Semiquantitative ^{67}Ga Scintigraphy as an Indicator of Response to and Prognosis After Corticosteroid Treatment in Idiopathic Interstitial Pneumonia

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The prognosis in some forms of idiopathic interstitial pneumonia (IIP), especially idiopathic pulmonary fibrosis (IPF) and fibrotic nonspecific interstitial pneumonia (NSIP), is still poor. A minority of patients will respond to immunosuppressive treatment. In patients with IPF or fibrotic NSIP, pulmonary ^{67}Ga scintigraphy may be useful for predicting response to therapy and prognosis. The objective of the present study was to evaluate whether semiquantitative ^{67}Ga scintigraphy can be used to predict responsiveness to therapy with high-dose corticosteroids in a well-defined population of patients with IIP (IPF and fibrotic NSIP). **Methods:** This study was performed in a tertiary referral center. We prospectively performed ^{67}Ga scintigraphy in 23 consecutive patients previously diagnosed with IIP (IPF and fibrotic NSIP) before and after treatment with 3 monthly courses of high-dose methylprednisolone. Lung function tests and bronchoalveolar lavage (BAL) were performed before and after these 3 courses, and patients were monitored for 1 y after the start of the treatment. **Results:** During follow-up, 5 patients died, none during the first 3 mo. Although pulmonary ^{67}Ga uptake significantly decreased after treatment ($P = 0.001$), there was no correlation between either initial ^{67}Ga uptake or change in ^{67}Ga uptake on treatment and 1-y prognosis. This finding was independent of prior immunosuppressive treatment, diagnosis of IPF or NSIP, or whether initial ^{67}Ga uptake was elevated or not. BAL cellularity was correlated with neither pulmonary ^{67}Ga uptake nor response to treatment. **Conclusion:** Pulmonary ^{67}Ga uptake cannot be used to predict response to corticosteroid treatment or prognosis in patients with IIP. Apparently, the (inflammatory) process influenced by treatment with methylprednisolone does not determine the progression of disease. This finding supports the hypothesis that although inflammation is present in IPF and fibrotic NSIP, it is neither the hallmark of the disease nor the major factor determining prognosis.

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Idiopathic interstitial pneumonia (IIP) comprises a group of disorders of unknown etiology and characterized by a variable pattern of inflammation or fibrosis of the pulmonary interstitium. They can be subclassified into several clinical entities, each with its own histopathologic pattern (*1*). Among these entities, idiopathic pulmonary fibrosis (IPF) and fibrotic nonspecific interstitial pneumonia (NSIP), histopathologically characterized as usual interstitial pneumonia (UIP) and fibrotic NSIP, respectively, still have a poor prognosis. However, the clinical course in individual patients is known to vary considerably (*2,3*). No therapy has so far been proven to have undoubted efficacy. The majority of patients will respond to immunosuppressive treatment either not at all or for a short period only, but in a subgroup of patients, stabilization or improvement can be achieved. However, the identification of these patients is difficult. In general, the histopathologic feature of a more cellular pattern was previously demonstrated to be associated with a more favorable outcome and responsiveness to therapy (*4,5*). On the other hand, in IPF, the extent of fibrosis and fibroblastic foci present in lung biopsy specimens was demonstrated to be associated with poorer survival (*6*). Furthermore, histopathologic subclassification into UIP and NSIP has been reported to have important prognostic implications (*7,8*).

Histopathologic classification of lung tissue, however, requires surgical lung biopsy. ^{67}Ga scintigraphy in patients with IIP may be useful for predicting response to therapy and prognosis (*9,10*). Therefore, in a search for less invasive methods to more precisely identify patients likely to respond to therapy, we hypothesized that semiquantitative pulmonary ^{67}Ga uptake may serve as a predictor of respon-

siveness to corticosteroid treatment and prognosis in patients with well-described IIP. Increased pulmonary ^{67}Ga uptake was demonstrated to be associated with local airway inflammation (cellular pattern), as estimated by a higher total white cell count as well as elevated percentages of both neutrophils (*11*) and macrophages (*12*) in bronchoalveolar lavage (BAL) fluid. Increased ^{67}Ga uptake has been demonstrated in patients with IIP. However, Fujishima et al. showed a lack of correlation between increased uptake and prognosis (*13*). On the other hand, increased pulmonary ^{67}Ga uptake was shown to be associated with a deterioration of pulmonary function after 1 y of corticosteroid treatment in patients with IPF (*14*). This lack of consistency in reports on the relationship between pulmonary ^{67}Ga uptake and prognosis may be related to heterogeneity in patient populations, different clinicopathologic entities, differences in methods of analysis of pulmonary ^{67}Ga uptake, and differences in treatment.

