The Prognostic Value of Quality-of-Life Scores: Preliminary Results of an Analysis of Patients with Breast Cancer

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Abstract: This study was conducted to elucidate the prognostic value of patient-assessed quality-of-life (QL) scores in cancer patients. QL was assessed in 47 consecutive patients with advanced or end-stage breast cancer using the Quality of Life Questionnaire for Cancer Patients Treated with Anticancer Drugs (QOL-ACD). The data collected from 19 of the 47 patients, who completed QL questionnaires more than twice before dying of cancer, were analyzed. The relationships between the QL scores and subsequent survival were examined at two assessment points, being the first and last assessment points of each of the 19 patients; corresponding respectively to median survival times of 14 and 4 months. The prognostic significance of the changes in QL scores that occurred over 3 months before the last assessment point was also examined. At the last assessment point, the scores of the physical aspects of QL were significantly related to survival. The change in scores of both overall QL and the physical aspects of QL were also significant predictors of survival. On the other hand, neither the scores nor the change in scores of the psychological and social aspects of QL was significant. This study indicates that both QL scores and changes in QL scores are promising prognostic predictors.

Key Words: breast cancer, prognosis, quality of life, palliative care

Introduction

It is well known that cancer patients sometimes experience problems in adjustment, depression, and consequent poor quality-of-life (QL) when faced with a diagnosis of cancer or a deterioration in their condition during anticancer treatment, as discussed in our previous papers.[1-5] It has recently been revealed that patient- or clinician-assessed QL scores in cancer patients correlate well with subsequent outcome.[6-14] Some researchers have reported that the psychological coping response to cancer affected the patients' outcome,[7-9] and that psychotherapy prolonged the patients' survival.[10] Others have stated that patient-assessed QL scores or changes in QL scores during anticancer therapy were prognostically significant and independent of other demographic and medical factors.[6,11-14] However, as the number of subjects in some of those studies was small, or the validity and reliability of the adopted measure of QL was not verified, the prognostic significance of QL scores remains controversial.

Thus, in the present study we assessed QL scores in 47 patients with advanced or end-stage breast cancer using a QL instrument with verified validity, reliability, and sensitivity to anticancer therapy. Furthermore, the prognostic value of QL scores and the serial changes in these scores were investigated. The possibility of the future clinical application of this type of evaluation is also discussed in this report.

Methods

Subjects and Data Collection

Between February 1993 and October 1995, 47 consecutive patients with advanced or end-stage breast cancer treated at Kawasaki Medical School Hospital were asked to participate in our QL evaluation studies, including the present study and previously reported studies,[3,15,16] after being informed of their purpose. All the patients had been told about their cancer and were well informed about the treatment they were given. All the

patients agreed to participate in these studies. During the study period patients were asked to fill in the QL questionnaire principally once a month. Of the 47 patients, 21 died of cancer before February 1996. The QL data collected from 19 of these 21 patients, who answered QL questionnaires more than twice, were analyzed in this study.

Quality-of-Life Instrument

The Quality of Life Questionnaire for Cancer Patients Treated with Anticancer Drugs (QOL-ACD)[17,18] was used in this study as a QL instrument. QOL-ACD was developed by Kurihara et al. in 1993[17] and was supported by the Japanese Ministry of Health and Welfare. This is the first patient-assessed QL evaluation system for Japanese cancer patients for which the reliability, validity, and sensitivity to anticancer treatment have been verified. It was primarily developed to assess outcome in clinical trials.

Briefly, the QOL-ACD consists of 22 items, 21 of which are investigated by the Likert scale and cover four domains, namely, activity aspects (six items); physical aspects (five items); psychological aspects (five items); and social aspects (five items). The remaining item covers the global aspects of QL as represented by a face scale consisting of five different faces selected from the 20 original ones by Lorish and Maisiak.[19] Patients are instructed to answer all questions by circling the number on the scale or the face that best describes their state. The score for each question (1 to 5) is totaled to give an overall QL score, the minimum being 22 and the maximum, 110. A higher score represents a higher QL.

