Surviving pediatric intensive care: from mortality to morbidity
Knoester, H.

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An explorative study on quality of life and psychological and cognitive function in pediatric survivors of septic shock

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Submitted
Abstract

Objective: To evaluate self-reported Health Related Quality of Life (HRQoL), anxiety, depression and cognitive function in pediatric septic shock survivors.
Design: A retrospective cohort study
Setting: A 14-bed tertiary pediatric intensive care unit.
Patients: Children aged ≥8 years at the time of the follow-up who were admitted between 1995 and 2004 for septic shock. Inotropic and or vasoconstrictive agents were administered to these patients for 24 hours or more.
Intervention: HRQoL was assessed with the KIDSCREEN-52, anxiety with the Trait Anxiety Inventory for Children (STAIC), depression with the Children's Depression Inventory (CDI) and cognitive function with the cognitive scale of the TNO-AZL Children's Quality of Life Questionnaire Child Form (TACQOL-CF).
Measurements and main results: Fifty of 82 eligible pediatric septic shock survivors were evaluated. The median age of the children at PICU admission was 4.2 years (range 0.0-17.0), while the median age at follow-up was 10.7 years (range 8.0-20.4). HRQoL and anxiety scores were comparable to the age-related Dutch norm population. Depression scores were significantly better than the norm population, while cognitive function was significantly lower than the norm population. 42% of the children had cognitive scores lower than 25% of the norm population. Young age at the time of PICU admission was predictive of cognitive problems, and cognitive problems were associated with poor emotional function.
Conclusions: In this group of septic shock survivors, HRQoL, anxiety and depression are equal to or slightly better than the age-related Dutch norm population. Cognitive function is decreased, especially in children admitted at younger ages. Follow-up studies with adequate neuropsychological testing are warranted to evaluate the association between septic shock, cognitive function and risk factors for cognitive problems.
Introduction

The incidence and mortality rate of sepsis in children are lower compared to those in adults, but sepsis is one of the leading causes of death in children. (1) Adult sepsis survivors suffer from persisting symptoms such as dyspnoea, fatigue, depression, impaired cognitive function and functional status and reduced health-related quality of life (HRQoL) compared to the general population. (2;3) Recognition of these long-term sequelae has resulted in ‘patient-centered outcome’ research in adult intensive care unit (ICU) survivors. (4) Studies on long-term sequelae and HRQoL in pediatric sepsis survivors are scarce.

Quality of Life (QoL) is defined as an individual’s perception of his or her position in life in the context of culture and value systems, as well as in relation to his or her goals, expectations, standards and concerns. HRQoL is defined as QoL in which a dimension of personal judgement of one’s health and disease is added. (5) In the case of children, HRQoL is also influenced by factors such as the ability to participate in peer groups and the ability to keep up with developmental activities. Difficulties in measuring HRQoL in children include (1) a lack of consensus on suitable (cross-cultural) instruments and (2) the need for different instruments in different age groups. (6) Recently, the KIDSCREEN-52 was developed in Europe as a generic, cross-national HRQoL questionnaire that evaluates HRQoL regardless of whether children are in good health or suffer from a chronic medical condition. It is a self-report questionnaire that evaluates HRQoL in children aged 8-18 years. (7) The self-report questionnaire is based on psychosocial aspects of well-being rather than physical function.

In the few studies evaluating HRQoL in pediatric intensive care unit (PICU) survivors, HRQoL was satisfactory in the majority of children. (8-12) In the few studies evaluating HRQoL in pediatric septic shock survivors, HRQoL was decreased on physical domains. (13;14) Long-term psychological problems like post-traumatic stress disorder (PTSD) have been reported, but other psychological problems such as anxiety and depression are hardly studied in PICU survivors. (15-18) Evaluation of cognitive function in pediatric meningitis survivors and adult septic shock survivors does show substantial problems that interfere with daily life. (19-23) Possible pathophysiologic mechanisms mediating cognitive dysfunction in septic shock survivors include hypoxemia, sedatives or analgesics, hypotension, delirium, hyperglycemia and sepsis and inflammation. (20) Based on these observations, we believe that follow-up research on pediatric septic shock survivors and their families is needed to evaluate long-term sequelae and to improve support after discharge.