Therefore, the aim of the present study was to evaluate whether semiquantitative pulmonary ^{67}Ga uptake can predict the response to high-dose methylprednisolone treatment in a well-defined population of patients with IIP (IPF and NSIP). In addition, we also studied whether a change in pulmonary ^{67}Ga uptake after methylprednisolone treatment was correlated with the 1-y outcome in these patients.

MATERIALS AND METHODS

Patient Characteristics

This study was performed in a tertiary referral center. Patients with previously "classic" IPF (*15,16*) (retrospectively including both IPF and fibrotic NSIP) were included between 1995 and 1999. All patients had progressive disease. If, at the time of referral, diagnosis had been histologically confirmed, the biopsy material was reviewed in the Department of Respiratory Medicine of the Academic Medical Center, Amsterdam. If this was not the case and the patient was able to undergo a surgical procedure, surgical lung biopsy was performed. If applicable, final confirmation was provided by histologic investigation of lung resection material at the time of lung transplantation or at the time of autopsy. In view of the more recent classification (*1,7*) and after a recent (second) review of the biopsy material and high-resolution CT scans by an external, masked expert panel, patients were classified as having IPF or NSIP. Pathology specimens at the time of review were judged according to the criteria described by Katzenstein and Myers (*17*). When histologic proof of diagnosis was not available (5 patients), diagnosis was made by the panel according to previously reported guidelines (*18,19*).

Study Design

Included patients were treated with 3 monthly intravenous courses of methylprednisolone, that is, 1 g daily for 3 consecutive days. The courses were separated and followed by 20 mg daily of oral prednisolone. For patients being treated with prednisolone at referral, the dosage was tapered to a maximum daily dose of 20 mg. Additional immunosuppressive drugs at referral were stopped at least 4 wk before enrollment in the study. Semiquantitative pulmonary ^{67}Ga scintigraphy, lung function tests (spirometry), and BAL were performed before the first course and 2 wk after the third course of methylprednisolone. To assess 1-y outcome, lung function tests were repeated 1 y after the start of therapy. The study was approved by the local medical ethics committee, and all patients gave written informed consent.

Semiquantitative ^{67}Ga Scintigraphy

Standardized quantitative ^{67}Ga scintigraphy was performed before and after 3 courses of methylprednisolone according to the method described by Van Unnik et al. (*20*). Scintigraphy was performed 48 h after the intravenous injection of 35–45 MBq of ^{67}Ga citrate by use of a γ-camera (Diacam; Siemens) with a medium-energy all-purpose collimator and a 128 × 128 matrix. Twenty percent windows were set for the 3 main energy peaks of ^{67}Ga (93, 184, and 296 keV). Anterior and posterior chest views were obtained, including a separate view of the skull. In both chest views, a region of interest was drawn around each lung, excluding the mediastinum and lung hili. A region of interest within the contours of the skull was used for background correction. Anterior and posterior counts from the regions of interest consisting of the left and right lungs were obtained. After correction for background and decay, a geometric mean was calculated [geometric mean = $\sqrt{}$ (anterior × posterior)] for each lung separately. The values so obtained for the right and left lungs were averaged, so that a single value was created as a measure for ^{67}Ga uptake for each patient. These values were compared with mean pulmonary uptake values obtained for a population of individuals without pulmonary disease and referred for other ^{67}Ga scintigraphy indications. Increased pulmonary ^{67}Ga uptake was defined as an uptake value higher than the mean plus 2 SDs of ^{67}Ga uptake for healthy subjects (n = 30; mean ± SD, 0.372 ± 0.065).