The Relationship Between Quality-of-Life Scores and Subsequent Survival

The length of survival was calculated from the time of QL assessment to the time of death, there being no censored subjects. We examined the relationships between QL scores and subsequent survival at two assessment points, namely, the first and the last assessment points of each of the 19 subjects. The median survival time after the first assessment point was 14 months, with a range of 1–37 months, and that after the last assessment point was 4 months, with a range of 0–21 months. Further assessments close to the time of death were not possible because of the deterioration in the patients' condition, although we simply overlooked opportunities of assessment in a few cases. The relationship between the clinician-assessed Eastern Cooperative Oncology Group — Performance Status (ECOG-PS)[20] and subsequent survival was also examined.

The Relationship Between the Changes in Quality-of-Life Scores and Subsequent Survival

The changes in QL scores (ΔQL scores) during the 3 months before the last assessment point were able to be obtained in 16 patients. In these 16 patients, the relationship between the changes in QL scores and subsequent survival was examined. The relationship between the changes in ECOG-PS (ΔPS) and subsequent survival was also examined.

Statistical Considerations

Descriptive statistics were used to characterize each sample. During the data processing, questionnaires with two or less unanswered questions among the 22 questions were judged as valid. The unanswered questions were substituted by the mean score for the rest of the questions. According to this criterion, all the data from the 19 patients were valid. The Cox-Mantel test was used to compare survival curves. Statistical analyses were carried out by the SPSS.

Results

Sociodemographic and Medical Characteristics of the Subjects

The sociodemographic and medical characteristics of the 19 subjects at the last assessment point are shown in Table 1. The clinical stage of each patient was determined by the UICC TNM classifications.[21] The types of therapy adopted in this study were those given within 1 month prior to the last QL questionnaire. All the subjects were married, and most had attained only 9–12 years of education (data not shown). The subjects reflected the clinical population where the study was carried out.

The Relationship Between Quality-of-Life Scores and Subsequent Survival

First, the relationship between the QL scores at the first assessment point and subsequent survival was examined. We dichotomized the sample into two groups, namely, a high QL group with QL scores greater or equal to 78.0, being the median score of the sample ($n = 9$), and a low QL group with QL scores less than 78.0 ($n = 10$). Using the Cox-Mantel test, no significant difference in survival was observed between these two groups. The median survival for the high QL group was 14 months compared with 8 months for the low QL group. The relationships between the mean scores of each of the four domains of QL, namely, activity, physical, psychological, and social aspects, at the first

Table 1. Sociodemographic and medical characteristics of the subjects at the last assessment point

Factor	
Age	Mean 56.0 (33–74)
Body weight (kg)	Mean 55.4 (42–67)
DFS (months)	Median 22.0 (0–85)
Months after first recurrence	Median 22.0 (6–143)

Factor		No. of patients
Clinical stage at initial diagnosis		
I / II / II / IV / unknown		4 / 6 / 4 / 2 / 3
Estrogen receptor status		
negative / positive / unknown		5 / 9 / 5
Pathology		
papillotubular		2
solid tubular		4
scirrhous		9
unknown		4
Marital status		
no / yes		0 / 19
Hospitalization		
no / yes		8 / 11
ECOG-Performance status		
0 / 1 / 2 / 3 / 4 / unknown		5 / 4 / 6 / 1 / 2
Comorbidity		
no / yes		16/3
Sites of lesion		
cutaneous	no / yes	11 / 8
lymph node	no / yes	9 / 10
skeletal	no / yes	7 / 12
lung	no / yes	15 / 4
pleura	no / yes	16 / 3
liver	no / yes	16 / 3
brain	no / yes	18 / 1
No. of lesions		
1 / 2 / 3 or more		7 / 9 / 3
Types of therapy given in the past month		
chemotherapy	no / yes	14 / 5
endocrine therapy	no / yes	16 / 3
chemoendocrine therapy	no / yes	12 / 7
irradiation with any therapy	no / yes	11 / 8
Ojbective response		
CR / PR / NC / PD		1 / 1 / 11 / 6

DFS, disease-free survival time; ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable

Fig. 1. Kaplan-Meier survival curves for subjects with a quality-of-life (QL) score >67.0 (*solid line*) and those with a QL score ≤67.0 (*dotted line*) at the last assessment point. No significant difference was observed between the two groups ($P = 0.53$ by Cox-Mantel test)

assessment point and subsequent survival, were examined in the same way. There were no significant differences in survival between the two groups in any of the four domains. Furthermore, the relationship between the clinician-assessed ECOG-PS and subsequent survival at the first assessment point was not statistically significant.

