Assessment of Functioning and Disability After Ischemic Stroke

Christian Weimar, MD; Tobias Kurth, MD; Klaus Kraywinkel, MD; Markus Wagner, MD; Otto Busse, MD; Roman Ludwig Haberl, MD; Hans-Christoph Diener, MD; for the German Stroke Data Bank Collaborators

Background and Purpose—Functioning and disability after ischemic stroke are clinically meaningful and of major relevance to patients. Despite many instruments available to assess these outcomes, little is known about their interrelation and predictive factors.

Methods—We prospectively identified 4264 patients with acute ischemic stroke from 30 hospitals in Germany during a 1-year period between 1998 and 1999 and registered them in a common data bank. The patients were centrally followed up via telephone interview after 100 days and 1 year to assess various scales such as the Barthel Index (BI), modified Rankin Scale (MRS), extended Barthel Index (EBI), Short Form-36 Physical Functioning (SF-36 PF), and Center for Epidemiologic Studies–Depression short form (CES-D).

Results—Outcome status could be assessed in 67.2% of patients 100 days after hospital admission. Of these, 13.9% had died, 53.7% had regained functional independence (BI <95), 46.3% had no or mild residual symptoms (MRS ≤1), and 44.6% had no higher cognitive deficits on the EBI. Of the patients who personally answered the follow-up questions, 67% had no major physical disability (SF-36 PF <60), and 32.9% reported symptoms classified as depression (CES-D ≥10). The high percentage of patients reaching the maximum score (ceiling effect) in the BI was less pronounced in the MRS and SF-36 PF. The predictive factors for dichotomized outcomes on each scale were similar for adverse functioning and disability but varied considerably for depression.

Conclusions—To avoid ceiling effects in outcome distribution of patients treated in specialized stroke centers, the MRS and SF-36 PF instruments are preferable to the BI. Parametric use of the SF-36 PF could further improve outcome measurement by considering individual treatment effects. (Stroke. 2002;33:2053-2059.)

Key Words: cerebral ischemia • depression • disability evaluation • outcome • stroke

The World Health Organization has recently proposed a new International Classification of Functioning, Disability and Health that defines components of functioning and disability, as well as activities and participation. The latter component describes 9 domains of activity and participation: learning and applying knowledge; general tasks and demands; communication; mobility; self-care; domestic life; interpersonal interaction and relationships; major life areas; and community, social, and civic life. Although clinical trials of stroke interventions routinely use mortality as an outcome, 2 other outcomes are both important for clinical investigations and relevant to patients. These include changes in body functions as measured by an available stroke scale and the proportion of surviving patients who regain functional independence after stroke (survival free of disability or with only minor disability) as measured by a functional outcome scale or a more global disability scale. Prior knowledge of the expected outcome after stroke and its predictors is important for selection of appropriate instruments and analyses of clinical trials in the stroke field. Several instruments for the assessment of functioning and disability have been developed. In clinical trials, the most widely used are the Barthel Index (BI) and the modified Rankin Scale (MRS). These scales are sensitive measures of stroke severity and show high interrater reliability. In addition, they can be assessed via telephone or proxy interview. The Short Form-36 (SF-36) is a frequently used generic instrument for the measurement of health-related quality of life that also has been validated in stroke patients. However, several of the SF-36 subscales are less sensitive for stroke severity and therefore less suitable for assessing stroke treatment effects. The SF-36 physical functioning (SF-36 PF) scale was developed to measure daily activities that are relevant to elderly patients. Because it shows a broader distribution across the whole range of the threshold.
scale rather than at one extreme, the SF-36 PF might represent a novel method for assessing disability after stroke. It could, moreover, be used as a continuous outcome variable, improving statistical power to detect differences in treatment effects among patients with different levels of disability. In addition to loss of speech and physical and cognitive impairments, depression represents a frequent impairment of body function in stroke patients. Depression has also been proposed as an independent predictor of poor functional outcome after stroke.

An understanding of functioning and disability after stroke is essential for selection of the appropriate instruments for intervention studies, given that the use of inappropriate instruments may obscure treatment effects. To gain a better understanding of what these outcome scales measure and to compare the efficacy of these scales in assessing outcome after ischemic stroke, we investigated the distribution, correlation, and prognostic variables of various end points in a large cohort of consecutive stroke patients.

