# Clinical Characteristics and Outcomes of Cyclin D1–Positive AL Amyloidosis

*Takafumi Tsushima, MD, Toshiki Terao, MD, Kentaro Narita, MD, Ami Fukumoto, MD, Daisuke Ikeda, MD, Yuya Kamura, MD, Ayumi Kuzume, MD, Rikako Tabata, MD, Daisuke Miura, MD, Masami Takeuchi, MD, and Kosei Matsue, MD, PhD*

From the Division of Hematology/Oncology, Department of Internal Medicine, Kameda Medical Center, Kamogawa, Japan.

## ABSTRACT

**Objectives**: To demonstrate the clinical features and prognostic impact of cyclin D1 positivity in patients with amyloid light chain amyloidosis (AL).

**Methods**: We consecutively included 71 patients diagnosed with AL with cyclin D1 positivity between February 2008 and January 2022. t(11;14) was examined through interphase fluorescence in situ hybridization using bone marrow cells.

**Results**: The median age of the patients was 73 years, and 53.5% were male. The underlying diseases included symptomatic multiple myeloma, smoldering multiple myeloma, Waldenström macroglobulinemia, and monoclonal gammopathy of undetermined significance, representing 33.8%, 26.8%, 2.8%, and 36.6%, respectively. The prevalence of cyclin D1 and t(11;14) was 38.0% and 34.7%, respectively. Higher frequency of light chain paraprotein type was seen in cyclin D1–positive patients with AL than in cyclin D1–negative patients (70.4% vs 18.2%). The median overall survival (OS) of patients with AL with and without cyclin D1 expression was 18.9 months and 73.1 months, respectively ($P = .019$). Early death occurred in 44.4% of cyclin D1–positive patients and 31.8% of cyclin D1–negative patients. Moreover, 83.3% of cyclin D1–positive patients and 21.4% of cyclin D1–negative patients died of cardiac causes.

**Conclusions**: Cyclin D1 immunohistochemistry accurately identified patients with t(11;14). Cyclin D1–positive patients had significantly inferior OS compared with cyclin D1–negative patients.

## INTRODUCTION

Amyloid light chain amyloidosis (AL) is a rare plasma cell (PC) disease caused by extracellular deposition of misfolded immunoglobulin light chains, leading to organ failure.[1,2] It is usually caused by a small population of abnormal PC or B-cell clones. Cardiac biomarkers, such as troponin-T and N-terminal pro–B-type natriuretic peptide (NT-proBNP), and the difference between the involved and uninvolved free light chains (dFLCs) are the most relevant factors associated with the prognosis of AL.[2,3] The prognosis is poor as the number of organ failures associated with amyloid deposition increases. However, the prognosis of AL has greatly improved with the use of proteasome inhibitors[4,5] and CD38 monoclonal antibodies.[6,7]

## KEY POINTS

- Detection of t(11;14) in amyloid light chain amyloidosis (AL) by interphase fluorescence in situ hybridization is often limited by the small proportion of clonal plasma cells in normal bone marrow aspirates. We performed immunohistologic detection of cyclin D1 to identify t(11;14) in AL.
- t(11;14) and cyclin D1 immunostaining showed extremely high concordance in AL.
- Patients with cyclin D1–positive AL had fewer secondary cytogenetic abnormalities and a poorer prognosis than those with cyclin D1–negative AL.

## KEY WORDS

AL amyloidosis; t(11;14); Prognosis; Cyclin D1

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Corresponding author: Kosei Matsue, MD, PhD; koseimatsue@gmail.com.

Translocation t(11;14) is the most prevalent genetic abnormality in AL, accounting for approximately 40% to 60% of patients, and is a genetically stable abnormality with a low rate of subclone formation and progression.[8] Unlike patients with multiple myeloma (MM), the survival of patients with AL with t(11;14) is generally inferior to that of those without t(11;14),[9] particularly those who were on regimens containing bortezomib.[10,11] Furthermore, the poor prognosis seen in such cases can be eliminated by autologous peripheral blood stem cell transplantation with high-dose melphalan therapy.[12] Recent reports on the efficacy of venetoclax in t(11;14) patients have increased the importance of detecting this abnormality.[13] Thus, examining the presence or absence of t(11;14) has important clinical implications for patients with AL.

