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Clinical Characteristics and Outcomes of Untreated AL-amyloidosis Patients in the Netherlands

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Amyloid light chain (AL)-amyloidosis is a malignant plasma cell disorder with poor prognosis where excessive produced light chains form amyloid fibrils. Treatment is intensive and often toxic. When left untreated, median overall survival (OS) varies in time between less than 6 months up to 13 months. There is a knowledge gap regarding the baseline characteristics and outcomes of untreated patients since they are infrequently referred to expertise centers and are rarely included in clinical trials. This population-based study provides a comprehensive overview on untreated AL-patients in The Netherlands.

AL-amyloidosis patients ≥18 years diagnosed between 2017-2022 were identified in the Netherlands Cancer Registry with survival follow-up until February 1, 2024. Patients post-mortem diagnosed with AL-amyloidosis (n=8) and patients under "active monitoring" (n=15) were excluded from all analyses. Patient-specific (age, World Health Organization [WHO] performance score), disease-specific characteristics (laboratory levels, cardiac involvement), diagnostic work-up (cardiac imaging, complete cytogenetic assessment) and survival were collected. First-line therapy was dichotomized into untreated and treated. Clinical characteristics and diagnostic work-up between untreated and treated patients were compared. Predictive factors for not receiving first-line therapy were identified using logistic regression analysis. Endpoint was overall survival (OS) defined as the time from diagnosis to all-cause death.

A total of 801 AL-amyloidosis patients were identified of whom 110 (14%) were untreated. Untreated patients, compared to treated, were older (median 73 years [range 48-89] *vs.* 68 years [range 34-90]; $p<0.01$), more frequently scored ≥WHO-3 (12% *vs.* 4%; $p<0.01$), and had more often had cardiac involvement (72% *vs.* 61%; $p<0.01$) with higher levels of NT-proBNP (median 5,500 *vs.*1,924pg/ml; $p<0.01$). Despite the higher frequency of cardiac involvement in untreated patients, ejection fraction (EF) was less frequent available (63% *vs* 76%; $p<0.01$). Cytogenetic work-up was less often performed compared to treated patients (36% *vs.*72%; $p<0.01$).

Predictive factors for the odds of not receiving therapy are older age (OR 1.05; 95%CI 1.02-1.08), a higher free light chain difference (≥180mg/l: [OR 2.13; 95%CI 1.23–3.65]), cardiac involvement (OR 2.81; 95%CI 1.32–6.67), EF<50% (OR 1.80; 95%CI 1.01-3.21) and a ≥WHO-3 (OR 5.30; 95%CI 2.12–13.33).

Median OS for untreated patients was 1.3 months compared to 56.2 months in treated patients. Mortality (1 *minus* survival probability) among untreated patients was almost 25% after 2 weeks post-diagnosis, illustrating the dire health status of these patients.

The prognosis of untreated AL-amyloidosis is dismal with a high mortality rate early after diagnosis. Untreated patients with AL-amyloidosis are older, more frequently have heart involvement and received less comprehensive cytogenetic work-ups. To initiate treatment requires a shared decision between physician and patient. Factors involved in this decision are age, disease characteristics (dFLC, cardiac involvement and ejection fraction) and patients' fitness.