의학석사 학위논문

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위 원 장 이동순 (인)

부 위 원 장 윤성수 (인)

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# The incidence and risk factors for thromboembolism in AL amyloidosis

by Hyunkyung Park

A thesis submitted in partial fulfillment of the requirements for the Degree of Master of Translational Medicine at Seoul National University College of Medicine

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Approved by Thesis Committee:

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# Abstract

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**Background:** AL amyloidosis may increase the risk for thromboembolism as well as other plasma cell dyscrasias; however, only a few reports have described the clinical features of thromboembolism. This study aimed to elucidate the clinical features of thromboembolic events and to identify risk factors for these events.

**Methods:** Medical records were retrospectively reviewed to define clinically significant thromboembolic events.

**Results:** A total of 106 patients with biopsy-proven AL amyloidosis were included. During a median follow-up of 18.1 months (range, 0.4–166.9 months), 13 thromboembolism events were identified in 13 patients: 9 patients (8.5%) experienced acute cerebral infarction, 2 patients (1.9%) experienced pulmonary embolism, and 2 patients (1.9%) experienced deep

vein thrombosis. Patients with higher serum free light chain (FLC) difference (≥375.2 mg/L) or beta-2 microglobulin (B2MG) levels (≥2.94 mg/L) experienced significantly more thromboembolic events than those with lower value according to multivariable analysis (hazard ratio [HR], 3.537 [95% CI, 1.051–11.898], *P*=0.041 for FLC difference; HR, 19.185 [95% CI, 1.848–199.195], *P*=0.013 for B2MG). Most thromboembolic events (11/13, 84.6%) occurred within the first year following AL amyloidosis diagnosis.

**Conclusions:** The incidence of thromboembolism was substantial in AL amyloidosis. Higher FLC difference and B2MG levels were risk factors for thromboembolic events.

**Keywords:** amyloidosis; plasma cell dyscrasia; thromboembolism; light chain; beta 2-microglobulin

**Student number:** 2015-22433

# 목차

# Introduction

Amyloidosis is a disorder characterized by the abnormal deposition of fibrillar proteins. This disorder results in various clinical manifestations that are dependent upon the involved organs [1]. According to the origin of the abnormal proteins that cause the disorder, amyloidosis can be classified as either AL amyloidosis, which is derived from immunoglobulin light chains, or AA amyloidosis, which is secondary to chronic inflammation [1]. Among these, AL amyloidosis develops due to underlying plasma cell dyscrasia and is the most common type of systemic amyloidosis with an occurrence rate of nine cases per million per year in Western countries [2].

Previous studies have revealed that plasma cell dyscrasias, such as multiple myeloma (MM), monoclonal gammopathy of undetermined significance (MGUS), and Waldenstrom's macroglobulinemia (WM)/lymphoplasmacytic lymphoma (LPL) increase the risk of thromboembolism. In MM, the incidence of thromboembolism has been

reported to be between 2.4 and 28% [3]. This increased risk results from the characteristics of the disease itself. The cytokines and small molecules produced by MM cells increase the activity of the procoagulant factors von Willebrand factor, factor VIII, and fibrinogen, resulting in the upregulation of coagulation pathways [4]. In addition, therapeutic drugs, such as dexamethasone/thalidomide and dexamethasone/lenalidomide, increase the risk of thromboembolism to 8–26% compared with dexamethasone alone [3, 5]. MGUS also increases the risk for thromboembolism by 6.1–8.0% [6, 7]. In a population-based study performed in Sweden, MM patients had a hazard ratio (HR) of arterial and venous thrombosis of 1.8 (95% confidence interval [CI], 1.7–1.9), and MGUS had a HR of 1.4 (95% CI, 1.4–1.5) compared with the matched controls during a 10-year follow-up [8]. Patients with WM/LPL also had an increased risk of thromboembolism compared to matched controls during a 10-year follow-up (HR, 2.0 [95% CI, 1.6–2.5]), and the highest risk was observed during the first year following diagnosis (HR, 4.0 [95% CI, 2.5–6.4], $P < 0.001$) [9].