Lung Function Tests, Fiber-Optic Bronchoscopy, and BAL

Spirometry was performed according to standardized guidelines (*21*). Carbon monoxide diffusion capacity (D_LCO) was measured by the single-breath technique according to standardized guidelines (*22*). A significant change in forced vital capacity (FVC) was defined as an amelioration or deterioration of more than 10% compared with the baseline, and a significant change in D_LCO was defined as ±20% of the baseline value, according to previous studies (*23*). BAL was performed in a standardized fashion as previously described (*24*) with a flexible fiber-optic video-bronchoscope. Seven successive 20-mL aliquots of prewarmed NaCl (0.9%) were instilled in a subsegment of the right middle lobe, and each was aspirated immediately with low suction. The total cell count, the number of leukocytes, and the differential white cell count in BAL fluid were measured. Cell numbers were expressed as 10^6 cells per liter. The differential cell count was expressed as a percentage of the total number of leukocytes measured.

Statistical Analysis

Differences in means between groups were analyzed with an independent-sample t test or the nonparametric Mann–Whitney U test, as appropriate. Correlations were calculated by linear regression. A P value of <0.05 was considered significant.

RESULTS

Patient Characteristics

Twenty-three consecutive patients with IIP, either IPF or NSIP, underwent initial ^{67}Ga scintigraphy. One patient was excluded because ^{67}Ga scintigraphy could not reliably be

interpreted because of a technical problem. Patient characteristics are summarized in Table 1.

Initial Measurements

Lung Function Tests. In both groups, mean FVC and mean D_LCO were severely impaired. FVC did not differ significantly between the IPF and NSIP groups. However, the mean D_LCO in the NSIP group was significantly lower than that in the IPF group ($P = 0.03$). This result indicates that NSIP patients were referred at a later stage of the disease than IPF patients, possibly because disease progression in fibrotic NSIP patients is slower than that in IPF patients. This situation can cause late referral to a tertiary center because patients are usually able to adapt their lifestyle to their pulmonary disease more easily and the perception of severe shortness of breath will occur only later in the course of the disease.

Semiquantitative Pulmonary ^{67}Ga Uptake. Table 2 shows mean pulmonary ^{67}Ga uptake. Before treatment, 13 of 22 patients (7 IPF patients and 6 NSIP patients) showed elevated pulmonary activity on ^{67}Ga scintigraphy. Pulmonary ^{67}Ga uptake showed a homogeneous distribution in all but 3 of these patients. In 2 patients, ^{67}Ga uptake was more pronounced in the basal lung fields; in 1 patient with an asymmetric distribution of the disease, ^{67}Ga uptake was more pronounced in the more severely affected lung. There was no difference in mean ^{67}Ga uptake between the IPF and the NSIP groups ($P = 0.61$). In addition, mean ^{67}Ga uptake did not differ between patients who had previously been treated and patients who had not previously been treated with immunosuppressive drugs ($P = 0.25$).

FVC and Semiquantitative Pulmonary ^{67}Ga Uptake. Neither in the group as a whole nor in the IPF or NSIP group could a significant correlation between initial FVC and ^{67}Ga uptake be demonstrated. In addition, there was no significant difference in FVC between patients with elevated ^{67}Ga uptake and patients with normal ^{67}Ga uptake ($P = 0.69$).

D_LCO and Semiquantitative Pulmonary ^{67}Ga Uptake. In the group as a whole, the correlation between initial D_LCO and ^{67}Ga uptake showed a trend toward statistical significance ($r = -0.4$; $P = 0.06$). Subgroup analysis, that is, previously treated patients versus untreated patients, revealed a correlation between initial D_LCO and ^{67}Ga uptake in the untreated patients ($r = -0.6$; $P < 0.05$). Further subgroup analysis, that is, IPF versus NSIP and elevated ^{67}Ga uptake versus normal ^{67}Ga uptake, however, revealed no significant correlation between initial D_LCO and ^{67}Ga uptake in either subgroup of patients.

TABLE 1
Patient Characteristics

Characteristic	IPF	NSIP
No. of patients studied	14	8
Sex (F/M) (*n*)	7/7	3/5
Age (y)*	55.3 ± 2.9	54.4 ± 4.5
Nonsmokers/current smokers/ ex-smokers (*n*)	8/1/5	4/2/2
Pretreated/not pretreated (*n*)	6/8	5/3
Histologically proven/not histologically proven (*n*)	11/3	6/2
FVC (% predicted)*	66.4 ± 5.7	70.1 ± 7.2
D_LCO (% predicted)*	40.7 ± 4.0	29.9 ± 2.2

*Mean ± SEM.

