiB PET/CT Results

During the 1-year follow-up, 23 patients died. Among 35 patients with a positive ^{11}C-PiB PET/CT, 16 (54.3%) patients died, whereas 4 (17.4%) died in those with a negative ^{11}C-PiB

PET/CT. In the entire cohort, the 1-year overall survival rate was 59.3%; the survival rates at 3-month and 6-month were 77.2% and 59.3%, respectively (Figure 2A). Kaplan-Meier survival curves showed that the 1-year overall survival rate was significantly worse in patients with a positive ^{11}C-PiB PET/CT (81.8% vs. 45.5%; *P*=0.003 by log-rank test, Figure 2B). In the multivariate analysis, a positive myocardial ^{11}C-PiB PET uptake was an independent predictor of 1-year overall survival (adjusted HR 3.382, 95% CI 1.011–11.316, *P*=0.048) (Supplemental Table 1).

Incremental Value of ^{11}C-PiB PET/CT in Addition to Serum Biomarkers for ALCA Prognostication

Among the 58 ALCA patients, 34, 39, and 47 patients had troponin I (median 0.14 ng/mL, IQR 0.07–0.39 ng/mL), NT-proBNP (median 3,733 pg/mL, IQR 1,117–7,232 pg/mL), and dFLC (median 291.7 mg/mL, IQR 155.2–744.8 ng/mL) values available, respectively. There were no statistically significant differences in the three serum biomarkers between the patients with positive versus negative myocardial ^{11}C-PiB PET uptake (Figure 3).

We performed subgroup analysis on the subset of patients with the levels of troponin I, NT-proBNP, and dFLC higher than the thresholds of the revised Mayo staging system (*8*), (troponin I ≥0.1 ng/mL, NT-proBNP ≥1,800 pg/mL, and dFLC ≥180 mg/mL), the subset of patients considered high risk. Among patients with troponin I ≥0.1 ng/mL, a positive myocardial ^{11}C-PiB PET uptake was associated with a worse overall survival rate during 1-year follow-up (*P*=0.013 by log-rank test, Figure 4A; unadjusted HR 8.884, 95% CI 1.121–70.410, *P*=0.039). This pattern was similar in the patients with NT-proBNP ≥1,800 pg/mL (*P*=0.020 by log-rank test, Figure 4B;

unadjusted HR 7.892, 95% CI 1.011–61.610, P=0.049) and in those with dFLC ≥180 mg/mL (P=0.050 by log-rank test, Figure 4C; unadjusted HR 5.923, 95% CI 0.783–44.82, P=0.085). Additionally, the cardiac staging system incorporating ^{11}C-PiB PET/CT in combination with the 2004 Mayo classification system (*26*) also significantly predicted the 1-year overall survival (Supplemental Figure 3).

To determine the incremental predictive value of ^{11}C-PiB PET/CT in regards to outcome, the NRI and IDI were measured when the results of ^{11}C-PiB PET/CT were added to the three conventional biomarkers, troponin I, NT-proBNP, and dFLC, respectively. Both the NRI and IDI for prediction of 1-year overall survival showed a consistent significant improvement, with NRIs of 0.861, 0.914, and 0.987 (all P<0.01) and IDIs of 0.200, 0.156, and 0.108 (all P<0.05), when the results of ^{11}C-PiB PET/CT was added to troponin I, NT-proBNP or dFLC, respectively (Supplemental Table 2).

Discussion

This study is the first to prove the incremental prognostic power of ^{11}C-PiB PET/CT in patients with ALCA, in addition to the conventional serum biomarkers including troponin I, NT-proBNP, and dFLC. The main findings of this study are; (1) ^{11}C-PiB PET/CT predicts 1-year overall survival in patients with ALCA; (2) a positive ^{11}C-PiB PET uptake in the myocardium is a robust prognosticator capable of reclassifying subjects stratified as high risk based on the conventional serum biomarkers commonly used for prognostication; and (3) ^{11}C-PiB PET/CT provides additional independent prognostic information for predicting 1-year survival over conventional biomarkers.