The aim of our study was (1) to evaluate HRQoL, psychological function (anxiety and depression), cognitive function and educational level in children who survived septic shock compared to normative data from the Dutch population, (2) to explore possible medical determinants that are related to cognitive problems and (3) to determine whether cognitive function is related to HRQoL and psychological function.
Chapter 6

Materials and methods

Protocol and procedure
This study was part of a retrospective study in which we evaluated cardiac function, HRQoL, psychological function (anxiety and depression) and cognitive function in pediatric septic shock survivors. The PICU of the Emma Children's Hospital/Academic Medical Center Amsterdam is a tertiary PICU with 14 beds that admits medical, surgical and trauma patients from the greater Amsterdam area. Previously healthy children that survived septic shock in our PICU between 1995 and 2004 were included in this study. The term previously healthy was defined as having no need for medical supervision at anytime before PICU admission. Inclusion criteria were survival of the clinical diagnosis of septic shock according to the Conference Consensus Criteria, the administration of inotropic and/or vasoconstrictive agents for 24 hours or more and age ≥ 8 years at the time of the follow-up study. (24;25) Children were invited to visit our outpatient follow-up clinic where they were evaluated for physical sequelae, HRQoL, anxiety, depression and cognitive function. Physical sequelae were defined as any physical complaints or abnormalities found at the outpatient follow-up clinic by physical examination (e.g. neurological abnormalities). Children with language barrier were excluded due to the inability to complete Dutch questionnaires. In addition, children younger than 8 years were excluded because they were unable to complete the questionnaires by themselves. Written informed consent was obtained from all participating parents and children. The Medical Ethical Board of the Academic Medical Centre Amsterdam has approved the study protocol.

Questionnaires
HRQoL was evaluated by the KIDSCREEN-52, a generic self-report questionnaire that uses questions derived from focus groups of children and adolescents across Europe. It is applicable for both healthy and chronically ill children and adolescents aged between 8 and 18 years. The KIDSCREEN-52 consists of three socio-demographic questions (gender, age and educational level) and ten domains of HRQoL: ’Physical well-being,’ ’Psychological well-being,’ ’Moods and emotions,’ ’Self perception,’ ’Autonomy,’ ’Parent relations and home life,’ ’Financial resources,’ ’Peers and social support,’ ’School environment’ and ’Bullying’. Items were scored on a five-point scale. Within each domain, item scores were summed and transformed to Rasch person parameters by an algorithm that gives children in the reference population a mean score of 50 with a standard deviation of 10. (26) This instrument was validated in a Dutch population of 1960 children, distributed across the age range of 8 to 11 years (n=641) and 12 to 18 years (n= 1270) with these data forming the normative groups for our analysis. The internal consistency (Cronbach's alpha) was satisfactory and ranged from 0.68 to 0.88 in all scales.

Psychological function comprises anxiety and depression. Anxiety was evaluated by the State-Trait Anxiety Inventory for Children (STAIC). (27) The trait scale, a 20-item self-report scale, measures differences between children in their tendency to experience anxiety states. The scale ranges from 20 to 60 points, and children with high scores are more prone to respond with anxiety
Quality of life and psychological and cognitive function

to situations perceived as threatening than children with low scores. This instrument was validated in a Dutch population of 1229 children, distributed across the age range of 8 to 12 years (n=643) and 13 to 17 years (n=586). Boys (n=596) and girls (n=633) differed significantly on STAIC in the Dutch population. Therefore, four normative groups were used for our analysis. (28) The internal consistency (Cronbach's alpha) was satisfactory and ranged from 0.73 to 0.83.

Depression was evaluated by the Children's Depression Inventory (CDI). (29) This questionnaire contains 27 items, each of which consists of three statements. For each item, the individual was asked to select the statement that best describes his or her feelings for the past two weeks. The CDI is designed to provide information about the presence and severity of depressive symptoms. This instrument was validated in a Dutch population of 886 children, distributed across the age range of 8 to 12 years (n=673) and 13 to 17 years (n=213). Boys (n=419) and girls (n=467) differed significantly on CDI in the Dutch population. Therefore, four normative groups were used for our analysis. (30) The internal consistency (Cronbach's alpha) was satisfactory and ranged from 0.71 to 0.89.