A few studies have reported the incidence of thromboembolism

in amyloidosis. A retrospective study found that thromboembolic events occurred in approximately 1.9% (40/2132) of patients with amyloidosis: 29 patients (73%) experienced venous thrombosis and 11 patients (28%) experienced arterial thrombosis [10]. In addition, thromboembolic events were reported in 33% of patients with cardiac amyloidosis [11]. The cumulative incidence and risk factors for thromboembolic events, however, remain to be elucidated in patients with AL amyloidosis. Thus, the goals of this study were to elucidate the clinical features of thromboembolic events and to identify risk factors for these events in patients with AL amyloidosis.

# Materials and Methods

## Patient enrollment

This study enrolled patients from three hospitals in Korea: Seoul National University Hospital, Seoul National University Bundang Hospital, and SMG-SNU Boramae Medical Center. We searched the electronic medical records using a term of ‘amyloidosis’ on the pathology report. And then, we manually selected patients with AL amyloidosis according to the inclusion and exclusion criteria. Patients with pathologically proven AL amyloidosis were eligible for this study. AL amyloidosis was diagnosed microscopically by the presence of an apple-green appearance upon Congo red staining. We included patients regardless of multiple myeloma-related organ or tissue impairment including hypercalcemia, renal failure, anemia, and bone lesions. We excluded those individuals who had experienced thromboembolic events before diagnosis with AL amyloidosis. Patient clinical information was retrospectively collected via a medical record review, and these data included patient demographics, laboratory exams, and imaging results. Thromboembolic events that were regarded as

clinically meaningful were those that were diagnosed by angiography, computed tomography, magnetic resonance image, and Doppler sonography with clinical suspicion.

## Study endpoints

The primary objective of this study was to evaluate the cumulative incidence of thromboembolism in patients with AL amyloidosis. The secondary objective was to evaluate risk factors for thromboembolic events in these patients.

## Statistical analysis

We calculated the time from the diagnosis to the occurrence of thromboembolism. The Kaplan-Meier method was used to display the cumulative incidence of thromboembolic events. Median values, receiver operating characteristics (ROC) curve or known normal ranges were defined as cutoff values for the clinical variables in the risk factor analysis. Clinical variables with *P*-values < 0.2 in univariable analyses

were considered for multivariable analyses. Multivariable analysis was performed using the Cox proportional hazard model. Spearman correlation was used to calculate the correlation coefficients (*rho*) and *P*-values. All statistical tests were two-sided, and significance was defined as $P < 0.05$. All analyses were performed using IBM SPSS version 22.0 (IBM, Armonk, NY, USA) and SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA).

## Ethical considerations

This study was reviewed and approved by the institutional review board (IRB) of each participating hospital. Informed consent of patients was waived by the IRB because of the retrospective nature of this study. This study was conducted in accordance with precepts established by the Declaration of Helsinki for biomedical research.

# Results

## Baseline characteristics of patients

From January 2001 to March 2014, a total of 120 patients were diagnosed with AL amyloidosis. Among them, 14 patients (11.7%) were excluded from the analysis due to a diagnosis of thromboembolism prior to the diagnosis of AL amyloidosis. In these 14 patients, the median time from the thromboembolic event to amyloidosis diagnosis was 16.3 months (range, 0.1–107.8 months). A total of 106 consecutive patients with AL amyloidosis were enrolled and analyzed in this study (Fig. 1). The baseline characteristics of the patients are summarized in Table 1. The median age of patients at the time of initial diagnosis was 59 years old (range, 24.0–80.0 years). A single organ involvement was observed in 71 patients (67.0%), and multiple organ involvement was observed in 35 patients (33.0%). Kidney (43.4%) and heart (43.4%) were the most frequently involved organs. The median follow-up period was 18.1 months (range, 0.4–166.9 months). The median overall survival was 20.9 months (95% CI, 5.7–36.2months).