^{11}C-PiB, the prototype PET amyloid tracer, is one of the most studied and widely used amyloid beta-peptide imaging agents. ^{11}C-PiB PET was first used to image and quantify the amyloid deposits in Alzheimer's dementia (*27,28*) and is effective in diagnosing CA and predicting its prognosis as in our previous studies (*16-18*). However, the lack of evidence for an independent predictive power apart from the previously well-validated biomarkers for cardiac staging, such as troponin I, NT-pro BNP, and dFLC (*8*), limits the clinical application of ^{11}C-PiB PET/CT in these patients. The current study expands upon our previous researches and demonstrates the clinical implication of ^{11}C-PiB PET/CT as a risk predictor for ALCA patients, independent of the commonly used biomarkers. Notably, we demonstrated that a positive ^{11}C-PiB PET uptake in the myocardium remains one of the strongest independent predictors of 1-year overall survival.

Patients with ALCA have a dismal prognosis, with nearly half of the patients dying within 1 year of the diagnosis as in the current study. Therefore, previous cardiac staging systems have recommended using cardiac biomarkers such as troponin I and NT-proBNP for risk stratification

of AL amyloidosis (*7,8*). However, circulating cardiac biomarkers are not generally specific to ALCA and are also elevated in heart failure of other etiologies (*29*). Given the strong association between myocardial ^{11}C-PiB PET uptake and worse clinical outcome in ALCA patients, we propose that performing ^{11}C-PiB PET/CT be considered for more accurate cardiac staging. The prognostic power of ^{11}C-PiB PET/CT was maintained even in patients with higher levels of dFLC. Therefore, it is expected that ^{11}C-PiB PET/CT could play greater roles in risk prediction of ALCA patients who are likely to be falsely considered high risk, possibly nonspecific elevations of the serum biomarkers.

It is important to note that among the biopsy-confirmed ALCA patients, there was a certain proportion with a very low myocardial uptake of ^{11}C-PiB when using standardized uptake values as a measure of the tracer uptake (*16*). In the current study, a visual assessment of the ^{11}C-PiB PET/CT images demonstrated that a significant number of patients who may be quantified as positive may actually have a negligible amount of myocardial ^{11}C-PiB PET uptake that could be considered as negative in the visual assessment, which is also supported by our previous works (*17*). It is interesting to note that these patients with a low and/or visually negative myocardial ^{11}C-PiB PET uptake had a significantly better prognosis than those with a strong and/or visually positive uptake, which suggest that myocardial ^{11}C-PiB PET uptake reflects the amount of the amyloid deposit in the myocardium that can be used to determine the prognosis of patients with ALCA (*17*). Similarly, a small pilot study of nine patients diagnosed with CA, using ^{11}C-PiB as the amyloid-targeting PET tracer, found that the cardiac function and symptoms remained stable if myocardial ^{11}C-PiB PET uptake was negative, whereas a positive myocardial ^{11}C-PiB uptake portended a poor prognosis (30). Taken together, it is expected that myocardial ^{11}C-PiB PET uptake

is strongly related to an advanced state of disease. Further studies may be needed on the standardized protocols using quantitative or semi-quantitative methods to define the cutoff values that could be used to identify high risk group.

To date, no imaging tool has been included in the cardiac staging of patients with AL amyloidosis. However, staging is essential for prognostication, such as the identification of high risk populations (*31,32*), and also, optimal management. Given the need for improved cardiac staging systems in AL amyloidosis, we provide evidence for using ^{11}C-PiB PET/CT to discriminate high risk patients. Furthermore, our findings warrant further investigation, possibly by multicenter studies, into whether an additive imaging study is needed to accurately predict the prognosis of ALCA patients.