Cognitive function was evaluated by the cognitive scale of the TNO-AZL Children's Quality of Life Questionnaire Child Form (TACQOL-CF) that included 8 items. (31;32) These items measure limitations concerning cognitive functioning and school performances (child's ability to pay attention, understand schoolwork, understand what others say, perform arithmetic, read, write, learn and say what he/she means). This self-report questionnaire is a generic Dutch instrument that measures health status problems and is weighted by the impact of health problems on the child's well-being. If a problem occurred in the past few weeks, the child can indicate how he or she felt about this problem on a four point Likert scale: (very) good (3); not so well (2); rather bad (1); and bad (0). The score was calculated by adding up item scores, and higher scores indicated a better QoL. Maximum domain scores for the cognitive scale were 32. The internal consistency (Cronbach's alpha) was satisfactory (0.79). This instrument was validated in a Dutch population of 2331 children, distributed across the age range of 8 to 11 years (n=1078) and 12 to 15 years (n=1253) with these data forming the normative groups for our analysis. Besides a scale score, the percentage of children with cognitive problems was determined. The definition of children with cognitive problems was based on the value of the 25th percentile in the norm population. (33) According to this concept, an individual scoring below the 25th percentile norm is in the quarter of the population most impaired. The 25th percentile for healthy children (8 to 11 years of age) is a score of 27, and the score for healthy adolescents (12 to 15 years of age) is 26.

Patient characteristics (age at PICU admission, length of PICU stay, (length of) artificial ventilation, risk of mortality, highest creatinine and lactate during PICU stay, causative organisms and number, dosages and duration of vasoactive agents) were retrospectively obtained from medical records and the Patient Data Management System. In our unit it is no standard procedure to perform a lumbar puncture in septic shock patients; therefore meningitis could not be evaluated as a risk factor for decreased HRQoL, and psychological and cognitive function.
Chapter 6

**Statistical analysis**
The Statistical Package for Social Sciences (SPSS), Windows version 12.0, was used for all analyses. First, missing values were handled according to the guidelines given in the manuals for the relevant questionnaires. In general, data were imputed if children completed at least 90% of the questionnaire by mean scores of the other items. Two missing items were allowed for the cognitive function scale. Second, Mann-Whitney U tests and Chi-square tests were used to compare participants and non-participants. Third, differences between patients and the norm group in their HRQoL, anxiety, depression and cognitive function were analysed by one-sample t-tests. In addition to this, effect sizes were calculated by dividing the difference in mean scores between the patients and the norm group by the standard deviation of the scores from the norm group. According to Cohen, effect sizes of about 0.2 were considered to be small, effect sizes of about 0.5-0.8 to be moderate and effect sizes of ≥0.8 to be large. (34) Fourth, cognitive function was also evaluated by analysing differences in educational levels between patients and healthy control subjects (data from Dutch Health Statistics); for this analysis we used a one-sample t-test. Fifth, cognitive function scores were dichotomized to determine cognitive problems. A score below the 25th percentile value for the appropriate age and gender population stratum indicated perceived impaired cognitive function. To analyse whether children with and without cognitive problems differed with regard to medical characteristics, Mann-Whitney U tests and Chi-square tests were used. Multivariate linear regression analysis with stepwise backward variable elimination was performed to explore risk factors (gender, length of stay in PICU, length of artificial ventilation, risk of mortality, age at follow-up and at PICU admission) for cognitive function. Finally, the relationship between cognitive function, HRQoL, anxiety and depression was analysed by calculating Spearman rank correlations.

Bonferroni correction was carried out in order to compensate for multiple testing. A significance level of p<0.005 was used in all tests, except for comparisons of patient characteristics. In these tests (participants versus non-participants), p<0.05 was used as the significance level.

**Results**

**Participants**
From 1995 through 2004, 124 previously healthy patients survived admission to our PICU with septic shock and inotropic and/or vasoconstrictive support for ≥ 24 hours. Of these 124 patients, 82 children were aged ≥ 8 years at the time of the follow-up study. Seventeen of these patients were lost to follow-up. Sixty-five children were invited to participate in the study. Fifty of these 65 children (77%) completed the questionnaires. Eight patients refused participation (for geographical reasons or lack of interest). Seven patients’ data were missing due to language problems or incomplete questionnaires. (Figure 1) No statistically significant differences were found between patient characteristics of participants (n=50) and non-participants (n=32). Mean follow-up time was 6.5 years, with a range of 1.5 to 10.1 years. (Table 1) No
statistically significant differences were found between participants and non-participants with regard to causative organisms and number, duration and dosages of vasoactive agents (Data not shown). We have no information on the number of children with meningitis and septic shock.