Materials and Methods

Patient Population

The German Stroke Data Bank is a hospital-based affiliation of 15 neurology departments with acute stroke units, 9 departments of general neurology, and 6 departments of internal medicine, each in a different hospital that provides a geographically representative sample of specialized stroke care centers. A total of 4246 patients with a final diagnosis of ischemic stroke and a delay of no more than 7 days between the event and admission were prospectively followed up for a 1-year period from 1998 to 1999.

According to the criteria established by the National Survey of Stroke, ischemic stroke was defined as a focal neurological deficit of presumably vascular origin lasting ≥24 hours and excluding primary hemorrhage on initial cerebral imaging. To ensure a representative documentation rate, this analysis includes only patients from the 30 hospitals that registered >50 patients with acute stroke during a 1-year registration period. If the registration period in a particular hospital was >1 year, those recruited during the last 12 months were considered. We also excluded patients with serious handicaps (MRS >3) before stroke to ensure that patients were functionally independent to a certain degree before the stroke event.

Assessment of Outcomes

Using standardized questionnaires, treating physicians in the participating hospitals collected information that included age, sex, time of event and admission to the hospital, risk factors for stroke, prior stroke, prior medication, baseline neurological impairments as rated on the US National Institutes of Health Stroke Scale (NIHSS), functional independence before the event and after hospital admission as rated on the BI and MRS, acute therapy, medical and neurological complications, and length of stay in different wards in the documenting hospital. At discharge from the documenting hospital and at 100 days and 1 year after admission, the BI, MRS, SF-36 PF, extended BI (EBI), and Center for Epidemiologic Studies—Depression short form (CES-D) were administered. Local review boards approved the protocol of the Stroke Data Bank, and all patients gave informed consent. Risk factors for stroke and cardiovascular comorbidity were categorized a priori on the basis of clinically used cut points: arterial hypertension (history of elevated blood pressure >160/90 mm Hg at 2 independent readings before the stroke event or on current antihypertensive medication), diabetes mellitus (history of elevated fasting blood glucose >120 mg/dl at 2 independent readings before the stroke event, elevated HbA1c >7.5% at admission, or on current antidiabetic medication), and cardiovascular disease (newly diagnosed or history of myocardial infarction, ischemic heart disease, or peripheral arterial disease).

The NIHSS with 15 items (level of consciousness, answers to questions, responses to simple commands, deviation of gaze, hemianopia, facial palsy, arm and leg weakness of each side, limb ataxia, sensory loss, dysarthria, aphasia, inattention) measures the severity of neurological impairments. The single items range from 0 for no deficit to up to 4 (depending on the item) for complete impairment. The scores were quantified by local investigators who were familiar with the NIHSS from other clinical trials or the NIHSS training video.

The CES-D is a 10-item scale used to assess symptoms of depressed mood. Results range from 0 to 30, with a suggested cutoff score at ≥10 for depressive symptoms.

The MRS is a global outcome rating scale ranging from 0 (no impairment) to 5 (bedridden, incontinent, requiring constant nursing care and attention) and 6 (fatal outcome). The BI evaluates 10 basic activities of self-care (feeding, grooming, dressing, toileting, bathing, and continence of bowel and bladder) and mobility (transferring, walking, stair climbing) on a total score from 0 (totally dependent) to 100 (totally independent) functioning.

The SF-36 PF is composed of 10 questions about mobility (moving a table, pushing a vacuum, lifting or carrying groceries, climbing several flights of stairs, climbing 1 flight of stairs, bending or stooping, walking >1 mile, walking several blocks, walking 1 block) and self-care (bathing or dressing oneself) on a summary score from 0 (maximum disability level) to 100. The SF-36 PF is a sensitive measure of mild functional losses relevant to independent living. Scores on the SF-36 PF have been normalized for age and sex in a German population.

Since none of the above scales target deficits from the other domains of activity and participation as defined by the International Classification of Functioning, Disability and Health, we assessed 6 additional items from the German EBI—comprehension, verbal expression, social interaction, problem solving, orientation, and vision/attention—on a 3-to 5-point scale for each item, with 0 meaning no deficit. The EBI, a valid and reliable instrument, highly correlates to the Functional Independence Measure, has a comparable interrater reliability, and is sensitive to changes over time.