Next, the relationship between the QL scores at the last assessment point and subsequent survival was examined. We dichotomized the sample into two groups, namely, a high QL group with QL scores greater than 67.0, being the median score of the sample ($n = 9$)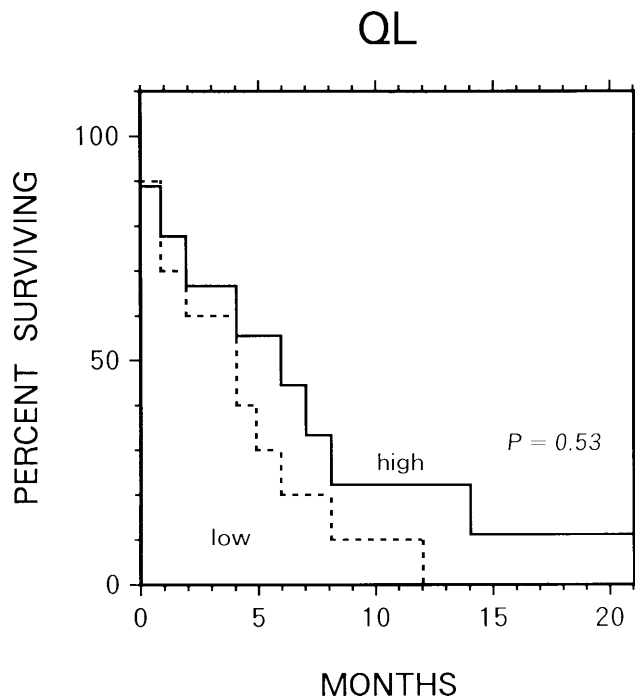, and a low QL group with QL scores less than or equal to 67.0 ($n = 10$). No significant difference in survival was observed between these two groups (Fig. 1). The median survival for the high QL group was 6 months compared with 4 months for the low QL group. On the other hand, when the relationships between the mean scores of each of the four domains of QL at the last assessment point and subsequent survival were analyzed, a significant difference was observed in survival between the two groups in the physical aspects of QL ($P = 0.04$) (Fig. 2). However, no significant differences were observed in the analyses of the remaining three aspects. There was also a significant relationship between the ECOG-PS and subsequent survival at the last assessment point ($P = 0.04$) (Fig. 3).

The Relationship Between the Change in Quality-of-Life Scores and Subsequent Survival

First, the relationship between the ΔQL scores and subsequent survival was examined. We dichotomized the sample into two groups, namely, a high ΔQL group with ΔQL scores greater or equal to −12.0, being the median score of the sample ($n = 8$), and a low ΔQL group with ΔQL scores less than −12.0 ($n = 8$). A significant difference in survival was observed between these two groups ($P = 0.03$) (Fig. 4). The median survival for the high
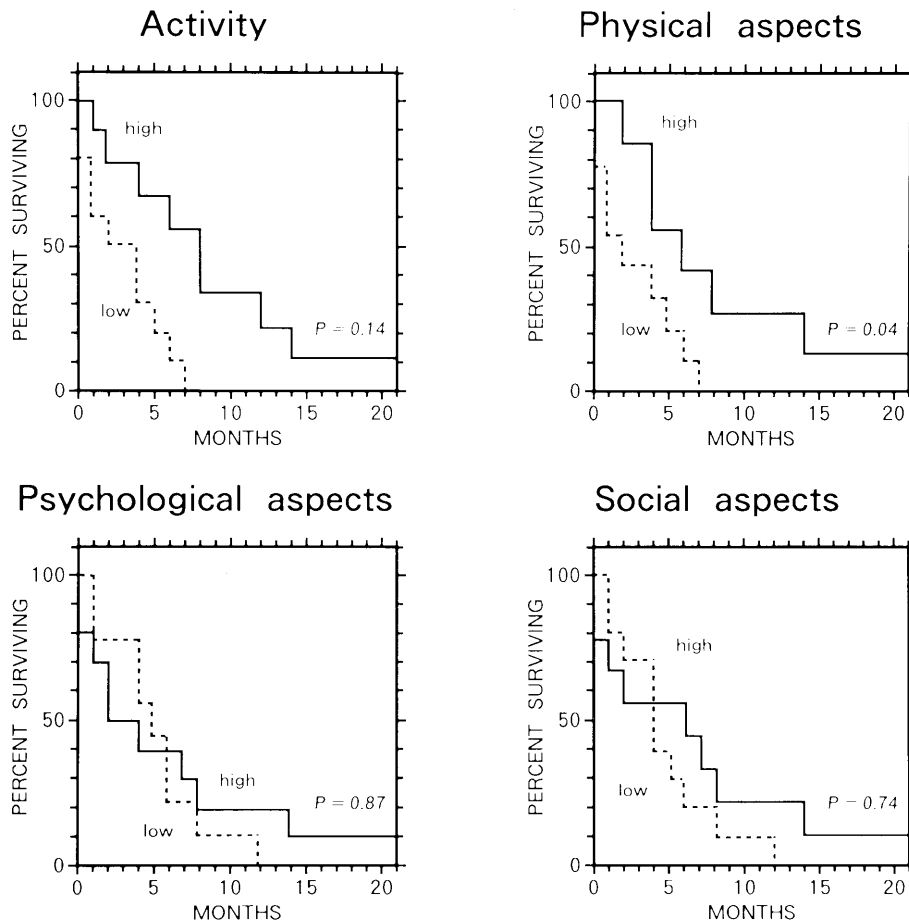
Activity

