ONLINE FIRST

Long-term Quality of Life After Surgical Intensive Care Admission

Tim K. Timmers, MD; Michiel H. J. Verhofstad, MD, PhD; Karl G. M. Moons, MSc, PhD; Ed F. van Beeck, MD, PhD; Luke P. H. Leenen, MD, PhD

Objectives: To quantify the long-term (>6 years) health-related quality of life (HRQOL) of a large cohort of patients admitted to a surgical intensive care unit (ICU). In addition, we aimed to explore the influence of different surgical classifications on long-term health status and to make comparisons with general population norms.

Design: Prospective observational cohort study.

Setting: A Dutch teaching hospital.


Main Outcome Measures: Patient-reported data on HRQOL were collected with the EuroQol-6D (EQ-6D) after a mean follow-up of 8 years (range, 6-11 years). Patient characteristics, surgical classification, length of ICU stay, and survival were prospectively registered. The EQ utility scores (measured with the EQ-5D US index tariff), EQ visual analog scale scores, and prevalences of domain-specific health problems were calculated. The effect of surgical classification on EQ utility scores and EQ visual analog scale scores was assessed by multivariable generalized linear regression analysis. Logistic regression was used to explore the influence of surgical classification on domain-specific health problems. Long-term HRQOL of surgical ICU patients was compared with an age- and sex-matched general Dutch population using t test analysis.

Results: Eight hundred thirty-four patients survived the ICU and were available for follow-up. In 575 patients (69%), the HRQOL was measured. For all surgical classifications combined, after 6 to 11 years, nearly half of all patients still had problems with mobility (52%), usual activity (52%), pain/discomfort (57%), and cognition (43%). Compared with the age- and sex-matched general population, HRQOL was worse, with a difference of 0.11 on the EQ utility score (range, 0-1). Oncological surgery patients had the best (EQ utility score, 0.83) and vascular patients had the worst (EQ utility score, 0.72) HRQOL. Trauma (odds ratio between 2.47-3.47) and vascular surgery (odds ratio between 2.27-5.37) patients showed significantly increased prevalences of problems in mobility, self-care, usual activities, and cognition.

Conclusions: More than 6 years after a surgical ICU admission, HRQOL of this patient population is largely reduced. Many patients still have a variety of health problems, including decreased cognitive functioning. Treatment advances should be made to reduce the current health deficit of surgical ICU survivors compared with the general population.


IN RECENT YEARS, THERE HAS BEEN an increased focus on outcome after intensive care treatment. Complications and prolonged hospital stay as well as the staggering costs of more extensive treatment have to be justified by favorable, preferably long-term outcome including health-related quality of life (HRQOL). A significant amount of resources in the intensive care unit (ICU) are devoted to patients with a poor prognosis, many of whom ultimately die. Consequentially, improvements of functional status and HRQOL of ICU patients have become important treatment goals. Accordingly, ICU research could shift focus from survival to HRQOL outcomes.

Assessments of HRQOL occurred infrequently in the ICU literature before 1995 and were of limited methodological quality. In the last decennium, various studies of long-term HRQOL after ICU admission appeared. Most of these studies did not exceed a follow-up period longer than 2 years. Only 2 studies had a somewhat longer follow-up. Both found a lower HRQOL at 6 years in ICU patients as compared with a general population, but included a relatively small cohort and did not


CME available online at www.jamaarchivescme.com and questions on page 378

©2011 American Medical Association. All rights reserved.
distinguish between subgroups, such as surgical vs non-surgical patients. The study of Livingston et al demonstrated that less than half of the patients who underwent trauma returned to work and more than two-thirds reported a lower level of activity than before the trauma after follow-up of 3 years. Longer-term follow-up will improve our understanding of the nature and duration of ICU-acquired deficits and what length of time is sufficient to accurately determine outcome. Furthermore, to our knowledge, which patient characteristics (such as age and sex) and surgical classifications are related to long-term HRQOL have yet to be addressed. Insight into problems with cognitive functioning should be expanded, since, to our knowledge, this was previously not addressed in the international literature. All these aims require larger and long-term cohort studies.