After a final consistency check with the source data at each site, the questionnaires were sent to the data management center at the German Stroke Foundation, where they were rechecked by 2 physicians for completeness and plausibility and entered into the data bank by trained personnel. Questions about missing or implausible data were relayed to the treating clinicians. Data quality was further improved by monthly reports and clinical site visits. If a patient did not consent to submission of his or her personal data, the participating center forwarded only anonymous data to the data management center and, on bimonthly request, performed the follow-up interview on site. Otherwise, trained interviewers of the German Stroke Foundation performed interviews via telephone 100 days and 1 year after hospital admission to assess the BI, MRS, SF-36 PF, EBI, and CES-D. The NIHSS cannot be performed by telephone interview. If neither the Stroke Foundation interviewers nor the treating physician was able to contact the participant by telephone, he or she was sent a written questionnaire to assess the BI, MRS, SF-36 PF, EBI, and CES-D.

Because of limited funding, follow-up efforts could not be completed for all participants. Of the initial cohort, 2853 patients (67.2%) received a complete follow-up or had died after 100 days, 1.3% refused participation, 9.0% could be reached only outside of the follow-up window, and 22.5% were not contacted. After 1 year, 2539 patients (59.8%) could be followed up or had died.

Statistical Analysis

All statistical analyses were performed with SPSS version 9.0. Continuous variables are presented as mean and median or percentiles. Categorical variables are presented as percentages. Spearman’s rank correlation coefficient (r) was used for comparisons between scales. To compare the variability over time of various scales, marked changes were defined as >20% difference on each of the scales. To compare the predictive variables for adverse outcome on various scales, we chose a priori cut points at the median of each
scale that coincided with clinically meaningful end points: BI <95 versus BI ≥95; MRS >1 versus MRS ≤1; SF-36 PF <60 versus SF-36 PF ≥60 for functional dependence; and CES-D ≥10 versus CES-D <10 for depression. The following variables were chosen for inclusion as independent variables in the multiple logistic regression models after a previous literature search: age (continuous), sex, MRS before the event (continuous), diabetes mellitus, prior stroke, other cardiovascular disease, living alone, and NIHSS items (continuous).

To test for univariate significance, we used χ² tests for categorical variables and Student’s t tests for continuous variables. After assessment of the univariate association between the potential predictors and the end-point variable, all significant variables were included in the model and retained if their resulting values were P ≤ 0.05. Any variable with P > 0.05 was eliminated stepwise. To the remaining set of variables, every previously eliminated variable was again added and kept in the model if it fulfilled the same criteria. Finally, all 2-way interactions of the remaining variables were investigated and kept if P ≤ 0.05. For the final models, odds ratios (ORs) with 95% confidence intervals (CIs) for all parameters were calculated.

**Results**

We included 4246 patients with a median age of 69 years: 58% were men, 30% had been living alone at the time of the stroke, and 22.5% were in the work force before the stroke. Neurology departments with an acute stroke unit documented 65.4% of the patients, departments of general neurology accounted for 25.8%, and departments of internal medicine accounted for 8.8%. Mean NIHSS at admission was 7.7 (median, 5). Patients with functional outcome assessed after 100 days were comparable to the initial cohort. The differences between patients with and without follow-up were minor and not significant for age and stroke severity. In contrast, patients with follow-up, including assessment of SF-36 PF and CES-D, significantly differed from all other patients in baseline characteristics. Baseline characteristics of all patients and those with complete assessment of various end-point variables are shown in Table 1. Figure 1 displays the inclusion of patients for assessment of various scales and time intervals.

Overall mortality after 100 days amounted to 13.9% and was higher for women (18.1%) than for men (11.0%). The BI after 100 days showed a marked ceiling effect (Figure 2), whereas the MRS had a more homogenous distribution across various degrees of functional status (Figure 3). The correlation between the 2 scales was r = 0.82.

A broad distribution of the SF-36 PF scores was observed among patients with personal follow-up after 100 days, with 16% reaching the maximum level (Figure 4). On this scale, 63.4% of men and 61.7% of women reached a score equivalent to the 75th percentile of an age- and sex-matched German standard population. The SF-36 PF was highly correlated with the MRS (r = 0.84) and moderately correlated with the BI (r = 0.65). On the CES-D, 42% of women, 26% of men, and 33% overall scored ≥10, indicating depression.
The respective correlation of the CES-D with SF-36 PF was \( r = 0.58 \), with the MRS was \( r = 0.54 \), and with the BI was \( r = 0.38 \). On the EBI, most patients (55.4%) showed \( \geq 1 \) deficits. The most common were related to orientation (37%), and problem solving (31%), whereas comprehension, verbal expression, social interaction, and vision/attention were reduced in \( \approx 20\% \) of patients.