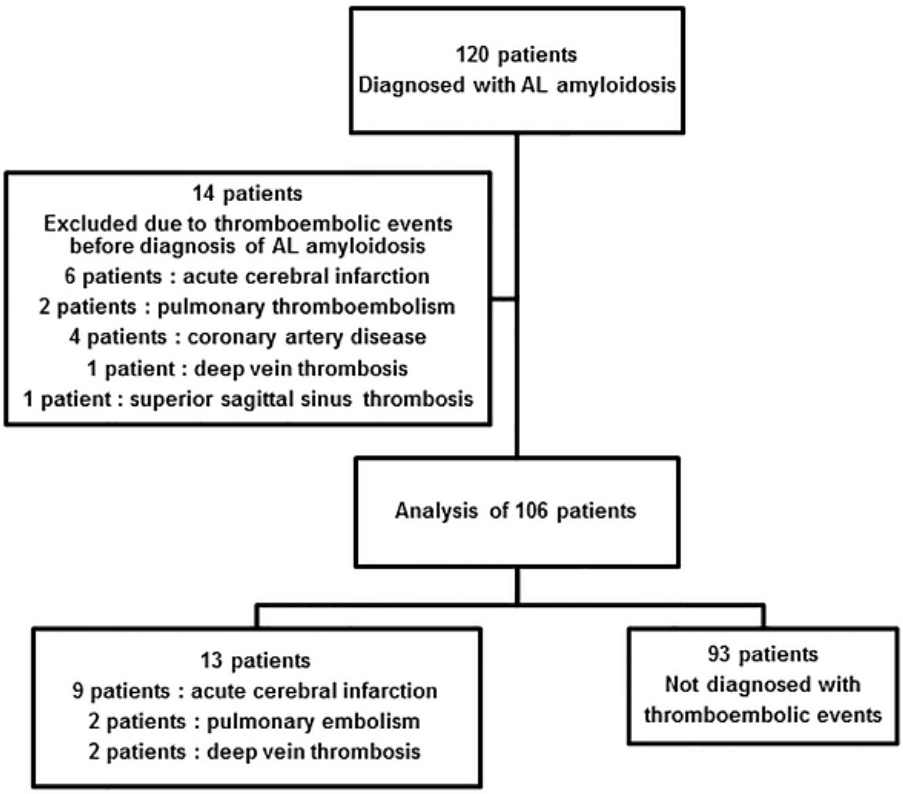



Figure 1. Diagram of patient selection.

Table 1. Baseline characteristics of patients. (N = 106)

| Variables | | Values |
|---|---|---|
| Age, years | Median (range) | 59.0 (24.0–80.0) |
| Gender–no. (%) | Male | 60 (56.6) |
| | Female | 46 (43.4) |
| BM plasma cells, % | Median (range) | 7.0 (0.3–54.0) |
| Organ involvement–no. (%) | Kidney | 46 (43.4) |
| | Heart | 46 (43.4) |
| | Gastrointestinal tract | 17 (16.0) |
| | Liver | 10 (9.4) |
| | Skin | 8 (7.5) |
| | Lung | 3 (2.8) |
| | Lymph node | 2 (1.9) |
| Number of organ involvement at diagnosis, No.–no. (%) | 1 | 71 (67.0) |
| | 2 | 28 (26.4) |
| | 3 | 6 (5.7) |
| | 4 | 1 (0.9) |
| Serum M protein–no. (%) | Positive | 48 (45.3) |
| | Negative | 57 (53.8) |
| | Not evaluated | 1 (0.9) |
| Urine M protein–no. (%) | Positive | 34 (32.1) |
| | Negative | 68 (64.2) |
| | Not evaluated | 4 (3.8) |
| Serum FLC difference, mg/L | Median (range) | 172.4 (0.8–4503.0) |
| Creatinine, mg/dL | Median (range) | 1.01 (0.37–8.69) |
| Albumin, g/dL | Median (range) | 3.0 (1.1–5.0) |
| Beta-2 microglobulin, mg/L | Median (range) | 2.78 (1.18–57.3) |
| Fibrinogen, mg/dL | Median (range) | 380.5 (130.0–876.0) |
| 24-hour urine protein–no. (%) | ≥3 g | 30 (28.3) |
| | <3 g | 45 (42.5) |
| | Not evaluated | 31 (29.2) |
| Atrial fibrillation–no. (%) | Present | 5 (4.7) |
| | Absent | 87 (82.1) |
| | Not evaluated | 14 (13.2) |

| | | |
|---|---|---|
| CRAB–no. (%) | Present | 23 (21.7) |
| | Absent | 83 (78.3) |
| Multiple myeloma | Present | 9 (8.5) |
| | Absent | 97 (91.5) |

Abbreviations: BM = bone marrow; FLC = free light chain; CRAB = C (hypercalcemia), R (renal failure), A (anemia) and B (bone lesions)