TABLE 2
Pulmonary ^{67}Ga Uptake

Group	No. of patients	^{67}Ga uptake (mean ± SEM U)
Whole	22	0.447 ± 0.034
Elevated ^{67}Ga uptake	13	0.534 ± 0.041
Normal ^{67}Ga uptake	9	0.322 ± 0.017
IPF	14	0.434 ± 0.046
NSIP	8	0.471 ± 0.049
Previously treated	11	0.488 ± 0.062
Not previously treated	11	0.407 ± 0.024

BAL Cellularity. Table 3 shows the mean counts of cells in BAL fluid in the different groups of patients. The total white cell count was significantly lower in IPF patients than in NSIP patients ($P = 0.03$). However, the mean percentages of neutrophils, lymphocytes, and eosinophils in BAL fluid did not differ significantly between IPF patients and NSIP patients ($P = 0.92$, $P = 0.82$, and $P = 0.27$, respectively). Previously treated patients showed a trend toward a lower percentage of lymphocytes in BAL fluid than patients not previously treated. This trend almost reached statistical significance ($P = 0.055$).

BAL Cellularity and Semiquantitative Pulmonary ^{67}Ga Uptake. There was no difference in total white cell count or in the percentages of neutrophils, lymphocytes, and eosinophils in BAL fluid between patients with elevated pulmonary ^{67}Ga uptake and patients with normal pulmonary ^{67}Ga uptake. There was also no significant correlation between the total white cell count or the percentages of neutrophils, lymphocytes, and eosinophils in BAL fluid and quantitative pulmonary ^{67}Ga uptake ($r = 0.05$, $r = -0.12$, $r = -0.21$, and $r = 0.16$, and $P = 0.81$, $P = 0.58$, $P = 0.35$, and $P = 0.49$, respectively). Similarly, analyses of these correlations in the individual subgroups (elevated vs. normal pulmonary ^{67}Ga uptake, IPF vs. NSIP patients, and previously treated vs. untreated patients) revealed no significant correlations (data not shown).

Changes After Treatment with Methylprednisolone

The mean pulmonary ^{67}Ga uptake in the whole group of patients was significantly reduced by treatment with high-dose methylprednisolone (Fig. 1). For the 13 patients showing elevated pulmonary ^{67}Ga uptake, there was normalization in 5 patients, whereas 8 patients still showed elevated uptake. In both the IPF and the NSIP subgroups, the mean reduction in ^{67}Ga uptake after methylprednisolone treatment

TABLE 3
BAL Cellularity

Group	Total white cell count (mean ± SEM 10^6/L)	Neutrophils (mean ± SEM %)	Lymphocytes (mean ± SEM %)	Eosinophils (mean ± SEM %)
Whole	269 ± 39	10.3 ± 1.7	7.4 ± 1.6	4.4 ± 1.2
Elevated ^{67}Ga uptake	304 ± 61	9.0 ± 2.3	6.3 ± 2.0	4.6 ± 1.9
Normal ^{67}Ga uptake	226 ± 35	12.1 ± 2.7	9.0 ± 2.7	4.0 ± 1.1
IPF	207 ± 31	10.2 ± 2.4	7.7 ± 2.0	3.1 ± 0.8
NSIP	385 ± 82	10.5 ± 2.4	6.9 ± 2.9	6.6 ± 2.8
Previously treated	256 ± 62	13.1 ± 2.4	4.3 ± 1.5	4.9 ± 2.2
Not previously treated	289 ± 51	7.5 ± 2.3	10.5 ± 2.6	3.8 ± 1.0

was statistically significant ($P = 0.02$ and $P = 0.02$, respectively). After methylprednisolone treatment, the total white cell count in BAL fluid decreased from (269 ± 39) × 10^6/L to (218 ± 29) × 10^6/L ($P = 0.07$). However, no correlation between the change in pulmonary ^{67}Ga uptake and the change in the total white cell count in BAL fluid could be demonstrated ($r = -0.1$; $P = 0.65$).