In the interval between 100 days and 1 year after admission, 18.6% of patients improved on the BI, 58.5% remained unchanged, and 23% worsened or died. On the MRS, 22.6% of patients improved, 61.3% remained unchanged, and 16.3% worsened or died. The changes in functional independence on the BI and MRS are shown in Figure 6.

On the SF-36 PF, 27% of patients with personal follow-up remained unchanged between 100 days and 1 year, whereas 47.3% improved and 25.7% worsened. On the CES-D, 22.6% of patients improved, 61.3% remained unchanged, and 16.3% worsened or died. The changes in functional independence on the BI and MRS are shown in Figure 6.

To assess the influence of predictive factors on various scales, 4 logistic regression models were fitted with the BI, MRS, SF-36 PF, and CES-D as dichotomous end-point variables. The independent variables yielded by each model, together with 95% CIs, are depicted in Table 2. Predictors for BI and MRS were largely identical except for prior stroke, left leg weakness, and living alone before stroke, which were marginally significant predictors for MRS \( \geq 1 \) but not for BI <95. The most important predictors in both models were MRS before the stroke event, diabetes mellitus, and severity of either arm weakness. We identified diabetes mellitus, female sex, severity of right leg weakness, increasing MRS before the event, severity of left arm weakness, and increasing age as predictors for adverse outcome according to SF-36 PF \( <60 \) in patients with personal follow-up. With respect to depression, we identified living alone before the stroke, female sex, MRS before the stroke, sensory deficit, and cardiovascular disease as predictors for depression according to the CES-D \( \geq 10 \).

**Discussion**

In this comparison of various scales, the SF-36 PF and MRS appear to be more efficient in assessing functioning and disability after ischemic stroke than the BI. MRS scores before a stroke event, diabetes mellitus, and severity of left arm weakness were the most relevant predictors for the chosen adverse outcome on the BI and MRS after ischemic stroke in a large cohort of stroke patients recruited in predominantly tertiary-care hospitals. The observed correlations between these 2 scales were high, as shown in previous studies.  

During follow-up after 100 days and 1 year, the MRS was more sensitive than the BI to changes in disability. Because of its ceiling effect, the BI is less useful for assessing minor deficits at a high functional level and more useful for differentiating between patients with more severe disabilities. Predictive factors for both scales at the chosen cut points were similar, except for a stronger emphasis on upper limb weakness of the BI and on mobility and social support of the MRS. The MRS is more susceptible to depression, as can be inferred from its higher correlation with the CES-D. More-
over, patients with depression according to the CES-D scored worse on the MRS than patients with the same BI but without depression.

According to the CES-D, 32.9% of patients with personal follow-up after 100 days had symptoms of depression. This percentage is lower than the 40% reported in another follow-up study of stroke patients based on Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, criteria, but is markedly higher than the 12% found in an elderly American population based on the CES-D.13 Because the CES-D cannot be assessed through proxy interview, data on this instrument are missing for a considerable number of patients who were unable to answer or could not be reached for follow-up in person. The main determinants of mood disorders are demographic, social, and endogenous factors present before and after the stroke event. This lowers the discrimination of the CES-D for stroke-related effects and caused high fluctuation between follow-up after 100 days and 1 year. Thus, the CES-D does not seem to be as suitable to detect treatment effects in outcome assessment after stroke as the other scales. In contrast, assessing more complex cerebral impairments like cognition, communication, and social competence may provide more objective information regarding the individual treatment-dependent outcome after stroke. In this study, which used 6 items from the EBI, deficits in orientation and problem solving were apparent in >30% of patients, and deficits of other cognitive functions were apparent in ≈20%. Such impairments present a substantial burden to the patient and his or her family or caregivers and thus should be considered in assessments of outcome after stroke. Clinical trials of neuroprotective agents in ischemic stroke have generally failed to detect significant treatment effects. This could be due to a lack of efficacy of the intervention. It could also be the result of inappropriate outcome measurements. For example, the U-shaped distribution of the BI in many studies makes it difficult to detect outcome effects if the shape of the association is not accounted for in the analysis. The MRS and SF-36 PF are better instruments for differentiating between changes in mild to moderate disability, especially after minor stroke. Although the SF-36 PF was designed as part of a larger, more comprehensive assessment tool and predominantly assesses limitations related to mobility, it has been validated and accepted as an independent instrument with sufficient test-retest reliability and thus may stand alone as a measure of subjective functioning and disability.13,24 This study supports the sensitivity of the SF-36 PF for stroke severity and shows that it is well correlated with other accepted outcome scales. Moreover, the SF-36 PF shows a broad distribution across the whole outcome range, which would enable its parametric use.24 Unlike the BI, the SF-36 PF is designed to assess a patient’s uniquely personal point of view and therefore shows higher fluctuations during follow-up.23,25 In our investigation, it also showed a moderate correlation with depression as measured by the CES-D. Because of the age- and sex-specific distribution of the SF-36 PF, this scale should be standardized.