Although t(11;14) is a common cytogenetic abnormality in AL,[9,14] its detection by interphase fluorescence in situ hybridization (iFISH) is often limited by the small percentage of clonal PCs in routine marrow aspiration. Translocation t(11;14) is associated with overexpression of the cyclin D1 protein, which can be detected by immunohistochemical staining in patients with AL as well as in patients with mantle cell lymphoma and MM. Detection of cyclin D1 expression using immunohistochemistry is less time- and cost-consuming compared with iFISH and more easily applied to formalin-fixed, paraffin-embedded bone marrow (BM) tissues.[15] In the present study, we explored cyclin D1 expression in patients with AL using immunohistochemistry and analyzed its impact on the clinical features and outcomes of the disease.

## MATERIALS AND METHODS

### Study Design and Patients, Collection of Specimens

From February 2008 to January 2022, 71 patients with AL diagnosed and fully evaluated at Kameda Medical Center, Kamogawa-shi, Japan, were consecutively included in our study. AL was diagnosed based on the histologic presence of amyloid deposits in various biopsied organs (usually the kidney, intestinal tract, skin, fat, heart, lips, and BM) through Congo red staining with apple green birefringence using crossed polarized light. Amyloid deposits have been screened in the BM, gastrointestinal tract, and fat, but the heart and kidney have been screened only in suspected cases. Cases diagnosed with AL were confirmed through immunohistochemistry and/or immunofluorescence, revealing amyloid deposition of κ or λ chains at the reference laboratory of Kumamoto University Hospital. When the diagnosis was unclear, proteomic analysis with laser dissection followed by mass spectrometry was performed.

The proportions of BM PCs were determined by counting the smears of BM aspirations or BM biopsy specimens stained with CD138 monoclonal antibody.[16] For the enumeration of BM PCs, both BM smears and BM biopsy specimens with CD138 immunohistochemical staining were used, and the higher percentage was used according to the International Myeloma Working Group Criteria.[17] The immunophenotype of PC was determined by multicolor flow cytometry.

Cyclin D1 positivity was assessed by comparing CD138-positve cells with CCND1-positive cells in BM biopsy specimens FIGURE 1. In many cases, tumor cells tend to cluster in PC dyscrasia, and it is relatively easy to determine the degree of concordance between CD138 and cyclin D1 positivity, and even loose concordance is considered positive.

Moreover, iFISH enumeration was performed to detect cytogenetic abnormalities according to the manufacturer's protocol using the following probes: del17p, 17p13.1, 17p21, 1q, 1q21 GKS1B, IgH, 14q32, FGFR3, 4p16, CCND1 (BCL1), 11q13, MAF, 16p23, del13, and 13q14.3 (all Abbott Molecular). Prior to iFISH, PCs were enriched using magnetic beads with CD138 monoclonal antibodies on 21 patients who were diagnosed after April 2013. For patients diagnosed before this time, iFISH was performed using whole BM cells.

Thus, we aimed at comparing the hematologic response and overall survival (OS) between patients with cyclin D1–positive and cyclin D1–negative AL amyloidosis. Hematologic response was evaluated according to the consensus criteria for AL. Remission was