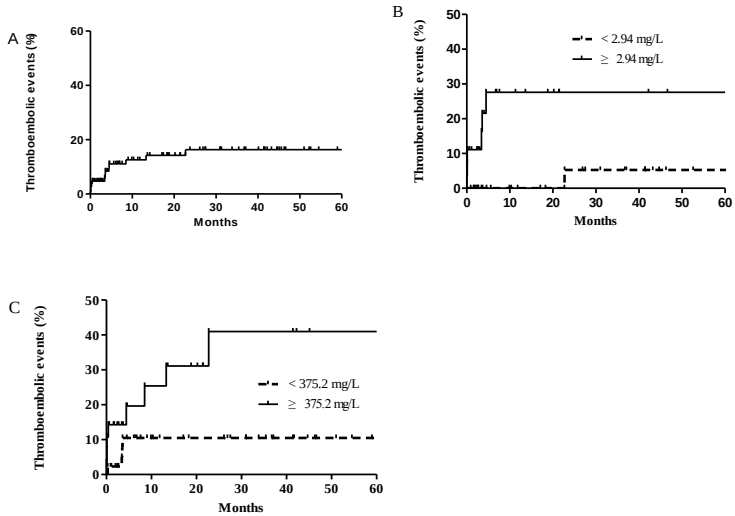
## Cumulative incidence of thromboembolism

The 1-year cumulative incidence of thromboembolic events was 12.6 ± 3.6% in 106 patients (Fig. 2A). During the follow-up period, 13 thromboembolic events developed in 13 patients (12.3%), acute cerebral infarction developed in 9 patients (8.5%), pulmonary embolism developed in 2 patients (1.9%), and deep venous thrombosis developed in 2 patients (1.9%). The median time to the occurrence of thromboembolism was about 3.5 months (95% CI, 0.0–7.2 months) from diagnosis with AL amyloidosis. Most thromboembolic events (11 of 13 events) developed within the first year after diagnosis. The one-year cumulative incidence of thromboembolism in these 13 patients was 84.6 ± 10.0%.

## Risk factors for thromboembolism

In univariable analysis (Table 2), patients with a serum free light chain (FLC) difference of higher than 375.2 mg/L showed significantly higher incidence of thromboembolic events (1-year cumulative incidence ± standard deviation [SD], 25.4 [± 9.3%] *vs.* 10.5 [± 5.0%], $P$ = 0.020; Fig. 2C, Table 2). In addition, patients with elevated serum beta-2 microglobulin (B2MG) levels (≥ 2.94 mg/L) also had increased thromboembolic events (1-year cumulative incidence ± [SD], 27.6 [± 8.8%] *vs.* 0, $P$ = 0.004; Fig. 2B, Table 2). Serum FLC difference values were significantly correlated with serum B2MG levels (*rho* = 0.302, $P$ = 0.043 by Spearman correlation). Based on this correlation, we performed multivariable analysis using two different models (Table 3). In multivariable analysis, serum FLC difference and B2MG levels were found to be risk factors for thromboembolic events (HR, 3.537 [95% CI, 1.051–11.898], $P$ = 0.041 for FLC difference; HR, 19.185 [95% CI, 1.848–199.195], $P$ = 0.013 for B2MG) (Table 3).

Figure 2. Cumulative incidence of thromboembolic events in patients with AL amyloidosis.




(A) The 1-year cumulative incidence of thromboembolic events was 12.6 ± 3.6% in the entire study population (n=106). (B) The 1-year cumulative incidence was 27.6 ± 8.8% in patients with higher beta-2 microglobulin levels (≥2.94 mg/L) and 0% in those with lower beta-2 microglobulin levels (<2.94 mg/L). *P*=0.004. (C) The 1-year cumulative incidence was 25.4 ± 9.3% in patients with higher serum FLC differences (≥375.2 mg/L) and 10.5 ± 5.0% in those with lower serum FLC differences (<375.2 mg/L). *P*=0.020.