### Figure 7. Changes in SF-36 PF and CES-D between follow-up after 100 days and 1 year in patients with personal follow-ups. *Markedly worsened or improved: change >20 (SF-36 PF) or >5 (CES-D).*

<table>
<thead>
<tr>
<th>SF-36 Physical Functioning</th>
<th>MRS</th>
<th>CES-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left leg palsy</td>
<td>1.25 (1.03–1.52)</td>
<td>1.32 (1.06–1.64)</td>
</tr>
<tr>
<td>Right leg palsy</td>
<td>1.25 (1.02–1.52)</td>
<td>1.25 (1.01–1.54)</td>
</tr>
<tr>
<td>Sensory deficit</td>
<td>1.32 (1.06–1.64)</td>
<td>1.25 (1.01–1.54)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>1.25 (1.03–1.52)</td>
<td>1.31 (1.08–1.59)</td>
</tr>
<tr>
<td>Visual field</td>
<td>1.27 (1.03–1.55)</td>
<td>1.36 (1.11–1.66)</td>
</tr>
<tr>
<td>Left arm palsy</td>
<td>1.91 (1.58–2.30)</td>
<td>1.58 (1.29–1.93)</td>
</tr>
<tr>
<td>Right arm palsy</td>
<td>1.70 (1.39–2.08)</td>
<td>1.53 (1.24–1.89)</td>
</tr>
<tr>
<td>NIHSS</td>
<td>1.52 (1.05–2.22)</td>
<td>1.67 (1.12–2.49)</td>
</tr>
</tbody>
</table>

### Table 2. OR and 95% CI of Independent Variables in Prognostic Models for Adverse Outcome on Various Scales

<table>
<thead>
<tr>
<th>Variable</th>
<th>BI&lt;95 (n=1978)</th>
<th>MRS&gt;1 (n=1963)</th>
<th>SF-36 PF&lt;60 (n=1148)</th>
<th>CES-D&gt;10 (n=1155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>...</td>
<td>...</td>
<td>1.75 (1.31–2.35)</td>
<td>1.82 (1.39–2.39)</td>
</tr>
<tr>
<td>Age difference of 1 y</td>
<td>1.04 (1.03–1.05)</td>
<td>1.03 (1.02–1.04)</td>
<td>1.03 (1.02–1.04)</td>
<td>...</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.87 (1.44–2.43)</td>
<td>1.67 (1.29–2.15)</td>
<td>2.03 (1.48–2.78)</td>
<td>...</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1.36 (1.04–1.78)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>...</td>
<td>1.38 (1.03–1.86)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>MRS before the event</td>
<td>1.92 (1.61–2.28)</td>
<td>1.77 (1.48–2.12)</td>
<td>1.57 (1.25–1.98)</td>
<td>1.48 (1.20–1.82)</td>
</tr>
<tr>
<td>Living single before the event</td>
<td>...</td>
<td>1.49 (1.12–1.96)</td>
<td>...</td>
<td>1.85 (1.43–2.05)</td>
</tr>
</tbody>
</table>

*Table 2. OR and 95% CI of Independent Variables in Prognostic Models for Adverse Outcome on Various Scales*
with the general population as a reference. In a previous study, the mode of interview (face-to-face interview, self-completed questionnaire, or telephone interview) did not affect the reproducibility of the SF-36.\textsuperscript{25} Segal and Schaff\textsuperscript{26} found an intraclass correlation coefficient of \( r = 0.67 \) between patient and proxy assessment of the SF-36 PF, which is reasonably high for justifying proxy assessments. Thus, the SF-36 PF could be a useful end-point measurement in clinical trials for stroke patients’ own assessments of their functioning, even among those without moderate or severe disability. Moreover, its parametric use in outcome analysis could improve the efficiency of clinical trials to detect treatment effects.