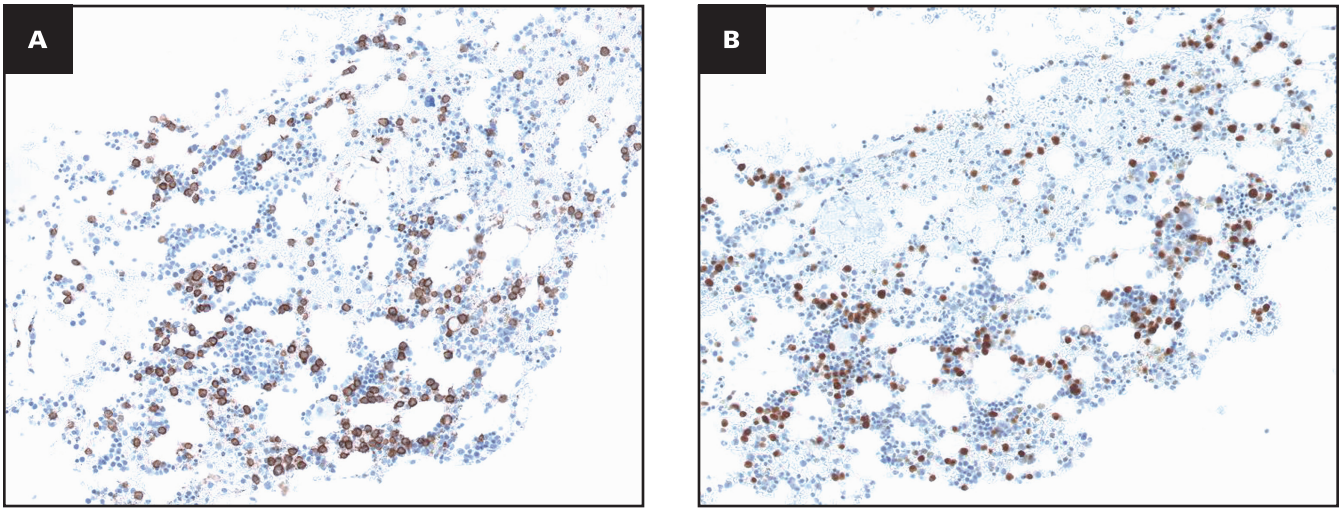


**FIGURE 1** Immunohistochemical staining of bone marrow biopsy by CD138 (**A**) and cyclin D1 (**B**) (×200).




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determined according to the consensus criteria for very good partial remission (VGPR).[10] OS was calculated from the time of diagnosis to death or last follow-up.

We collected data from electronic medical records within the study period. Written informed consent was obtained from all patients prior to data collection. This study was conducted in accordance with the Declaration of Helsinki 2013 and approved by the Ethical Review Committee of the Kameda Medical Center.

### Statistical Analysis

The baseline characteristics of patients with AL were compared using the Mann-Whitney *U* test for continuous variables and Fisher exact test for categorical variables. Univariate and multivariate logistic regression analyses were used to evaluate predictors of AL. Various factors associated with poor prognosis were elucidated, including cyclin D1 expression, NT-proBNP greater than 1,800 ng/L, revised Mayo stage higher than II, VGPR achievement, t(11;14), 17p13 deletion, and 1q21.[3]

The Kaplan-Meier method was compared using the log-rank test to evaluate all-time OS and progression-free survival (PFS). All statistical analyses were conducted using the EZR software (Saitama Medical Center, Jichi Medical University),[18] a graphical user interface for R version 3.1.2 (The R Foundation for Statistical Computing). Two-sided *P* values less than .05 were considered statistically significant.

## RESULTS

### Clinical Characteristics of Patients With and Without CCND1

The clinical characteristics of patients with AL with and without cyclin D1 are summarized in TABLE 1 and TABLE 2. The median age of all patients was 73.0 years, and 53.5% were male. The prevalence of cyclin D1 positivity and negativity was 38.0% and 61.9%, respectively. The most prevalent paraprotein type was the light chain–only type in cyclin D1–positive patients and the IgG type in cyclin D1–negative patients. The prevalence of the light chain–only type was significantly higher in CNND1-positve patients than in cyclin D1–negative patients. The underlying diseases included symptomatic MM, smoldering myeloma, Waldenström macroglobulinemia, and monoclonal gammopathy of undetermined significance in 33.8%, 26.8%, 2.8%, and 36.6% of patients, respectively. High rates of amyloid deposits were observed in the heart and kidneys, since these are examined only in suspected cases. No difference in organ deposition was observed between cyclin D1–positive and cyclin D1–negative AL.

No differences were found between cyclin D1–positive and cyclin D1–negative AL in terms of revised Mayo stage, heart and kidney involvement, NTpro-BNP level, dFLC level, BM PC percentage, and CD56 positivity of tumor cells.