Physical aspects

Psychological aspects

Social aspects

Fig. 2. Kaplan-Meier survival curves for subjects with higher mean scores (*solid line*) and those with lower mean scores (*dotted line*) of each of the four domains of QL at the last assessment point. A significant difference was observed between the two groups only in the physical aspects of QL (*P* = 0.04 by Cox-Mantel test)

ΔQL group was 6 months compared with 2 months for the low ΔQL group. On the other hand, when the relationships between the Δmean scores of each of the four domains of QL and subsequent survival was analyzed, a significant difference was observed in survival between the two groups only in the physical aspects of QL (*P* = 0.03) (Fig. 5). However, no significant differences were observed in the analyses of the remaining three aspects. There was no significant relationship between the ΔECOG-PS and subsequent survival.

Discussion

The results of the present study indicate that patient-assessed QL scores are a promising prognostic predictor, in accordance with the findings of other researchers[6–9,11,12,22,23] who have conducted studies using Functional Living Index-Cancer (FLIC),[24] Linear Analog Self-Assessment (LASA),[25–27] or the Quality-of-Life Index (QLI)[26] as QL instruments for patients with various types of cancer.

Our study revealed that the physical aspects of the QL score could predict survival, while the psychological and social aspects could not. Coates et al.[11] also reported that the scores for physical well-being (PWB) were independent of other prognostic factors in a randomized clinical trial using LASA and QLI which compared intermittent and continuous therapy policies for patients with advanced breast cancer. Furthermore, a study by Ringdal et al.[12] on patients with various cancers revealed significant effects on prognosis for the general QL scale and for the physical aspects of QL in a multivariate analysis of covariance of eight QL scales, but only marginal and nonsignificant effects on prognosis according to social and psychological functioning.

On the other hand, some researchers[7–9,22,23] have reported the prognostic significance of the psychological aspects of QL. For instance, Greer et al.[7,8] and Pettingale et al.[9] observed that patients' psychological responses to cancer were significantly related to disease outcome after 5, 10, and 15 years. That is, patients who responded with a fighting spirit or with denial (positive avoidance) were significantly more likely to be alive and
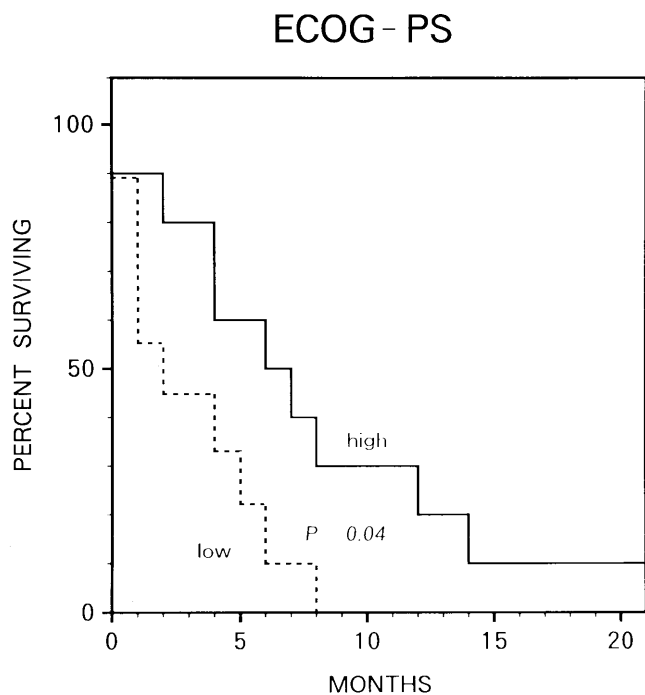
ECOG - PS