Outcome at 1 y

No patients were lost to follow-up. During the 1-y study period, 5 patients died (3 with IPF and 2 with NSIP), none during the first 3 mo. For the remaining IPF patients, FVC improved in 5 patients (mean, +18%; SEM, 2.8%), remained stable in 2 patients (mean, +5.5%; SEM, 0.5%), and deteriorated in 4 patients (mean, −27%; SEM, 4.4%). For the NSIP patients, the corresponding values were 1 (+33%), 2 (mean, 0%; SEM, 5%), and 3 (mean, −21%; SEM, 8.2%), respectively.

Outcome at 1 y and Semiquantitative Pulmonary ^{67}Ga Uptake. Figures 2A and 2B show that neither the initial value nor the methylprednisolone-induced change in quantitative ^{67}Ga uptake correlated with 1-y outcome, as determined by the percent change in FVC ($P = 0.33$, $r = 0.25$, and $P = 0.91$, $r = 0.03$, respectively). Subclassification into IPF versus NSIP, previously treated versus not treated, or elevated versus normal ^{67}Ga uptake also produced no significant correlations. Multiple regression analyses showed that initial pulmonary ^{67}Ga uptake, change in uptake, or initial FVC or D_LCO was not an independent variable explaining death.

Prognosis at 1 y and BAL Cellularity. There was no significant correlation between change in total white cell count in BAL fluid and 1-y prognosis, as measured by percent change in FVC. Subclassification into UIP versus NSIP or elevated versus normal ^{67}Ga uptake did not change this finding.

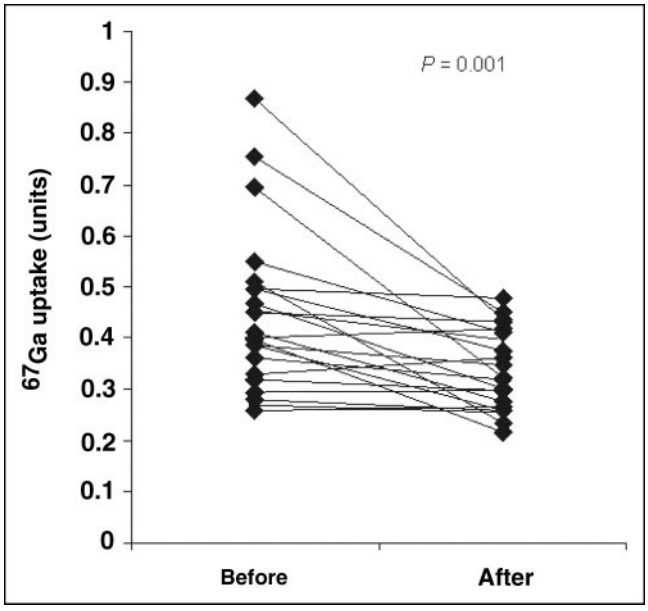

FIGURE 1. ^{67}Ga uptake before and after treatment with methylprednisolone.

DISCUSSION

In this prospective study, we assessed whether semiquantitative analysis of pulmonary ^{67}Ga uptake can predict responsiveness to treatment with high-dose methylprednisolone in patients with IIP. Additionally, we studied whether the methylprednisolone-induced change in pulmonary ^{67}Ga uptake can predict the 1-y outcome in these patients, as determined by the change in FVC.

Treatment with 3 courses of methylprednisolone induced a significant reduction in pulmonary ^{67}Ga uptake, indicating that the (inflammatory) process measured by ^{67}Ga scintigraphy is influenced by treatment with methylprednisolone. Interestingly, though, no association between pulmonary ^{67}Ga uptake and the 1-y prognosis (as measured by the change in FVC after 1 y) could be demonstrated. Because macrophages, neutrophils, and lymphocytes accumulate ^{67}Ga, ^{67}Ga uptake is considered to reflect the level of inflammation (*25*). Apparently, the (inflammatory) process influenced by treatment with methylprednisolone, reflected by a reduction in pulmonary ^{67}Ga uptake, did not determine the 1-y prognosis in the group of IIP patients examined in this study. Although the presence of inflammatory cells is not a major hallmark of IPF or fibrotic NSIP and, in particular, IPF is regarded more and more as an "epithelial-fibrotic" disorder and less as a primarily inflammatory disorder (*26,27*), there usually are limited numbers of inflammatory cells in the interstitium in both diseases.