**TABLE 1** Clinical Characteristics According to CCND1 Positivity[a]

| Characteristic | Total (n = 71) | Cyclin D1–Positive AL (n = 27) | Cyclin D1–Negative AL (n = 44) | *P* Value |
|---|---|---|---|---|
| Age, median (IQR), y | 73.0 (41.5-89.0) | 73.0 (41.5-88.8) | 73.5 (49.5-89.0) | .492 |
| Male sex, No. (%) | 38 (53.5) | 16 (59.3) | 22 (50.0) | .474 |
| Paraprotein type, No. (%) | | | | |
| IgG | 24 (33.8) | 7 (25.9) | 17 (38.6) | .311 |
| IgA | 17 (23.9) | 1 (3.7) | 16 (36.4) | .001 |
| IgM | 2 (2.8) | 0 (0.0) | 2 (4.5) | .522 |
| IgD | 1 (1.4) | 0 (0.0) | 1 (2.3) | 1.000 |
| Light chain only, No. (%) | 27 (38.0) | 19 (70.4) | 8 (18.2) | <.001 |
| Light chain type, No. (%) | | | | |
| κ | 17 (23.9) | 7 (25.9) | 10 (22.7) | .781 |
| λ | 54 (76.1) | 20 (74.1) | 34 (77.3) | |
| Underling disease, No. (%) | | | | |
| Symptomatic MM | 24 (33.8) | 7 (25.9) | 17 (38.6) | .311 |
| Smoldering MM | 19 (26.8) | 9 (33.3) | 10 (22.7) | .410 |
| MGUS | 26 (36.6) | 11 (40.7) | 15 (34.1) | .618 |
| Waldenström macroglobulinemia | 2 (2.8) | 0 (0.0) | 2 (4.5) | .522 |
| Positivity of amyloid deposit, No. of positive/No. of examined, % | | | | |
| Kidney | 31/32 (96.9) | 11/11 (100) | 20/21 (95.2) | 1.000 |
| Heart | 16/17 (94.1) | 9/9 (100) | 7/8 (87.5) | .471 |
| Lip | 12/14 (85.7) | 3/4 (75.0) | 9/10 (90.0) | .505 |
| Gastrointestinal tract | 42/56 (75.0) | 19/24 (79.2) | 23/32 (71.9) | .756 |
| Fat | 26/63 (41.2) | 11/25 (44.0) | 15/38 (39.5) | .796 |
| Bone marrow | 31/67 (46.3) | 13/27 (52.0) | 18/40 (45.0) | .809 |
| Skin | 15/32 (46.9) | 7/16 (43.8) | 8/16 (50.0) | 1.000 |

AL, amyloid light chain amyloidosis; IQR, interquartile range; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma.
[a]The number of positive biopsy specimens of involved organs is listed.






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**TABLE 2** Clinical Characteristics According to the CCND1 Positivity