Table 2. Hazard ratios (HRs) and P-values of thromboembolic events using Cox regression analysis in univariable analysis.

| Characteristics | | Number of patients (%) | 1-year cumulative incidence±SD (%) | P-value |
|---|---|---|---|---|
| Age | ≥ 60 years | 46 (43.4) | 7.5 (± 4.3) | 0.189 |
| | < 60 years | 60 (56.6) | 15.7 (± 5.2) | |
| Gender | Male | 60 (56.6) | 8.7 (± 4.2) | 0.122 |
| | Female | 46 (43.4) | 17.9 (± 6.3) | |
| BM plasma cells | ≥ 10% | 29 (27.4) | 10.7 (± 5.8) | 0.869 |
| | < 10% | 53 (50.0) | 17.3 (± 5.6) | |
| Number of organ involvements | 1 – 2 | 97 (91.5) | 12.1 (± 3.7) | 0.836 |
| | 3 – 4 | 9 (8.5) | 13.9 (± 4.0) | |
| Kidney | Involvement | 46 (43.4) | 9.6 (± 4.1) | 0.400 |
| | No involvement | 60 (56.6) | 16.5 (± 6.3) | |
| Heart | Involvement | 46 (43.4) | 15.4 (± 5.9) | 0.390 |
| | No involvement | 60 (56.6) | 10.4 (± 4.5) | |
| Gastrointestine | Involvement | 17 (16.0) | 8.3 (± 8.0) | 0.486 |
| | No involvement | 89 (84.0) | 13.4 (± 4.0) | |
| Liver | Involvement | 10 (9.4) | 0.0 | 0.300 |
| | No involvement | 96 (90.6) | 13.5 (± 3.9) | |
| Skin | Involvement | 8 (7.5) | 12.5 (± 11.7) | 0.990 |
| | No involvement | 98 (92.4) | 12.0 (± 3.8) | |
| Lung | Involvement | 3 (2.8) | 0.0 | 0.456 |
| | No involvement | 103 (97.2) | 13.0 (± 3.7) | |
| Lymph node | Involvement | 2 (1.9) | 0.0 | 0.546 |
| | No involvement | 104 (98.1) | 12.9 (± 3.7) | |
| Serum M protein | Positive | 48 (45.3) | 13.9 (± 4.5) | 0.932 |
| | Negative | 57 (53.8) | 15.0 (± 5.8) | |
| Urine M protein | Positive | 34 (32.1) | 7.2 (± 5.0) | 0.359 |
| | Negative | 68 (64.2) | 10.4 (± 4.1) | |
| FLC difference | ≥ 375.2 mg/L | 28 (26.4) | 25.4 (± 9.3) | 0.020 |
| | < 375.2 mg/L | 43 (40.6) | 10.5 (± 5.0) | |

| | | | | |
|---|---|---|---|---|
| Creatinine | ≥ 1.4 mg/dL | 27 (25.5) | 13.9 (± 7.5) | 0.928 |
| | < 1.4 mg/dL | 72 (67.9) | 12.2 (± 4.1) | |
| Albumin | ≥ 3.5 g/dL | 29 (27.4) | 13.0 (± 7.0) | 0.944 |
| | < 3.5 g/dL | 77 (72.6) | 12.3 (± 4.2) | |
| Beta-2 microglobulin | ≥ 2.94 mg/L | 27 (25.5) | 27.6 (± 8.8) | 0.004 |
| | < 2.94 mg/L | 36 (34.0) | 0 | |
| Fibrinogen | ≥ 380.5 mg/dL | 44 (41.5) | 10.8 (± 6.6) | 0.999 |
| | < 380.5 mg/dL | 44 (41.5) | 15.9 (± 6.1) | |
| 24-hour urine protein | ≥ 3 g | 30 (28.3) | 6.8 (± 4.6) | 0.379 |
| | < 3 g | 45 (42.5) | 10.1 (± 4.9) | |
| Atrial fibrillation | Absent | 87 (82.1) | 11.9 (± 3.8) | 0.691 |
| | Present | 5 (4.7) | 25.0 (± 21.7) | |
| CRAB | Absent | 83 (78.3) | 12.8 (± 4.0) | 0.726 |
| | Present | 23 (21.7) | 11.7 (± 8.1) | |
| Multiple myeloma | Absent | 97 (91.5) | 12.5 (±3.8) | 0.806 |
| | Present | 9 (8.5) | 11.1 (± 10.5) | |

Abbreviations: BM = bone marrow; FLC = free light chain; SD = standard deviation; CRAB = C (hypercalcemia), R (renal failure), A (anemia) and B (bone lesions)