Fig. 3. Kaplan-Meier survival curves for subjects with Eastern Cooperative Oncology Group (ECOG)-Performance status (PS): 0 to 1 (*solid line*) and those with ECOG-PS: 2 to 4 at the last assessment point. A significant difference was observed between the two groups (*P* = 0.04 by Cox-Mantel test)

⊿ QL

Fig. 4. Kaplan-Meier survival curves for subjects with a ΔQL score ≥−12.0 (*solid line*) and those with a ΔQL score <−12.0 (*dotted line*). A significant difference was observed between the two groups (*P* = 0.03 by Cox-Mantel test)

free of recurrence at these time points than patients with fatalistic or helpless responses. According to some researchers, the prognostic significance of the psychological aspects of QL may be explained by the fact that psychological stress can suppress the immune system. An animal experimental study by Shavit et al.[28] revealed that exposure to inescapable footshock stress in rats induced a reduction of natural killer (NK) cell activity. The opioid, but not the nonopioid, form of stress suppresses the cytotoxic activity of NK cells and this suppression is blocked by the opioid antagonist, naltrexone. Furthermore, this suppression is mimicked by morphine administration.[28] Stress may accelerate the tumor proliferating potential or shorten survival by affecting both the hypothalamus-pituitary-adrenal (HPA)-axis and the autonomic nervous system through the opioid receptor, and consequently by affecting the immune system and cancer proliferation. Moreover, tumor necrosis factor, interleukin-1, -2, -6, and interferon, all of which are the subject of much attention, presumably because they are related to cancer cachexia, may affect the central nervous system. It is known that around 25% of cancer patients suffer depression, which could also be the result of an activation of the HPA-axis.[29,30]

In our study, the change in QL scores was a significant predictor of survival, whereas the change in the ECOG-PS score could not predict survival. These results indi-
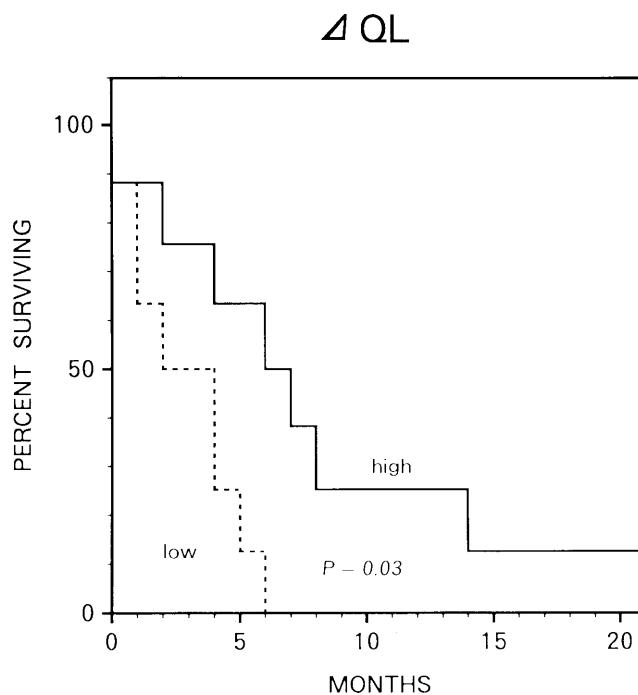
cate the significance of repeated measurements of patient-assessed QL scores. We previously reported[15,16] finding a close relationship between tumor response to anticancer therapy and changes in QL scores in advanced breast cancer patients, and a study by Coates et al.[11] supported these results.