| Characteristic | Total (n = 71) | Cyclin D1–Positive AL (n = 27) | Cyclin D1–Negative AL (n = 44) | *P* Value |
|---|---|---|---|---|
| Revised Mayo stage, No. (%) | | | | .567 |
| I | 7 (10.3) | 1 (3.8) | 6 (13.6) | |
| II | 14 (20.6) | 6 (22.2) | 8 (18.1) | |
| III | 20 (29.4) | 9 (33.3) | 11 (25.0) | |
| IV | 27 (39.7) | 10 (37.0) | 17 (38.6) | |
| Cardiac involvement, No. positive/total (%) | 50/69 (72.5) | 21/27 (77.8) | 29/42 (69.0) | .582 |
| Renal involvement, No. positive/total (%) | 42/62 (67.7) | 14/23 (60.9) | 28/39 (71.8) | .410 |
| NT-proBNP, median (IQR), pg/mL | 2,934.0 (12.0-69,830.0) | 3,285.5 (186.0-64,930.0) | 2,724.0 (12.0-69,830.0) | .65 |
| dFLC, median (IQR), mg/dL | 335.9 (2.7-16,290.6) | 371.8 (7.1-16,290.6) | 283.4 (2.7-15,193.5) | .470 |
| Bone marrow plasma cells, median (IQR), % | 13.3 (1.4-90.0) | 13.2 (1.4-90.0) | 20.0 (3.0-80.0) | .713 |
| Positivity of CD56, No. (%) | 45 (63.4) | 15 (55.6) | 30 (68.2) | .318 |
| iFISH, No. (%) | | | | |
| t(11;14) | 24/66 (36.4) | 22/24 (91.7) | 2/42 (4.8) | <.001 |
| t(4;14) | 7/64 (10.9) | 0/24 (0.0) | 7/40 (17.5) | .039 |
| t(14;16) | 1/63 (1.6) | 0/24 (0.0) | 1/39 (2.3) | 1.000 |
| Deletion of 17p13 | 2/65 (3.1) | 0/24 (0.0) | 2/41 (4.9) | .527 |
| Deletion of 13q14 | 19/58 (32.8) | 5/22 (22.7) | 14/36 (38.9) | .256 |
| Gain of 1q | 17/44 (38.6) | 3/15 (20.0) | 14/29 (48.3) | .104 |
| Induction regimen, No. (%) | | | | |
| With PI | 52 (89.7) | 19 (70.3) | 33 (75.0) | .664 |
| With IMiDs | 8 (13.8) | 3 (11.1) | 5 (11.4) | 1.000 |
| Received auto-SCT, No. (%) | 3 (5.2) | 1 (3.7) | 2 (4.5) | 1.000 |
| Use of daratumumab, No. (%) | 20 (34.5) | 7 (25.9) | 13 (29.5) | .783 |
| Achievement of VGPR, No. (%) | 35 (59.3) | 13 (48.1) | 22 (50.0) | 1.000 |

AL, amyloid light chain amyloidosis; dFLC, difference between involved and uninvolved free light chain; iFISH, interphase fluorescence in situ hybridization; IMiD, immunomodulatory drug; IQR, interquartile range; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PI, proteasome inhibitor; SCT, stem cell transplantation; VGPR, very good partial response.

Among the 27 cyclin D1–positive and 44 cyclin D1–negative patients with AL, t(11;14) iFISH was performed in 24 and 42 patients, respectively. Two CCND1-positive patients were t(11;14) negative, and 2 cyclin D1–negative patients were t(11;14) positive. The most common iFISH abnormalities were 1q+ (38.6%) and t(11; 14) (36.4%), followed by del 13q14 (32.8%). In line with a previous report, patients with AL with cyclin D1–positive AL had less frequent abnormalities than those with cyclin D1–negative AL.[8] Patients with cyclin D1–negative AL had a similar prevalence of iFISH abnormalities as symptomatic patients with MM.[19] Most patients (89.7%) received bortezomib-based therapy, while some (13.8%) with symptomatic myeloma received therapy, including immunomodulatory drugs. After approval, daratumumab was used in 20 patients for intensification, maintenance, or remission induction therapy.

### Survival of Patients With and Without Cyclin D1 Positivity

The median OS and PFS of all patients were 32.6 months and 22.5 months, respectively. When patients were divided into cyclin D1–positive and cyclin D1–negative groups, the former had an OS and a PFS of 18.9 and 14.7 months, respectively, whereas the latter had an OS and a PFS of 73.1 and 32.3 months, respectively **FIGURE 2**. The cyclin D1–positive group had a significantly worse OS and PFS than the negative group. Early death within 12 months occurred in 44.4% of patients in the cyclin D1–positive group and 31.8% of patients in the cyclin D1–negative group. Among these deaths, 10 (83.3%) in the cyclin D1–positive group and 3 (21.4%) in the cyclin D1–negative group were due to cardiac causes ($P = .05$). Cyclin D1–positive patients had a higher rate of early death due to cardiovascular complications.

Since amyloidosis with symptomatic MM usually has a poor prognosis, the prognosis of patients with AL was evaluated after excluding symptomatic MM. The median OS and PFS for cyclin D1–positive patients were 21.2 months and 8.8 months, respectively, and it was not reached and 61.0 months for negative patients **FIGURE 3**. There was no difference in the frequency of cardiopathies between patients with and without cyclin D1, but compared with patients with mild cardiac disease (revised Mayo stages I and II), patients with negative cyclin D1 had a significantly better OS and PFS than those with positive cyclin D1 (OS, not reached vs 32.6 months, $P = .02$; PFS not reached vs 32.6 months, $P = .005$). A similar trend was observed in patients with advanced heart disease (revised Mayo stages III and IV); however, this difference was not significant (OS, 24.8 vs 18.9 months, $P = .292$; PFS, 13.5 vs 8.8 months, $P = .541$).