The primary aim of this study was to quantify the HRQOL, specified by health domain (including cognition), of a large cohort of patients more than 6 years after admission to a surgical ICU. In addition, we aimed to explore the influence of different surgical classifications, adjusted for age, sex, and severity of the underlying condition, on long-term health status and to make comparisons with general population norms.

**METHODS**

**PATIENTS**

The study was a prospective observational cohort study. All consecutive surgical patients who entered the ICU of the St Elisabeth Hospital, a 673-bed teaching hospital and a level 1 trauma center in Tilburg, the Netherlands, between January 1995 and February 2000 were included. Follow-up of each patient was continued until a minimum follow-up of 6 years was achieved (until February 2006).

The 32-bed ICU admits medical and surgical critically ill patients and is staffed by intensive care specialists with an internal medicine, anesthesiological, or surgical background. To ascertain a more homogeneous study population, the current research was restricted to surgical patients only with a single ICU admission during the study period and who were alive when contacted for the HRQOL questionnaire. Exclusion criteria were age younger than 18 years, readmission to the ICU during the same hospital admission, multiple admissions to the ICU over the study period, and gynecological and nontrauma neurosurgery.

**PATIENT CHARACTERISTICS**

From each patient, sex, age, type of surgical ICU diagnosis, and ICU length of stay (LOS) were documented. Surgical ICU admissions were divided into 5 different surgical classifications: trauma, vascular (excluding cardiac surgery and including aneurysmatic and occlusive disease), gastrointestinal, oncological, and general surgery. All patients with a surgical oncological pathology were included in the oncological classification group. The LOS was defined as the period from the day of admission until the day of ICU discharge.

**FOLLOW-UP AND HRQOL MEASUREMENT**

Survival was determined by reviewing the hospital’s electronic patient data management and medical record system. If the patient’s death (either in or outside the hospital) could not be confirmed by the database, the general practitioner was consulted. Finally, if a date of death could not be found, the patient or his or her relatives were directly consulted. Patients living in February 2000 were sent an HRQOL questionnaire (EuroQol-6D [EQ-6D]). Patients were reminded and contacted by telephone if the questionnaire was not returned.

A number of questionnaires that aim to measure specific dimensions of HRQOL have been developed, using different criteria depending on the aim of the study and the patient population. One such instrument is the EQ-6D, a generic HRQOL instrument that was developed at a European level and based on the EQ-5D by adding a question on cognitive functioning. The questionnaire has been translated into Dutch and tested on its reproducibility in prior studies. The original EQ-5D questionnaire is a generic instrument designed to measure health outcome on the following dimensions: mobility, self-care or autonomy, usual activities, pain/discomfort, and anxiety/depression. We selected EQ-6D because of the added cognitive dimension.

The EQ-6D consists of 2 parts: the EQ-6D self-classifier and the EQ-6D visual analog scale (VAS), a self-rated health status using a VAS recording the participants’ perceptions of their current overall health state. The VAS score ranges from 0 (the worst imaginable state) to 100 (the best imaginable state).

The EQ-6D self-classifier scores the severity of problems (1 = no problem, 2 = some/moderate problems, and 3 = severe/extreme problems). Because there is no international validated tariff for the EQ-6D health states, the EQ utility score was obtained with the help of the EQ-5D US index tariff for all possible health states defined by the EQ self-classifier and the cognitive dimension was ignored. This index tariff links a single index value for all hypothetical health states. Full health is represented by an index of 1.00. This single index value is also referable and comparable with the patients’ health status scored by the patients on the EQ VAS. To compare the European EQ utility score with the United States, we have also included the EQ-5D UK tariff utility score. This questionnaire has 3 different outcomes: the EQ utility score, the VAS score, and the percentage of reported problems in the 6 EQ-6D dimensions.