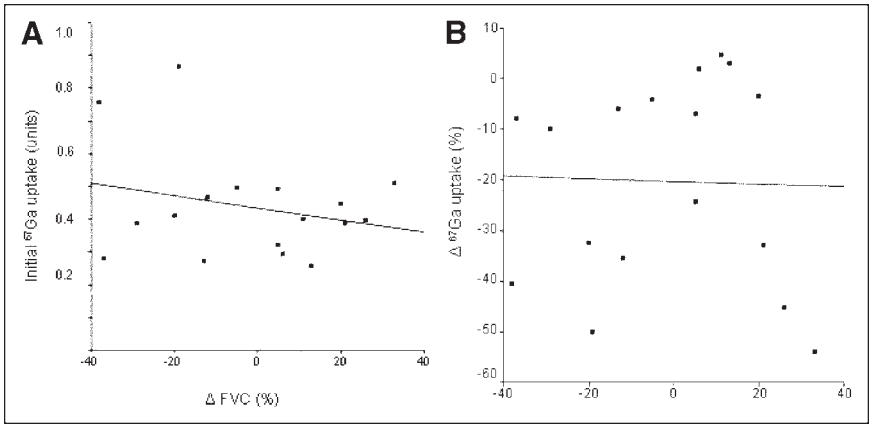

FIGURE 2. Correlation of initial ^{67}Ga uptake (A) and change in ^{67}Ga uptake after treatment (B) (*y*-axis) with percent change (Δ) in FVC 1 y after start of treatment with 3 courses of high-dose methylprednisolone (*x*-axis). Change in ^{67}Ga uptake is defined as difference between ^{67}Ga uptake before treatment and ^{67}Ga uptake after treatment and is expressed as percent change from baseline.

Moreover, recent data suggest that epithelial cell apoptosis and not inflammation may be an early hallmark of pulmonary fibrosis (*28,29*). Inflammation may be present to a limited extent and may be influenced by treatment with methylprednisolone but obviously is not a major determinant of progression of the disease. In fact, our data indicate that pulmonary ^{67}Ga uptake, reflecting the degree of inflammation, does not reflect the extent of the primary pathogenic process that determines the course of the disease in IIP patients.

Theoretically, the degree of inflammation reflected by the amount of pulmonary ^{67}Ga uptake may have been influenced by prior immunosuppressive treatment. Half of the patients in the studied population had received immunosuppressive treatment before the start of the study. It is feasible to suggest that had these patients not received prior immunosuppressive treatment, there would have been a more significant effect of 3 courses of methylprednisolone (i.e., larger differences between pulmonary ^{67}Ga uptake at the beginning and at the end of the study). However, the subgroup of patients who had not received immunosuppressive treatment before the study did not differ in outcome or results from the group as a whole or from the subgroup of patients who had received immunosuppressive treatment before the study. Apparently, pulmonary ^{67}Ga uptake was not significantly influenced by prior immunosuppressive therapy. Therefore, the effect of prior immunosuppressive therapy on the final results can be considered minimal.

After methylprednisolone treatment, we observed a trend toward a decrease in the total white cell count in BAL fluid. However, the decrease in pulmonary ^{67}Ga uptake did not correlate with the observed decrease in the total white cell count. Whereas in previously mentioned studies, conflicting data were reported on the presence of a correlation between the different cells in BAL fluid and pulmonary ^{67}Ga uptake (*12,30,31*), we found no correlation between the percentages of neutrophils, lymphocytes, and eosinophils in BAL fluid and pulmonary ^{67}Ga uptake in the examined population. A possible explanation for this lack of correlation is that cells recovered from BAL fluid do not reflect the amount of interstitial inflammation, which is, in fact, assessed by pulmonary ^{67}Ga uptake.

CONCLUSION

Despite increased levels of ^{67}Ga uptake at baseline, we found in patients with IPF or fibrotic NSIP no correlation between pulmonary ^{67}Ga uptake or change in ^{67}Ga uptake and 1-y change in FVC. This finding indicates that semiquantitative analysis of pulmonary ^{67}Ga uptake is not useful for predicting responsiveness to treatment with corticosteroids or prognosis in patients with IIP. Apparently, the (inflammatory) process influenced by treatment with methylprednisolone does not determine the progression of disease. This finding supports the hypothesis that although inflammation is present in IPF and fibrotic NSIP, it is neither the hallmark of the disease nor the major factor determining prognosis.

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