### Univariate and Multivariate Analyses

Next, we performed univariate and multivariate analyses to identify factors independently associated with survival **TABLE 3**. In the univariate analysis, NT-proBNP, revised Mayo stage greater than II, and VGPR or higher were significantly associated with PFS, while cyclin




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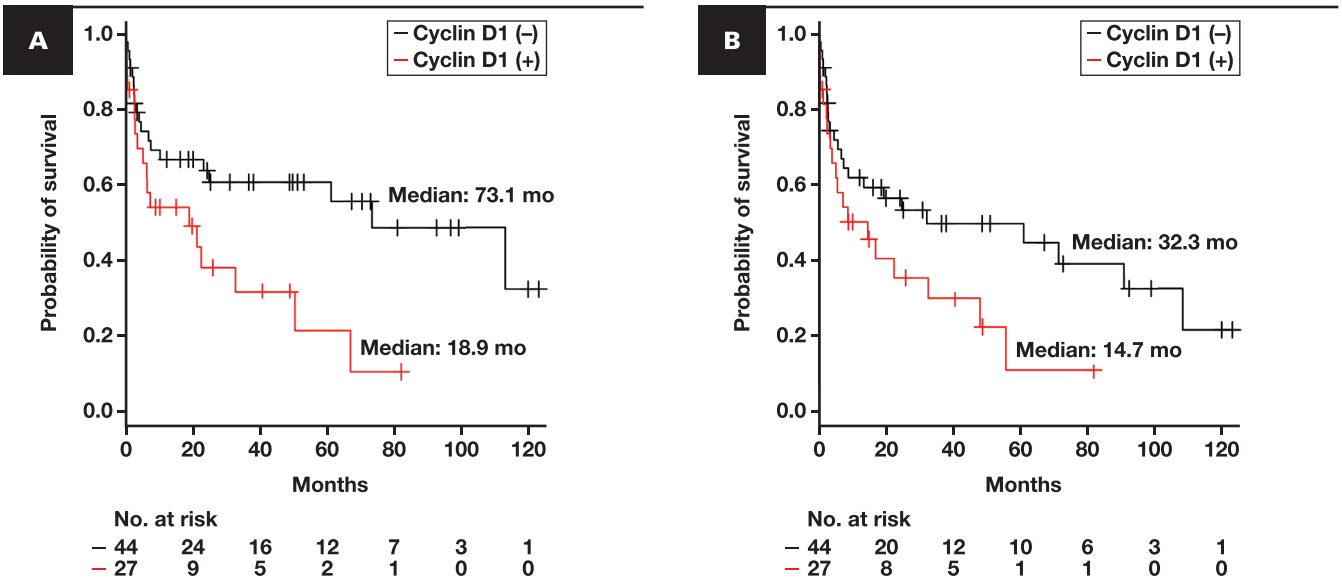


**FIGURE 2** Overall ($P$ = .019) (**A**) and progression-free ($P$ = .060) (**B**) survival of patients according to the cyclin D1 positivity in patients with amyloid light chain amyloidosis.