Table 3. Hazard ratios (HRs) and P-values of thromboembolic events using Cox regression analysis in multivariable analysis.

| | | Characteristics | HR | HR (95% CI) | P-value |
|---|---|---|---|---|---|
| Model A | Age | ≥ 60 years | 1 | | 0.340 |
| | | < 60 years | 1.928 | 0.501–7.417 | |
| | Gender | Male | 1 | | 0.122 |
| | | Female | 2.629 | 0.771–8.961 | |
| | FLC difference | ≥ 375.2 mg/L | 3.537 | 1.051–11.898 | 0.041 |
| | | < 375.2 mg/L | 1 | | |
| Model B | Age | ≥ 60 years | 1 | | 0.415 |
| | | < 60 years | 1.991 | 0.380–10.432 | |
| | Gender | Male | 1 | | 0.153 |
| | | Female | 3.143 | 0.653–15.140 | |
| | Beta-2 microglobulin | ≥ 2.94 mg/L | 19.185 | 1.848–199.195 | 0.013 |
| | | < 2.94 mg/L | 1 | | |

Abbreviations: FLC = free light chain; HR = hazard ratio; CI = confidence interval

# Discussion

Venous thromboembolism has been identified as a major complication in patients with plasma cell dyscrasias, such as MM or MGUS. Previous studies have found that the incidence of thromboembolism was approximately 2.4–11% in MM and 6.1–8.0% in MGUS. In addition, treatment with immunomodulatory agents further increases the risk up to 28%, particularly in newly diagnosed MM patients [3, 12]. However, arterial thromboembolism including stroke has been found to occur at low incidence compared with venous thromboembolism: the incidence was approximately 3.8–5.6% in patients with MM and most events occurred during chemotherapy [8, 13, 14].

During a median follow-up of 18.1 months (range, 0.4–166.9 months), the present study demonstrated that the one-year cumulative incidence of thromboembolic events was approximately 12.6 ± 3.6% in AL amyloidosis patients without a previous history of thromboembolic events. In our study, however, a substantial portion of patients (11.7%) with newly diagnosed AL amyloidosis were found to have a prior history of thromboembolic events before diagnosis with AL amyloidosis. Thus,

this finding suggests that AL amyloidosis, even before it is diagnosed, may increase the risk of thromboembolism. In addition, arterial and venous thromboembolic events occurred in 12.3% (13/106) of patients; the most common events (9/13) were cerebral infarctions, although most of our patients did not have atrial fibrillation at baseline, which is a well-known risk factor for cerebral infarction [15]. When compared with MM, the incidence of cerebral infarctions was higher in our patients [8, 13, 14]. Therefore, it appears not to be negligible in clinical practice.

In AL amyloidosis, although a retrospective study suggested that the incidence of thromboembolism was low (approximately 1.9%), some previous studies demonstrated that thromboembolic events could occur more frequently, with the incidence ranging from 7% to 33% [10, 11, 16, 17]. Bever, *et al.* [17] identified, in a retrospective study, that the 65 of 929 patients (7%) with AL amyloidosis experienced at least one venous thromboembolic event less than one year prior to or following diagnosis with amyloidosis. However, in this study, arterial thromboembolism and cumulative incidence of thromboembolism were not investigated, which is different from our study. Feng, *et al.* [11, 16] performed two sequential

studies in 116 autopsy cases and echocardiography (echoCG) of 156 cardiac amyloidosis patients and derived the same conclusion. Intracardiac thrombosis was frequently found (27–33%) in cardiac amyloidosis. Especially, AL amyloidosis was associated with more frequent intracardiac thrombosis (51% *vs.* 16%, $P < 0.001$ for autopsy cases; 35% *vs.* 18%, $P = 0.02$ for echoCG cases) than amyloidosis of any other etiology, including transthyretin, AA, and familial, although patients with AL amyloidosis had less atrial fibrillation (22% *vs.* 45%, $P = 0.008$ for autopsy cases; 56% *vs.* 72%, $P = 0.03$ for echoCG cases). These results indicate that atrial fibrillation, which is a major risk factor for intracardiac thrombosis *per se* may not be a key player in intracardiac thrombus formation in cardiac amyloidosis [18]. In line with previous studies, our results suggest that the high incidence of acute cerebral infarction in patients with AL amyloidosis may not be solely attributable to atrial fibrillation: AL amyloidosis itself may have a mechanism that could increase the risk of thromboembolism.