Our study is not without limitations. First, although a prospective study, the sample size was small, and therefore, there is a possibility of overfitting in the multivariate analysis. Second, not all patients had their troponin I, NT-proBNP, and dFLC levels measured for the study and therefore, a selection bias may exist. Third, for patients with ALCA defined by clinically acceptable imaging-based criteria, not all patients underwent an endomyocardial biopsy. However, all patients underwent non-cardiac biopsies for histological confirmation of systemic amyloidosis and the diagnosis of ALCA followed the universally accepted diagnostic criteria. Finally, in contrast to most studies using the dynamic ^{11}C-PiB PET for the early detection of CA, we used the static ^{11}C-PiB PET/CT images for analysis as this has also been demonstrated to be a good alternative to dynamic ^{11}C-PiB PET (*33*). Additionally, the static scan has the advantages of patient convenience, practicability for routine clinical usage, and the potential to evaluate the whole body for amyloid deposit.

Conclusion

^{11}C-PiB PET/CT is a strong independent predictor of 1-year overall survival in patients with ALCA, additive to well-validated serum biomarkers such as troponin I, NT-proBNP, and dFLC. Therefore, ^{11}C-PiB PET/CT may potentially be useful as a novel imaging marker for cardiac staging beyond established predictors in ALCA. Considering the recent developments of numerous amyloid-targeting molecular imaging agents, future prospective studies are warranted on whether PET/CT should be included in the risk stratification for the ALCA patients.

Financial Disclosures

None

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Key points

QUESTION: Does ^{11}C-PiB PET/CT provide an independent incremental prognostic value over conventional serum biomarkers in patients with ALCA?

PERTINENT FINDINGS: We analyzed the 1-year overall survival rate in a prospective cohort of 58 patients with ALCA. ^{11}C-PiB PET/CT is a strong independent predictor of 1-year overall survival in patients with ALCA and provides incremental prognostic benefits that are additive to well-established serum biomarkers such as troponin I, NT-proBNP, and dFLC.

IMPLICATIONS FOR PATIENT CARE: ^{11}C-PiB PET/CT may potentially be useful as a novel imaging marker for cardiac staging beyond established predictors in ALCA patients.

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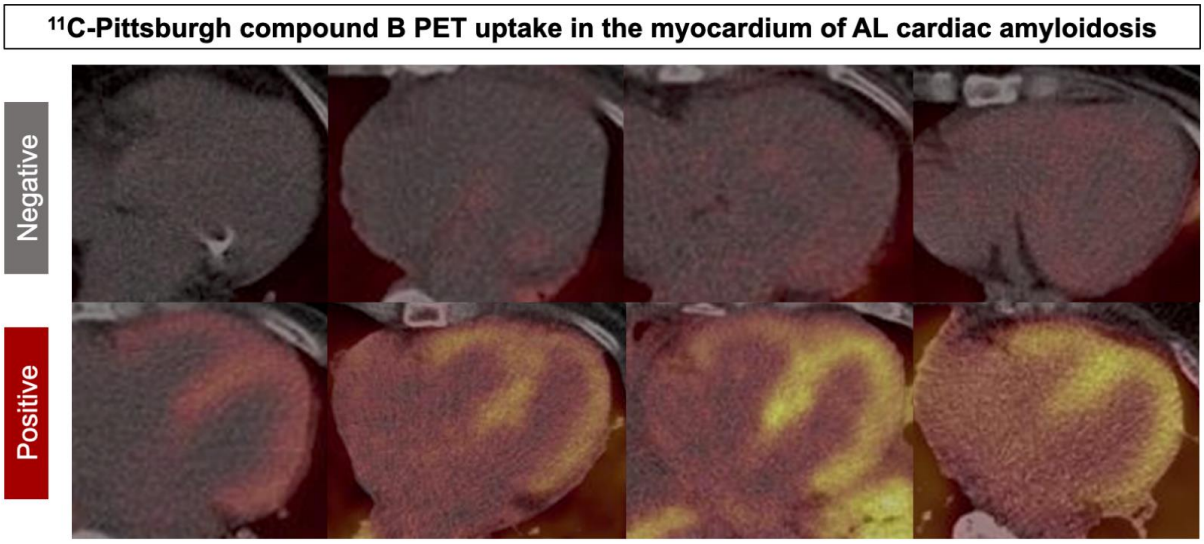


FIGURE 1. Representative positive versus negative ^{11}C-PiB PET/CT images.