**DATA ANALYSIS**

Normal distribution of the EQ-6D scores was established first. The HRQOL values (continuous) of the EQ-6D index and the VAS measured at follow-up are given as mean values with standard deviation. This was also done for patient subgroups defined by sex, age, surgical diagnosis, and ICU LOS. Subsequently, multivariable linear regression modeling was used to assess an association of the different surgical diagnosis groups with the long-term HRQOL (dependent variable), corrected for age, sex, and severity of the health condition at ICU admission (as approximated by ICU LOS, elective or emergency admission, and mechanical ventilation). Continuous independent variables were analyzed as linear terms because there were no indications of nonlinearity based on cubic spline analysis. In an additional analysis, we dichotomized the outcome scales of the EQ-6D dimensions from no problems, mild problems, and severe problems to no problems vs problems. Through multivariable logistic regression, we analyzed the independent association of sex, age, surgical classification, and duration in the ICU with this dichotomized outcome.

Finally, the average HRQOL of our study population was compared with an age- and sex-adjusted general population using t test analysis. The reference population was a representative sample of the Dutch population without ICU care: aged 18 to 97 years, 37.3% male, and 38% with long-standing illness such as diabetes mellitus, asthma, hypertension, angina pectoris, or low back pain.
**RESULTS**

A total of 2145 patients were admitted to the surgical ICU in the study period. One thousand eight hundred twenty-two patients met the inclusion criteria. The mean (SD) follow-up was 8.4 (1.4) years, with a minimum of 6 years and a maximum of 11 years. Eight hundred thirty-four patients (46%) were living after at least 6 years of follow-up. The HRQOL could be measured in 598 of these 834 patients (72%). Twenty-three patients did not answer 1 or more questions and/or did not answer the VAS questions (Figure). Accordingly, 575 patients (69%), aged 18 to 93 years, fully completed the questionnaire. Sixty-four percent were male (Table 1). Most patients were in their seventh and eighth year after ICU discharge (136 and 129 patients, respectively); 103 and 109 patients were in their ninth and tenth follow-up year, respectively; and lower numbers of patients were seen at the sixth (n=52) and eleventh (n=46) year after ICU discharge.

**LONG-TERM HRQOL: ALL SURGICAL ICU PATIENTS COMBINED**

As shown in Table 1, the overall percentages of patients reporting problems in the 6 EQ dimensions were 52% for mobility, 19% for self-care, 52% for usual activities, 57% for pain/discomfort, 29% for anxiety/depression, and 43% for cognitive ability. The EQ utility score (using the US index tariff) was higher than the patient’s own actual self-rated health status (VAS) for the total study group and for each surgical group separately.

**LONG-TERM HRQOL BY SURGICAL DIAGNOSIS GROUP**

When dividing the total study population into the different surgical classifications, patients with an oncological diagnosis appeared to have the best and patients with a vascular diagnosis had the worst EQ utility score (mean [SD], 0.83 [0.20] and 0.72 [0.22], respectively). These low EQ utility scores were particularly related to problems reported in the EQ-6D dimensions mobility, self-care, usual activity, and cognition (Table 1).

Using the oncological surgery group as the reference group, a significant decrease in EQ utility score was found only in trauma and vascular surgery patients after correction for age, sex, emergency admission, the use of mechanical ventilation, and ICU LOS (Table 2). Age and sex were also independently associated with long-term