The mechanism of increased thromboembolism in AL amyloidosis is not yet fully understood. In our study, serum B2MG and FLC differences,

which reflect the disease burden, were risk factors for thromboembolism. Therefore, we thought that a hypercoagulable state caused by increased disease activity in AL amyloidosis could be a risk factor for not only venous but also arterial thromboembolism in AL amyloidosis [11, 16, 19-21].

B2MG levels, part of the International Staging System, serve as a well-known prognostic factor in plasma cell dyscrasias, including MM, WM, and amyloidosis [22-24]. Previous reports suggested that serum B2MG level is a reliable marker of disease burden and reflects the proliferative activity of myeloma cells [23, 25]. In addition, serum FLC differences, which are included in the recently revised AL amyloidosis staging system, reflect increased disease burden [26, 27]. Higher disease burden increases the activity of tumor-associated pro-coagulant factors and inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-$\alpha$ which, in turn, may activate endothelial cells and induce activation of platelets and coagulation factors. In addition, impaired fibrinolysis and down-regulation of the protein C and S system could increase arterial and venous thromboembolic risk [19, 28, 29].

Our study has two specific limitations. The retrospective nature and relatively small sample size are clear limitations. Therefore, our results should be cautiously interpreted and will require further validation in a large-scale study. Despite these reservations, this study clearly demonstrates that levels of FLC and B2MG are associated with thromboembolic risk in patients with AL amyloidosis.

# Conclusions

In summary, the incidence of thromboembolic events was substantial in patients with AL amyloidosis; most events developed within the first year after diagnosis. Especially, arterial thromboembolism, such as cerebral infarction, occurred more frequently than did venous thromboembolism. In addition, higher serum FLC differences and B2MG levels were identified as risk factors for thromboembolic events. Our results suggest that newly diagnosed AL amyloidosis patients, if they exhibit higher serum FLC differences or B2MG levels, may require initial examination and close monitoring for thromboembolism, particularly within the first year of diagnosis.

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# 요약

박현경

의학과 중개의학전공

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**연구의 배경**: 일차성 아밀로이드증은 다른 형질세포 질환들과 마찬가지로 혈전이 높은 빈도로 발생한다고 알려져 있는 질환이다. 하지만 혈전 발생의 임상적 특징 및 위험요인에 관해서는 자세히 보고된 바가 없다. 이에 본 논문에서는 일차성 아밀로이드증 환자에서의 혈전 발생과 위험요인 등의 임상학적 특징에 대해 알아보고자 한다.

**연구 방법**: 본 연구는 후향적 방법의 연구로, 병리학적 검사에서 일차성 아밀로이드증으로 진단된 환자들을 대상으로 추적 관찰 기간 동안 누적 혈전발생률 및 혈전 발생의 위험요인에 대해 조사 하였다.

**연구 결과**: 본 연구는 조직학적 검사에서 일차성 아밀로이드증으로 진단된 환자 총 106명을 대상으로 하였다. 이 중 13명 (12.3%)의 환자에서 추적 관찰 기간 동안 혈전이 발생하였으며, 13명의 환자들 중, 급성 뇌졸증은 9명, 폐색전증 2명, 심부정맥 혈전증은 2명의 환자에게서 발생하였다.

혈전 발생은 혈청 경쇄값의 차이가 클수록 (≥375.2 mg/L), 혈청 베타-2 마이크로글로불린 수치가 높을수록 (≥2.94 mg/L) 유의하게 높은 누적혈전 발생률을 보였다 (경쇄값의 차이: 위험도, 3.537, 유의확률 = 0.041; 베타-2 마이크로글로불린 수치: 위험도, 19.185, 유의확률 = 0.013). 대부분의 혈전은 (84.6%) 일차성 아밀로이드증 진단 후, 1년 안에 발생하였다.

**결론**: 일차성 아밀로이드증 환자는 높은 혈전 발생률을 보이며, 특히 혈청 경쇄값의 차이가 클수록, 베타-2 마이크로글로불린의 수치가 높을수록 높은 혈전 발생을 보인다.

**주요 단어**: 아밀로이드증; 형질세포 질환; 혈전; 경쇄; 베타-2 마이크로글로불린

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