^{11}C-PiB PET/CT findings were classified into either negative (upper panels) or positive (lower panels) based on the visually estimated retention of ^{11}C-PiB in the myocardium.

^{11}C-PiB PET/CT, ^{11}C-Pittsburgh compound B positron emission tomography/computed tomography; AL, amyloid light chain.

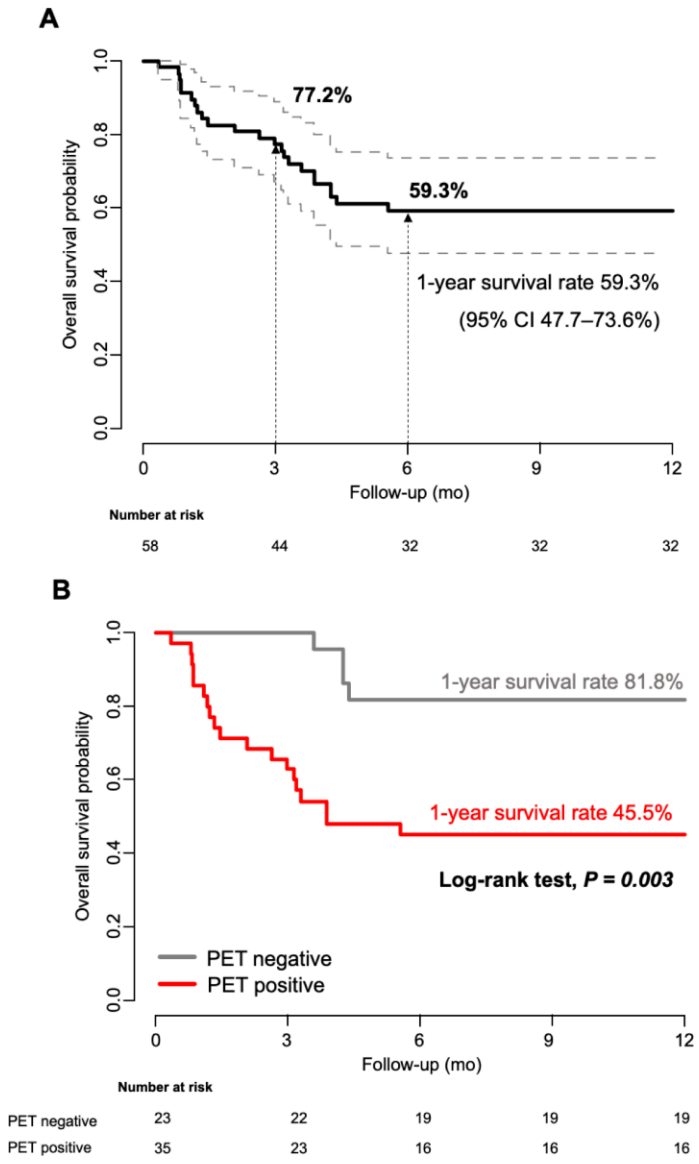


FIGURE 2. Kaplan-Meier curves for 1-year overall survival in patients with ALCA.

Kaplan-Meier survival curves for (A) the entire ALCA population in the current cohort and (B) according to myocardial ^{11}C-PiB PET uptake as in Figure 1.

^{11}C-PiB PET, ^{11}C-Pittsburgh compound B positron emission tomography; ALCA, light chain type cardiac amyloidosis; CI, confidence interval.