---

**Table 1. Study Group Demographics**

<table>
<thead>
<tr>
<th>Overall (N=575)</th>
<th>Trauma (n=194; 34%)</th>
<th>Vascular (n=175; 30%)</th>
<th>Gastrointestinal (n=84; 15%)</th>
<th>Oncology (n=78; 12%)</th>
<th>General (n=52; 9%)</th>
<th>Reference Population (n=9685)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline statistic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>205 (36)</td>
<td>47 (24)</td>
<td>53 (30)</td>
<td>43 (51)</td>
<td>33 (47)</td>
<td>28 (56)</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>61 (16)</td>
<td>49 (15)</td>
<td>72 (10)</td>
<td>62 (16)</td>
<td>66 (11)</td>
<td>57 (16)</td>
</tr>
<tr>
<td>APACHE II score, mean (SD)</td>
<td>10 (6)</td>
<td>10 (7)</td>
<td>10 (5)</td>
<td>11 (6)</td>
<td>11 (5)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Length of stay, d, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>5 (8)</td>
<td>7 (11)</td>
<td>3 (6)</td>
<td>6 (9)</td>
<td>4 (4)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Hospital</td>
<td>19 (21)</td>
<td>21 (28)</td>
<td>13 (12)</td>
<td>27 (22)</td>
<td>15 (11)</td>
<td>19 (18)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ utility score (UK index tariff), mean (SD)</td>
<td>0.71 (0.26)</td>
<td>0.74 (0.22)</td>
<td>0.65 (0.28)</td>
<td>0.71 (0.27)</td>
<td>0.77 (0.23)</td>
<td>0.72 (0.31)</td>
</tr>
<tr>
<td>EQ utility score (US index tariff), mean (SD)</td>
<td>0.77 (0.21)</td>
<td>0.79 (0.19)</td>
<td>0.72 (0.22)</td>
<td>0.78 (0.21)</td>
<td>0.83 (0.20)</td>
<td>0.80 (0.24)</td>
</tr>
<tr>
<td>VAS score, mean (SD)</td>
<td>69 (21)</td>
<td>73 (19)</td>
<td>63 (22)</td>
<td>69 (23)</td>
<td>74 (17)</td>
<td>68 (26)</td>
</tr>
<tr>
<td>Problems in dimension, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td>52</td>
<td>44</td>
<td>72</td>
<td>44</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Self-care</td>
<td>19</td>
<td>15</td>
<td>29</td>
<td>15</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>Usual activity</td>
<td>52</td>
<td>53</td>
<td>57</td>
<td>57</td>
<td>57</td>
<td>47</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>57</td>
<td>60</td>
<td>57</td>
<td>57</td>
<td>57</td>
<td>51</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>29</td>
<td>27</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>Cognition</td>
<td>43</td>
<td>45</td>
<td>49</td>
<td>41</td>
<td>41</td>
<td>33</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; EQ, EuroQol; ICU, intensive care unit; NA, not available; VAS, visual analog scale.

*The VAS was not measured in the age- and sex-matched Dutch population.*
This significant decrease in EQ utility score for trauma and vascular surgery patients was most profound in the dimensions mobility, self-care, usual activity, and cognition (Table 3).

Odds ratios for the dichotomized EQ-6D outcomes of the trauma diagnosis group were between 2.47 and 3.47 and of the vascular diagnosis group, between 2.27 and 5.37. The ICU LOS, emergency admission, and use of mechanical ventilation did not show any association with long-term HRQOL, as a continuous or dichotomized variable.

## COMPARISON WITH AGE- AND SEX-MATCHED GENERAL POPULATION NORMS

In comparison with the general Dutch population, a lower EQ utility score (using the US index tariff) was found for the total study population (difference of 0.11) and for each
surgical diagnosis (difference between 0.05-0.16). The almost equal EQ utility score of patients with an oncological diagnosis compared with the general population was remarkable. Comparing the single EQ dimensions of the study population and the different surgical classifications with the reference population, 3 to 5 times higher percentages of reported problems were seen in mobility, self-care, usual activity, and cognition (data not shown).

A significantly lower HRQOL was observed in the whole study population when categorized by different surgical classifications and age groups (18-49, 50-69, and 70-97 years), except for oncological surgery patients (Table 4).

### Table 4. Mean EQ Utility Score by Age of the General Dutch Population and for Our Study Group, Both Overall and per Diagnosis at Admission in 575 Patients