This study has several strengths and limitations. Patients were included consecutively and, in a number of the participating hospitals, without application of selection criteria. Although the baseline characteristics are most likely representative of all patients admitted with ischemic stroke. Despite these scales was significantly younger and had less severe neurological deficits at baseline compared with the general population as a reference. In a previous study, the mode of interview (face-to-face interview, self-completed questionnaire, or telephone interview) did not affect the reproducibility of the SF-36.\textsuperscript{25} Segal and Schaff\textsuperscript{26} found an intraclass correlation coefficient of \( r = 0.67 \) between patient and proxy assessment of the SF-36 PF, which is reasonably high for justifying proxy assessments. Thus, the SF-36 PF could be a useful end-point measurement in clinical trials for stroke patients’ own assessments of their functioning, even among those without moderate or severe disability. Moreover, its parametric use in outcome analysis could improve the efficiency of clinical trials to detect treatment effects.

This study has several strengths and limitations. Patients were included consecutively and, in a number of the participating hospitals, without application of selection criteria. Although the baseline characteristics are most likely representative of all patients admitted with ischemic stroke. Thus, the subgroup with complete assessment of these scales was significantly younger and had less severe neurological deficits at baseline compared with the initial cohort and therefore cannot be regarded as representative of all patients admitted with ischemic stroke.

In conclusion, data from this large prospective cohort study of stroke patients demonstrate the limitations of the BI for assessing outcome among patients with minimal functional limitations. At the same time, they show that the MRS and SF-36 PF are more sensitive for assessing mild to moderate disability and thereby might be better tools to differentiate between treatment effects. Because of its great fluctuations and dependence on various non-stroke-related factors, the CES-D seems unsuitable for use as an end-point variable in the design of future randomized trials. More appropriate selection of outcome measures in the design of intervention trials for ischemic stroke might help to reveal true benefits or harms that are currently obscured.

\section*{Appendix}

Collaborators (responsible investigators) of the German Stroke Data Bank who contributed data to this study are listed here. Departments of Internal Medicine: Städtisches Krankenhaus Gütersloh (H. Dittr), Elisabeth-Krankenhaus Gütersloh (H. Hasler), St. Georg Hospital Leipzig (M. Sterker), Städtisches Krankenhaus Friedrichshafen (H. Lorenz-Meyer), Bethanien Krankenhaus Heidelberg (C. Marburger), and St. Joseph-Stift Bremen (T. Brabant), Departments of Neurology: Klinikum Minden (J. Glahn), Krankenhaus München-Harlaching (M.L.J. Wimmer), University of Essen (C. Weimar), University of Heidelberg (P.A. Ringleb), University of Leipzig (D. Clark), Rheinische Landesklinik Bonn (C. Kley), Asklepiosklinik Seesen (R. Brodhun), Asklepiosklinik Bad Salzhausen (G.-M. v Reutern), Klinikum Nürnberg Süd (G. Krocze), University of Regensburg (T. Hölscher), University of Greifswald (J. Machetanz), University of Tübingen (J. Weise), University of Ulm (M. Riepe), Bürgerhospital Stuttgart (H. Wiethölder), Krankenanstalten Gideon Bielefeld (A.H. Schacker), Städtische Klinik Karlsruhe (H. Rickman), University of Freiburg (A. Hetzel), St. Johannes Hospital Hagen (H. Ruf), Klinikum Krefeld (C. Buck-Rumphorst), Philippusstift Essen (A. Rogozinski), Klinikum Frankfurt/Oder (M. Mindach), Krankenhaus Würsele (A. Gruger), St. Barbara Hospital Gladbeck (E. Thöne), and Westfälische Klinik Gütersloh (R. Dümke).

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\section*{References}


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