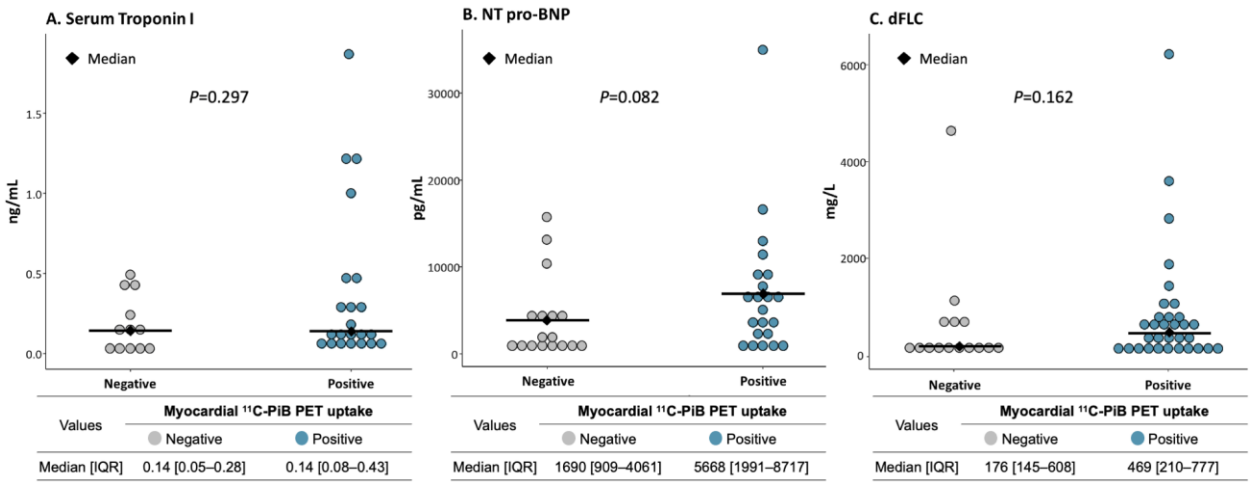


FIGURE 3. Circulating biomarkers in patients with ALCA stratified by myocardial ^{11}C-PiB PET uptake.

Dot plot of each cardiac biomarker according to myocardial ^{11}C-PiB PET uptake; (A) troponin I, (B) NT-proBNP, and (C) dFLC. The black diamond point with the horizontal bar marks the median value of each parameter in each group.

^{11}C-PiB PET, ^{11}C-Pittsburgh compound B positron emission tomography; ALCA, light chain type cardiac amyloidosis; dFLC, an absolute difference between the involved and uninvolved free light chain; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

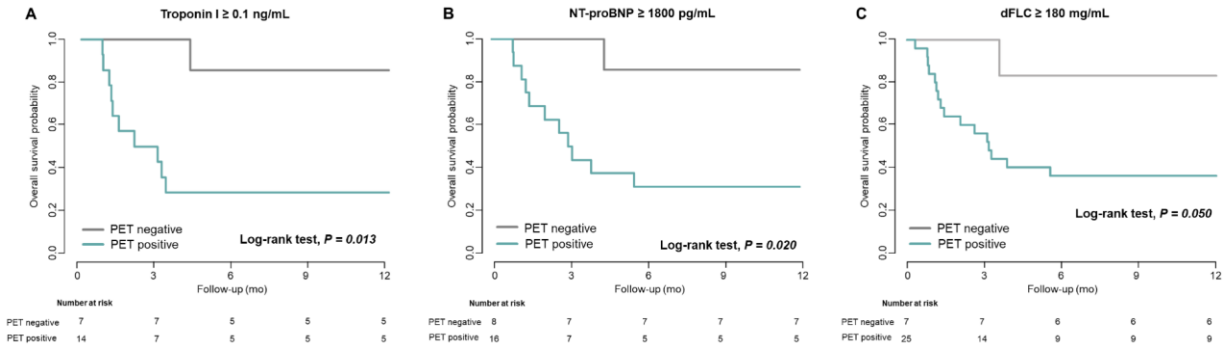


FIGURE 4. Kaplan-Meier curves for 1-year overall survival in ALCA patients with high level of serum biomarkers.

Kaplan-Meier survival curves for patients with ALCA according to myocardial ^{11}C-PiB PET uptake in patients with (A) troponin I ≥0.1 ng/mL, (B) NT-proBNP ≥1,800 pg/mL, and (C) dFLC ≥180 mg/ml.

^{11}C-PiB PET, ^{11}C-Pittsburgh compound B positron emission tomography; ALCA, light chain type cardiac amyloidosis; dFLC, an absolute difference between the involved and uninvolved free light chain; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Tables

Table 1. Baseline characteristics of the study participants.