After examining the mechanisms of the prognostic significance of QL and discussing the possible effects of psychological distress, the clinical application of all these results should be considered in at least three ways. First, if the QL score is an equally, or more significant prognostic factor than any other known biological or demographic prognostic factor, QL scores assessed before treatment could affect the treatment plans. Furthermore, QL scores might be helpful in determining the application of psychotherapy. Second, if QL scores in end-stage patients have prognostic significance, these might offer appropriate objective criteria by which we can decide whether the patient should be treated more intensively or palliatively, and if the patient should be moved to a palliative care unit or a hospice. Third, some life insurance policies allow patients to receive payment while alive if a medical certificate predicting survival of less than 6 months is submitted. As these life insurance polices are drawing much public attention, QL scores might offer more objective information.

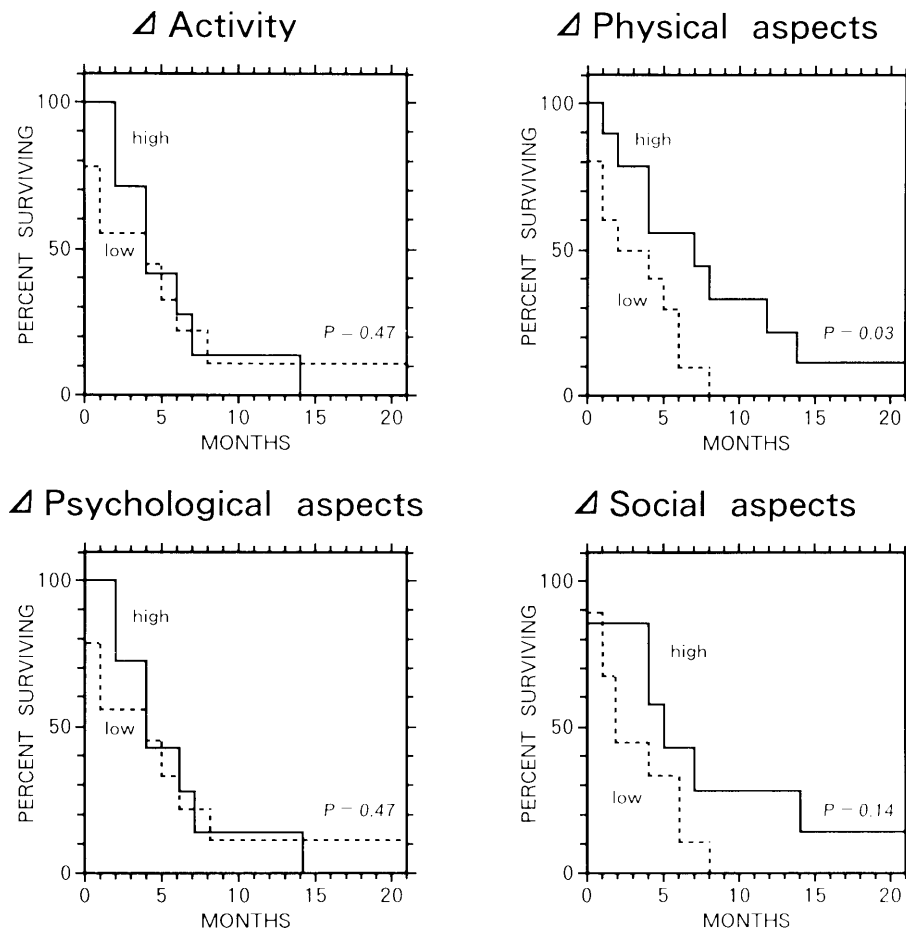In conclusion, the results of this study indicate that the score of the physical aspects of QL as well as

Fig. 5. Kaplan-Meier survival curves for subjects with higher Δmean scores (*solid line*) and those with lower Δmean scores (*dotted line*) of each of the four domains of QL. A significant difference was observed between the two groups only in the physical aspects of QL ($P = 0.03$ by Cox-Mantel test)

clinician-assessed PS scores in patients with end-stage breast cancer patients is a good prognostic predictor. Moreover, the change in score of overall QL and the physical aspects of QL are also significant prognostic predictors. Further investigations need to be conducted to confirm whether QL scores are prognostic predictors independent of other demographic and therapeutic characteristics.

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