HRQoL
Fifty children completed the KIDSCREEN-52. No statistically significant differences were found in HRQoL in the 31 children and the 19 adolescents compared to age-related Dutch norm populations. Moderate effect sizes were found in the 'psychological well being' domain in both age groups; the
study group was shown to have better psychological well being than the norm group. Effect sizes for the other domains were small. (Table 2)

### Psychological function

Fifty children (23 girls, 27 boys) completed the anxiety questionnaire and 48 children (22 girls, 26 boys) completed the depression questionnaire. Overall good psychological function was

### Table 2. HRQoL of survivors of septic shock compared to Dutch norm data

<table>
<thead>
<tr>
<th></th>
<th>Child (n=31)</th>
<th>Norm (n=641)</th>
<th>Adolescent (n=19)</th>
<th>Norm (n=1270)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>Effect size</td>
<td>M (SD)</td>
<td>Effect size</td>
</tr>
<tr>
<td>Physical well being</td>
<td>59.2 (11.2)</td>
<td>0.2</td>
<td>57.3 (9.5)</td>
<td>52.5 (13.8)</td>
</tr>
<tr>
<td>Psychological well being</td>
<td>60.5 (9.1)</td>
<td>0.5</td>
<td>55.7 (9.1)</td>
<td>57.3 (9.1)</td>
</tr>
<tr>
<td>Moods and emotions</td>
<td>56.4 (11.1)</td>
<td>0.4</td>
<td>52.5 (9.5)</td>
<td>52.5 (9.1)</td>
</tr>
<tr>
<td>Self-perception</td>
<td>61.6 (9.8)</td>
<td>0.4</td>
<td>57.4 (9.8)</td>
<td>51.0 (9.4)</td>
</tr>
<tr>
<td>Autonomy</td>
<td>56.2 (9.5)</td>
<td>0.0</td>
<td>56.5 (8.6)</td>
<td>55.7 (7.3)</td>
</tr>
<tr>
<td>Parent relations and home life</td>
<td>58.4 (8.6)</td>
<td>0.3</td>
<td>55.5 (8.4)</td>
<td>54.8 (6.7)</td>
</tr>
<tr>
<td>Financial resources</td>
<td>51.9 (10.7)</td>
<td>0.1</td>
<td>51.4 (10.6)</td>
<td>56.1 (7.0)</td>
</tr>
<tr>
<td>Peers and social support</td>
<td>55.0 (10.8)</td>
<td>0.2</td>
<td>53.1 (9.1)</td>
<td>55.0 (7.1)</td>
</tr>
<tr>
<td>School environment</td>
<td>59.0 (11.1)</td>
<td>0.1</td>
<td>58.4 (10.2)</td>
<td>53.0 (9.7)</td>
</tr>
<tr>
<td>Bullying</td>
<td>48.0 (11.4)</td>
<td>0.0</td>
<td>48.1 (11.0)</td>
<td>47.0 (9.0)</td>
</tr>
</tbody>
</table>

Higher scores represent better HRQoL. M (SD) mean (Standard deviation).

*p<0.005 study group versus norm data.

### Table 3. Anxiety, depression and cognitive function compared to Dutch norm data.

<table>
<thead>
<tr>
<th></th>
<th>All children with septic shock</th>
<th></th>
<th>Norm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n M (SD) Effect size M (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxietya</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>23 28.3 (6.7)* 0.7 33.0 (6.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>15 29.1 (7.2) 0.6 33.4 (6.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>8 26.9 (5.8) 0.9 32.5 (6.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>27 28.2 (6.1) 0.3 30.0 (6.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>22 27.6 (6.3) 0.7 31.2 (5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>5 31.0 (4.1) 0.4 28.7 (6.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressionb,c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>22 5.1 (4.1)* 0.6 9.3 (6.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>15 5.4 (4.4)* 0.5 8.9 (6.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>7 4.5 (3.5)* 1.0 10.5 (6.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>26 5.5 (4.1)* 0.5 8.2 (5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>21 5.5 (4.5)* 0.5 8.4 (5.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>5 5.4 (2.1) 0.5 7.7 (4.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive functiond</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child</td>
<td>31 25.2 (4.9)* 0.8 28.4 (3.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescent</td>
<td>19 27.3 (3.0) 0.1 27.6 (4.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Anxiety scores range from 20-60: higher scores represent more anxiety

b Depression scores range from 0-54: higher scores represent more depression

c One girl and one boy did not fill in the depression questionnaire

d Cognitive function scores range from 0-32: higher scores represent better HRQoL