Variables	Entire population N=58	Negative ^{11}C-PiB PET/CT N=23	Positive ^{11}C-PiB PET/CT N=35	*P*
Demographics				
Age, years	64.0 ± 9.1	61.7 ± 7.6	65.5 ± 9.8	0.121
Male, n (%)	25 (43.1)	9 (39.1)	16 (45.7)	0.787
Systolic blood pressure, mmHg	109.5 [100.2–119.5]	111.0 [104.5–122.5]	104.0 [92.5–114.0]	0.034
Diastolic blood pressure, mmHg	68.0 ± 7.5	68.5 ± 7.7	67.6 ± 7.5	0.663
Body mass index, kg/m^2	22.6 ± 3.1	23.1 ± 3.4	22.2 ± 3.9	0.270
Comorbidities, n (%)				
Hypertension	13 (22.4)	5 (21.7)	8 (22.9)	0.999
Diabetes	13 (22.4)	2 (8.7)	11 (31.4)	0.087
Dyslipidemia	6 (10.3)	1 (4.3)	5 (14.3)	0.386
End-stage renal disease	4 (6.8)	2 (8.7)	2 (5.7)	1.000
Atrial fibrillation	5 (8.6)	4 (17.4)	1 (2.98)	0.075
Chemotherapy	51 (87.9)	22 (95.7)	29 (82.9)	0.224
Autologous PBSCT	10 (17.2)	7 (30.4)	3 (8.6)	0.040
Echocardiography data				
LV end-diastolic dimension, mm	43.8 ± 5.2	45.1 ± 6.0	43.0 ± 4.4	0.134
LV end-systolic dimension, mm	28.8 ± 5.2	29.2 ± 6.0	28.5 ± 4.7	0.640
LV mass index, kg/m^2	121.2 ± 34.7	116.8 ± 36.8	124.2 ± 33.5	0.430
LV ejection fraction, %	56.5 [52.0–62.0]	58.0 [51.5–66.5]	56.0 [52.5–60.5]	0.321
LV ejection fraction <60%, n (%)	19 (32.8)	10 (43.5)	9 (25.7)	0.261
E velocity, m/s	0.85 ± 0.28	0.76 ± 0.23	0.91 ± 0.31	0.021
e' velocity, cm/s	4.1 ± 1.1	4.4 ± 1.0	3.8 ± 1.1	0.043
E/e' ratio	19.9 [14.9–29.5]	16.7 [13.4–21.0]	22.5 [17.0–33.3]	0.004
Estimated PASP, mmHg	38.0 [32.5–45.0]	37.0 [31.5–42.5]	40.5 [32.8–45.0]	0.441
Left atrial size, mm	43.3 ± 6.7	43.1 ± 7.2	43.4 ± 6.4	0.863

Data were presented as mean±standard deviation or median [interquartile range] for continuous variables and frequencies (percentages) for categorical variables. *P* for comparison between the positive versus the negative ^{11}C-PiB PET/CT groups.

^{11}C-PiB PET/CT, ^{11}C-Pittsburgh compound B positron emission tomography/computed tomography; E velocity, early diastolic transmitral inflow velocity; e' velocity, early diastolic septal mitral annular tissue velocity; LV, left ventricular; PASP, pulmonary arterial systolic pressure; PBSCT, peripheral blood stem cell transplantation.

Supplemental Table 1. Cox proportional hazards regression analysis for all-cause mortality in patients with ALCA.