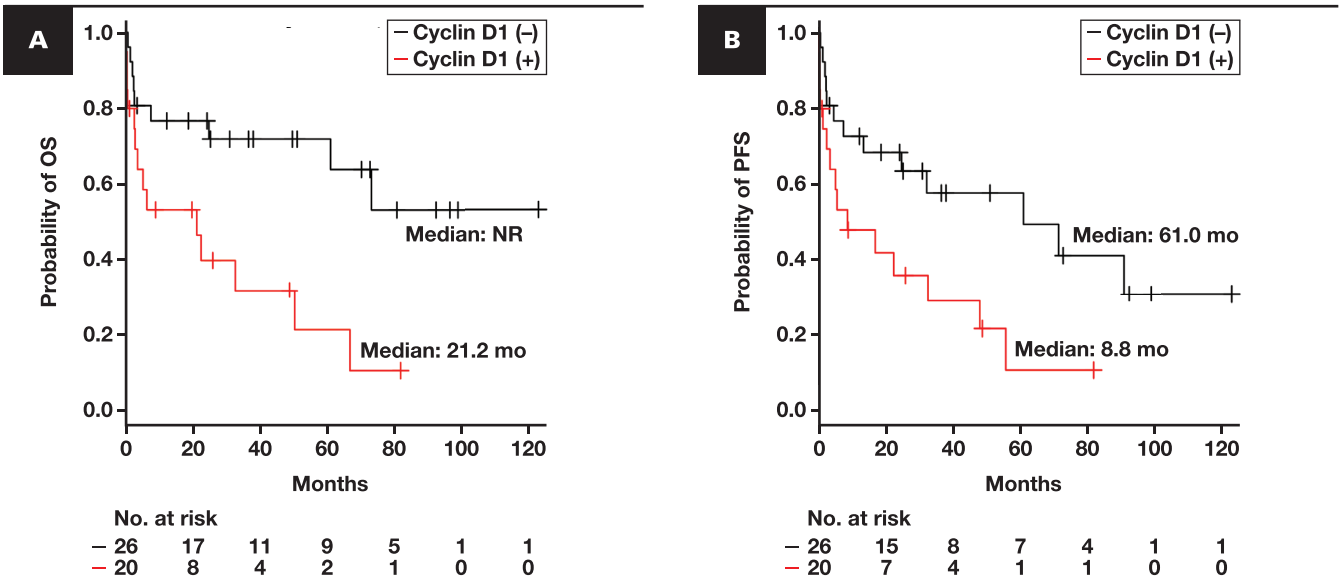


**FIGURE 3** Overall ($P$ = .005) (**A**) and progression-free ($P$ = .018) (**B**) survival of patients according to the cyclin D1 positivity excluding the patients with symptomatic myeloma.

D1, NT-proBNP, and VGPR or higher were significantly associated with OS. In multivariate analysis, cyclin D1 and NT-proBNP greater than 1,800 ng/mL for PFS and cyclin D1 positivity and light chain–only phenotype remained significant for OS.

## DISCUSSION

We retrospectively examined the impact of cyclin D1 positivity in neoplastic PCs on the outcomes of Japanese patients with AL. We accurately identified t(11;14) by comparing immunohistochemical staining with CD138 monoclonal antibody and cyclin D1 in BM specimens. Although cyclin D1 is not specific for PCs with t(11;14), and its expression is found in some myeloma cells with trisomy 11[20] and in endothelial cells, it is not usually found in normal hematopoietic cells. We observed a high frequency of cyclin D1 positivity in Japanese patients with AL (38.0%). Excluding patients with symptomatic MM, the proportion of patients with cyclin D1–positive AL amyloidosis was 44%. This frequency is similar to that reported by Warsame et al.[14] Similar to patients with MM,[21] the paraprotein type of patients with cyclin D1–positive amyloidosis had significantly more frequent light chain–only types, whereas that of cyclin D1–negative amyloidosis was similar to that of symptomatic MM without amyloidosis.





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**TABLE 3** Univariate and Multivariate Cox Regression Analysis of OS and PFS