<table>
<thead>
<tr>
<th>Mean EQ Utility Score (No. of Patients)</th>
<th>Age 18-49 y</th>
<th>Age 50-69 y</th>
<th>Age 70-97 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference population</td>
<td>0.91</td>
<td>0.87</td>
<td>0.80</td>
</tr>
<tr>
<td>Study group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.82 (148)</td>
<td>0.78 (239)</td>
<td>0.74 (188)</td>
</tr>
<tr>
<td>Trauma</td>
<td>0.81 (102)</td>
<td>0.79 (74)</td>
<td>0.72 (18)</td>
</tr>
<tr>
<td>Vascular</td>
<td>NA</td>
<td>0.72 (65)</td>
<td>0.72 (107)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0.78 (21)</td>
<td>0.79 (33)</td>
<td>0.77 (30)</td>
</tr>
<tr>
<td>Oncology</td>
<td>0.88 (5)</td>
<td>0.83 (43)</td>
<td>0.81 (22)</td>
</tr>
<tr>
<td>General surgery</td>
<td>0.89 (17)</td>
<td>0.78 (25)</td>
<td>0.69 (11)</td>
</tr>
</tbody>
</table>

Abbreviations: EQ, EuroQol; NA, not applicable (conclusive numbers when n ≥ 5 patients).

The EQ-5D index values are based on the EQ-5D US index tariff (D1).28,29

Age at time of answering questionnaire.

Only 3 patients in this group.

Intensive care unit care is undoubtedly useful for most critically ill patients. The outcome of ICU treatment is usually reported as mortality and most studies have focused on a specific diagnostic group.4,12,30 While mortality is a clear outcome measure, HRQOL is largely subjective and difficult to describe using objective measures.

We demonstrated that the long-term (>6 years) HRQOL (EQ utility score, using the US index tariff) of the total study population was worse in comparison with an age- and sex-matched general Dutch population19 and with other published population norms.31-34 Patients who underwent oncological surgery had the best EQ utility scores whereas those who had vascular surgery had the worst EQ utility scores of all surgical classifications. The low EQ utility scores directly show that the reported problems of (nearly) half of our study population could be attributed to problems in the EQ dimensions mobility, self-care, usual activity, and cognition. Undergoing trauma and vascular surgery were both independently associated with long-term HRQOL loss.

Unfortunately, we did not find any similar long-term HRQOL study that used the same validated HRQOL measurement to compare our findings. There is indeed no uniformly accepted standard test for HRQOL in general or for ICU patients in particular. A review of HRQOL assessments in the critical care literature between 1995 and 2009 showed that 108 different instruments had been used in 64 publications. In only 7% of these instruments were the reliability and validity of the test reported.3 Normative scales, such as the Short-Form Health Survey (SF-36) and Sickness Impact Profile, assess difficulty and disability against a general population.35 Watson et al26 used the SF-36, found that the baseline for injured patients was not necessarily representative for a general population. To our knowledge, previous data of HRQOL measured by the EQ-5D for a Dutch ICU population are not available. Tian and Miranda37 used the Sickness Impact Profile to conclude that HRQOL 6 months after ICU discharge had decreased in a large cohort of patients in the Netherlands in comparison with the general population. They noted that the physical dimension (ambulation, mobility, and body care) was responsible for the highest variance of the total score, which is in line with our results. Kaarloa et al14 used the RAND-36 Health Survey 6 years after ICU discharge and reported that 9% (15 of 169 patients) considered their present health status to be excellent; 37%, good; 45%, satisfactory; and 9%, poor. Our study population more than 6 years after ICU discharge (n=52 patients) resulted in a higher proportion of patients with an “excellent” health state (37%) and a slightly lower proportion in a “poor” health state (6%). Norwegian investigators used the SF-36 to study the HRQOL 12 years after ICU care.13 The HRQOL indexes physical and social functioning, and physical and emotional role limitations appeared statistically worse (P < .05) than the values for the general Norwegian population.

Several studies have focused on resumed employment as an outcome (patients who underwent trauma). Most of these studies showed that even after a long follow-up period (2-8 years) high percentages of their study population did not resume work. However, the results improved with a longer follow-up period.38-41

As described in other HRQOL studies, our patients most frequently reported problems in the dimensions mobility, usual activity, and pain/discomfort. To our knowledge, the cognition dimension has not yet been addressed. We found a high percentage of cognitive problems in our total study population (43%). Further research on this important issue is required to replicate and explain this largely unexpected finding. Also, a recalibration of the EQ-5D tariff formula with the inclusion of the cognition dimension should be done for a more accurate description of HRQOL of patients after severe illness.