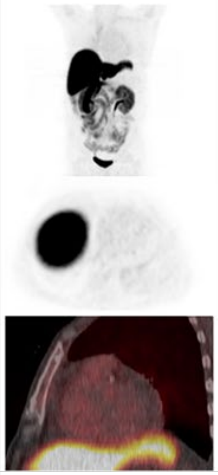
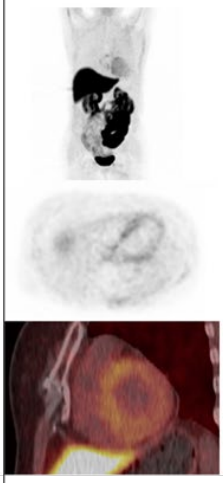
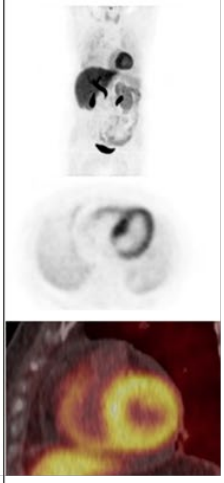
Variables	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Positive myocardial ^{11}C-PiB PET uptake	4.441	1.505–13.110	0.007	3.382	1.011–11.316	0.048
Age, years	1.066	1.013–1.122	0.014	1.033	0.968–1.102	0.323
Male	3.183	1.372–7.383	0.007	3.020	1.266–7.206	0.013
Systolic blood pressure, mmHg	0.989	0.963–1.017	0.441			
LV ejection fraction, %	0.969	0.940–0.999	0.041	0.958	0.919–0.999	0.046
E/e' ratio	1.032	0.995–1.071	0.093			
Autologous PBSCT	0.114	0.015–0.845	0.034	0.224	0.024–2.112	0.191

^{11}C-PiB PET, ^{11}C-Pittsburgh compound B positron emission tomography; CI, confidence interval; E/e', early diastolic transmitral inflow velocity to early diastolic septal mitral annular tissue velocity ratio; HR, hazard ratio; LV, left ventricular; PBSCT, peripheral blood stem cell transplantation.

Supplemental Table 2. Net reclassification improvement and integrated discrimination improvement for prediction of all-cause mortality.

Model	NRI	95% CI	*P*	IDI	95% CI	*P*
Troponin I ≥0.1 ng/mL plus ^{11}C-PiB PET/CT	0.861	0.299–1.420	0.003	0.200	0.066–0.334	0.004
NT-proBNP ≥1800 pg/mL plus ^{11}C-PiB PET/CT	0.914	0.383–1.445	<0.001	0.156	0.056–0.256	0.002
dFLC ≥180 mg/mL plus ^{11}C-PiB PET/CT	0.987	0.202–1.173	0.006	0.108	0.021–0.196	0.015

^{11}C-PiB PET/CT, ^{11}C-Pittsburgh compound B positron emission tomography/computed tomography; CI, confidence interval; dFLC, an absolute difference between the involved and uninvolved free light chain; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

^{11}C-PiB PET/CT				
Grade	**0**	**1**	**2**	**3**
Visual estimation	**Negative**	**Positive**	**Positive**	**Positive**
Description	Myocardial uptake not discernible from blood pool	Myocardial uptake much lower than liver	Myocardial uptake Mildly lower than liver	Myocardial uptake similar to or higher than liver
Myocardial SUVpeak	1.77±0.41 [0.97–2.61]	2.40±0.65 [1.53–3.68]	5.19±2.11 [3.21–10.87]	8.66±2.38 [5.48–12.02]
Myocardial SUVpeak-to-mean LV blood pool ratio	1.57±0.14 [1.43–1.81]	2.81±0.71 [1.58–4.23]	4.99±1.32 [3.06–7.13]	6.57±1.57 [4.03–8.83]

Supplemental Figure 1. Interpretations of ^{11}C-PiB PET/CT by visual estimation.