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| **Variable** | **HR (95% CI)** | ***P* Value** | **HR (95% CI)** | ***P* Value** |
| PFS | | | | |
| Cyclin D1 (+) | 1.80 (0.97-3.36) | .064 | 2.92 (1.32-6.43) | .007 |
| NT-proBNP >1,800 ng/L | 2.67 (1.34-5.42) | .005 | 3.15 (1.49-6.65) | .002 |
| Revised Mayo stage >II | 2.77 (1.27-6.04) | .01 | NA | NA |
| dFLC >180 mg/dL | 2.45 (1.26-4.79) | .008 | 2.12 (1.02-4.43) | .043 |
| Achievement of VGPR | 0.17 (0.08-0.35) | <.001 | NA | NA |
| t(11;14) | 1.57 (0.83-2.97) | .163 | NA | NA |
| Deletion of 17p13 | 2.20 (0.52-9.33) | .282 | NA | NA |
| Light chain only | 1.06 (0.57-1.98) | .847 | 0.46 (0.21-1.03) | .059 |
| 1q+ | 1.41 (0.61-3.23) | .418 | NA | NA |
| OS | | | | |
| Cyclin D1 (+) | 2.16 (1.11-4.21) | .023 | 4.20 (1.82-9.73) | <.001 |
| NT-proBNP >1,800 ng/L | 2.18 (1.04-4.59) | .039 | 3.07 (1.35-6.94) | .007 |
| Revised Mayo stage >II | 2.03 (0.91-4.50) | .080 | NA | NA |
| dFLC >180 mg/dL | 1.83 (0.91-3.63) | .085 | 1.62 (0.75-3.47) | .211 |
| Achievement of VGPR | 0.17 (0.08-0.38) | <.001 | NA | NA |
| t(11;14) | 1.64 (0.82-3.26) | .159 | NA | NA |
| Deletion of 17p13 | 0.91 (0.12-6.72) | .929 | NA | NA |
| Light chain only | 0.92 (0.47-1.83) | .830 | 0.35 (0.15-0.84) | .018 |
| 1q+ | 1.45 (0.58-3.62) | .429 | NA | NA |

dFLC, difference between involved and uninvolved free light chain; HR, hazard ratio; NA, not assessed; NT-proBNP, NT-proBNP, N-terminal pro–B-type natriuretic peptide; OS, overall survival; PFS, progression-free survival; VGPR, very good partial response; 1q+, a gain of 1 or more copies of chromosome 1q.

Overexpression of cyclin D1 is closely associated with t(11;14), the most frequent chromosomal translocation in AL; however, reports on its prognostic impact are not straightforward. This is because the prognosis varies depending on the treatment administered.[22] Investigators from Heidelberg reported that treatment with bortezomib-based regimens is associated with poorer prognosis[10]; although not significant, patients treated with lenalidomide, melphalan, and dexamethasone tended to have shorter PFS and OS,[23] but a better prognosis was observed when patients with AL with t(11;14) were treated with regimens including daratumumab.[24] As in previous studies, positive cyclin D1 and NT-proBNP greater than 1,800 ng/mL, which is thought to represent cardiac involvement of AL, were identified as an independent prognostic factor for OS in our study. Overexpression of cyclin D1 in PC clones of patients with AL was consistent with an abnormal t(11;14) and associated with a poorer prognosis compared with patients without AL (median OS, 73.1 vs 18.9 months, $P = .023$). This could be explained by the fact that approximately 90% of patients were treated with a regimen that included bortezomib. The frequency of gain 1q in our patient cohort was comparable to the iFISH results reported previously[25,26] and less frequent in patients with cyclin D1–positive AL than in those with cyclin D1–negative AL (11.1% vs 48.3%, $P = .104$). The prognostic impact of the 1q gain was not suitable for analysis because of the small sample size.

The limitations of this study include the small sample size and the retrospective nature of the study. Treatment was heterogeneous because of the long study period. A small number of cases were found to have t(11;14) but no expression of cyclin D1. This may be due to the fact that CD138-positive cells include nontumorigenic PCs with negative t(11;14) and that the degree of cyclin D1 protein expression is not uniform. Despite these limitations, to our knowledge this study is the first to describe the real-world clinical picture and prognosis of cyclin D1–positive and cyclin D1–negative AL in Japan.

In conclusion, we identified t(11;14) abnormalities using cyclin D1 immunochemistry in AL. Detection of cyclin D1 expression by immunohistochemistry is less time- and cost-consuming compared to that with iFISH and more easily applied to formalin-fixed, paraffin-embedded BM tissues. We also showed that cyclin D1–positive patients with AL had an inferior prognosis compared to those with cyclin D1–negative AL. This negative impact was also seen in patients with less advanced cardiac disease and in patients with AL who died within 12 months. To confirm our results, we recommend studies with larger samples and full prospective evaluation methods.

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Availability of data and material: The data sets generated and/or analyzed during the current study are available from Takafumi Tsushima or Kosei Matsue on reasonable request.

Conflict of interest disclosure: The authors have nothing to disclose.

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