Several limitations have to be considered. First, in an ideal study, HRQOL should be measured in each subject before and after ICU admission, because the real interest is not “absolute” health but rather the change in perceived health. However, the HRQOL before treatment could only be scored retrospectively in the patients acutely admitted. This is difficult if not impossible without bias, because patients are still influenced by their critical illness. In a UK study, different authors used the SF-36 questionnaire at the time of discharge from the ICU as an instrument to score the premorbid HRQOL.
However, their patients (medical and mixed ICU population) appeared to have a much lower pre-ICU score than the general population. Nevertheless, the study of Watson et al showed that the preinjury scores in trauma patients were better compared with a general population. Also, there have been problems reported with the recall bias influencing predmission HRQOL. The possibility exists that the worse long-term HRQOL seen in our study could be associated with the higher prevalence of comorbidities and not solely the ICU admission. The systematic follow-up of ICU patients by Kvåle and Flaatten agrees that ICU patients in general have more comorbidity than the normal population. Nevertheless, only 30 patients (5%) had the presence of a predmission disease (comorbidities, as scored in the chronic health points of the Acute Physiology and Chronic Health Evaluation [APACHE II]) in our study population. This could be an underestimation. The use of a different, more detailed scoring system may have yielded more specific information regarding the degree of comorbidities for the study cohort. From a methodological point of view, the nearest approach is to compare the self-reported health status of patients with that of a healthy reference population of corresponding age without ICU care. A second limitation of our study is that the HRQOL assessment was conducted only once. Ideally, assessment of HRQOL is conducted in a longitudinal design with multiple measurements over time. However, a design like ours does provide important and relevant findings, since health problems have most often stabilized some years after ICU admission. This hypothesis is also likely from our data; a comparison of the group with 6 years’ follow-up and the group with 10 or more years’ follow-up after ICU discharge revealed no significant difference in HRQOL (results not shown). Third, HRQOL measurement was done in 2006 at the end of the study follow-up time. Before HRQOL could be measured, 50% of the total study population (all surgical ICU patients, n = 1822) had already died. A group of 92 patients who died did survive a follow-up period of more than 6 years but were not alive anymore when HRQOL was measured. We chose to exclude these patients from this study. We assume that HRQOL would decrease even more if these patients were included and that our estimates of reported health problems should even be seen as conservative or optimistic.

In conclusion, our results show that 6 or more years after ICU discharge, patients still experience considerable difficulties in their HRQOL. Patients who underwent vascular surgery had the worst and patients who underwent oncological surgery had the best HRQOL. Many patients still have a variety of health problems, including decreased cognitive functioning. Because this study shows a high percentage of problems in the cognition dimension, a recalibration of the EQ-5D tariff including the cognitive dimension should give a better insight of the HRQOL. To compare the results of future HRQOL studies, the ICU community should agree on a limited list of questionnaires to measure HRQOL, eg, the SF-36 and the EQ-5D. Treatment advances should be made to reduce the current health deficit (a difference of 0.11 on the EQ utility score) of surgical ICU survivors compared with the general population.

Accepted for Publication: September 24, 2010. Published Online: December 20, 2010. doi:10.1001/archsurg.2010.279

Correspondence: Tim K. Timmers, MD, Department of Surgery, University Medical Center Utrecht, Heidelberglaan 100, 3524DA Utrecht, the Netherlands (tk.timmers@gmail.com).

Author Contributions: Study concept and design: Timmers, Verhofstad, Moons, and Leenen. Acquisition of data: Timmers. Analysis and interpretation of data: Timmers, Verhofstad, Moons, van Beeck, and Leenen. Drafting of the manuscript: Verhofstad. Critical revision of the manuscript for important intellectual content: Timmers, Verhofstad, Moons, van Beeck, and Leenen. Statistical analysis: Moons and Leenen. Administrative, technical, and material support: Verhofstad. Study supervision: Verhofstad, Moons, and Leenen.

Financial Disclosure: None reported.