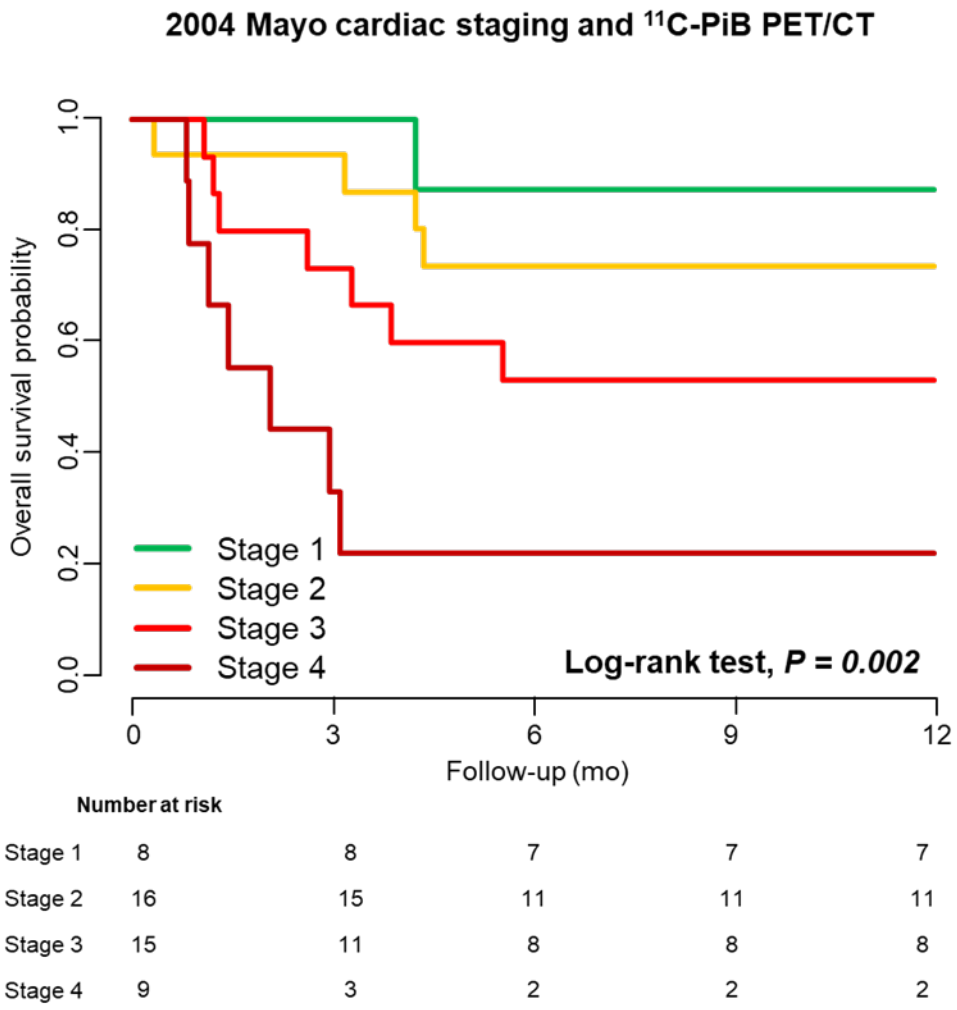
A myocardial uptake of ^{11}C-PiB that was discernible from the blood pool (i.e., LV cavity) was considered positive. Specifically, a myocardial uptake of grade 1 or higher was considered a positive myocardial ^{11}C-PiB uptake on the visual estimation.

^{11}C-PiB PET/CT, ^{11}C-Pittsburgh compound B positron emission tomography/computed tomography; LV, left ventricular; SUV, standardized uptake value.

Supplemental Figure 2. Images of ^{11}C-PiB PET/CT for all patients with ALCA in this study.

The upper panels contain the ^{11}C-PiB PET/CT images interpreted as negative, whereas the lower panels contain those interpreted as positive. The number in the image indicates the subject number of each patient.

^{11}C-PiB PET/CT, ^{11}C-Pittsburgh compound B positron emission tomography/computed tomography; ALCA, light chain type cardiac amyloidosis.



Kaplan-Meier survival curves of patients with ALCA, stratified by a 4-stage system incorporating ^{11}C-PiB PET/CT findings with the 2004 Mayo cardiac staging system. The 4-stage system allocated 1 point for each abnormal variable, such as elevated troponin I, NT-proBNP or a positive myocardial ^{11}C-PiB uptake.

^{11}C-PiB PET/CT, ^{11}C-Pittsburgh compound B positron emission tomography/computed tomography; ALCA, light-chain type cardiac amyloidosis; NT-proBNP, N-terminal pro B-type natriuretic peptide.