*p<0.005 study group versus norm data. M (SD) Mean (Standard deviation)
determined. No statistically significant differences were found in the anxiety scores. Girls surviving septic shock reported less anxiety compared to the Dutch norm population. Statistically significant differences were found in all depression scores except in boys attending secondary school (≥13 years of age). Children surviving septic shock reported less depression compared to the Dutch norm population. Moderate and large effect sizes were found for all anxiety and depression scores except for anxiety scores in boys attending secondary school (Table 3).

**Cognitive function**

Fifty children completed the cognitive scale of the TACQOL-CF. However, only 45 children (≤15 years) were compared with norm data. Children reported significantly worse cognitive function compared to the norm population. Adolescents reported scores comparable to the norm population. Twenty (44%) of the 45 children reported scores lower than the 25th percentile of the norm population, indicating cognitive problems.

**Education**

Thirty-seven participants (15 girls, 22 boys) attended primary school at the time of the follow-up study, while 13 (8 girls, 5 boys) attended secondary school. Five (14%) of the primary school students and two (15%) of the secondary school students visited schools for special education. In total, 7 out of 50 (14%) of children attended special education schools. In the Dutch population, generally 3% of children and 3.5% of adolescents attend special education schools. (Data from Dutch Health Statistics, www.cbs.nl). The number of children attending special education at primary school (t=1.845, df=36, p=0.073) and adolescents at secondary school (t=1.172, df=11, p=0.266) did not significantly differ with the general Dutch population.

**Table 4.** Patient characteristics of children with and without self-reported cognitive problems.

<table>
<thead>
<tr>
<th></th>
<th>Children with cognitive problems (n=20)</th>
<th>Children without cognitive problems (n=25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of child at PICU admission (yrs)</strong></td>
<td>1.8 (0.0-7.0)</td>
<td>5.0 (0.1-17.0)*</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Length of stay in PICU (days)</strong></td>
<td>6.5 (2.0-15.0)</td>
<td>4.0 (2.0-35.0)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Length of artificial ventilation (days)</strong></td>
<td>5.0 (0.0-14.0)</td>
<td>2.0 (0.0-25.0)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Risk of Mortality, PIM2 (%)</strong></td>
<td>9.2 (1.1-26.2)</td>
<td>6.5 (1.0-26.1)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Age of child at follow-up study (yrs)</strong></td>
<td>9.7 (8.1-13.0)</td>
<td>12.0 (8.0-20.4)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Highest creatinine in PICU (μmol/l)</strong></td>
<td>60.0 (18.0-227.0)</td>
<td>55.5 (26.0-296.0)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Highest lactate in PICU (mmol/l)</strong></td>
<td>3.1 (0.7-16.4)</td>
<td>3.0 (0.8-23.0)</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>10 (50.0)</td>
<td>9 (36.0)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Physical sequelae (yes)</strong></td>
<td>9 (45)</td>
<td>6 (24)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Artificial ventilation (yes)</strong></td>
<td>15 (75.0)</td>
<td>17 (68.0)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Note children with cognitive problems scored <25% of the norm population.

*p<0.005 children with compared to children without self-reported cognitive problems
Chapter 6

**Table 5.** Correlations between cognitive function and HRQoL domains, anxiety and depression in 45 children.

<table>
<thead>
<tr>
<th>Cognitive function correlations</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRQoL</td>
<td></td>
</tr>
<tr>
<td>Physical well being</td>
<td>0.351</td>
</tr>
<tr>
<td>Psychological well being</td>
<td>0.375</td>
</tr>
<tr>
<td>Moods and emotion</td>
<td>0.568*</td>
</tr>
<tr>
<td>Self-perception</td>
<td>0.335</td>
</tr>
<tr>
<td>Autonomy</td>
<td>0.363</td>
</tr>
<tr>
<td>Parents relation and home life</td>
<td>0.483*</td>
</tr>
<tr>
<td>Financial resources</td>
<td>0.274</td>
</tr>
<tr>
<td>Peers and social support</td>
<td>0.396</td>
</tr>
<tr>
<td>School environment</td>
<td>0.367</td>
</tr>
<tr>
<td>Bullying</td>
<td>0.610*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-0.359</td>
</tr>
<tr>
<td>Depression</td>
<td>-0.581*</td>
</tr>
</tbody>
</table>

*significant at p<0.005

**Risk factors for cognitive problems**

Children who reported cognitive problems were significantly younger at PICU admission compared to children without cognitive problems. (Table 4) A backward regression analysis for cognitive function showed a final model ($R^2=0.13$, $F=6.5$, $p=0.015$) with one significant risk factor: age of the child at PICU admission ($B=0.59$, 95% CI 0.1-1.1, $p=0.015$). No statistically significant correlations were found between follow-up time and HRQoL, anxiety, depression and cognitive function. (Data not shown)

**Relationship between cognitive function and HRQoL, anxiety and depression**

Children and adolescents who reported worse cognitive function had significantly more negative emotions, more problems with their parents, and reported significantly more bullying, higher anxiety, and depression scores compared to children who reported better cognitive function. (Table 5)

**Discussion**

This is one of the first studies to describe self-reported HRQoL, psychological function and cognitive function of children surviving septic shock. HRQoL, anxiety, and depression scores of children who survived septic shock are on average better or similar to the scores of children and adolescents of the same age and gender in the general Dutch population. However, cognitive function, as reported by the children themselves, is worse in septic shock survivors compared to the norm population. A younger age of the child at PICU admission is associated with lower
cognitive function. In addition, a larger number of septic shock-surviving children, although not significant, attend special education schools.

Studies in adult survivors of severe sepsis and septic shock showed HRQoL outcomes similar to those in other adults surviving ICU admission, but lower than the general population. (2) Studies focusing on HRQoL after surviving pediatric septic shock are scarce. (13;14) In contrast with our findings, HRQoL is decreased in the physical domains of these studies. The severity of illness and chronic complaints negatively affect HRQoL. (13;14) One study focusing on HRQoL in children surviving bacterial meningitis showed a lower HRQoL compared to the general population, especially in children with worse cognitive function due to the meningitis. (21) Since most effect sizes were small to moderate in this study, the clinical importance of these differences in HRQoL are relative. Similar to our findings, several studies in pediatric oncology show better or comparable HRQoL, anxiety and depression scores compared to the norm population. (35;36) Patients confronted with a life-threatening disease are faced with the necessity to accommodate to the illness. Two mechanisms describing adaptation to stressful events give a possible explanation for this positive outcome: (1) the concept of posttraumatic growth, defined as 'the experience of significant positive change arising from the struggle with a major life crisis;' and (2) the concept of response shift, defined as 'the experience of hardship changing the internal standard of patients, resulting in changes in the meaning of self-evaluation and hence in a possibly different experience of problems and values.' (37;38) These two mechanisms describe a process of adaptation to trauma, leading to a possible change for better-perceived HRQoL and decreased scores for anxiety and depression questionnaires. We do not know how parental perceptions of the child surviving influences children's psychological function. More detailed studies focusing on these mechanisms are needed in children surviving critical illnesses.

Few studies describe psychological adjustment in PICU survivors after discharge. (16;39) PICU admission is associated with emotional, behavioural and psychiatric symptoms. In contrast with these findings, anxiety and depression scores in our study group were similar to or even better than normative data from the Dutch population. Our results are difficult to compare with these earlier studies considering the differences in follow-up time.

Almost half (42%) of the children studied reported cognitive function problems and 14% of the children attended special education schools. Cognitive function problems are especially reported by children who were younger at the time of PICU admission. In the present study cognitive function was measured with a short self-report questionnaire. Yet, diagnostic clarification and grading of clinical severity of cognitive disorders should be evaluated by comprehensive neuropsychological testing. These tests are designed to examine a variety of cognitive abilities, including speed of information processing, attention, memory, language, and executive functions. Neuropsychological testing of PICU survivors is only done in specific diagnostic groups, such as survivors of traumatic brain injury or bacterial meningitis. (21;40) In one case-control study, the neurodevelopmental outcome in 115 children 10 years after meningococcal disease was determined. Four of these survivors had major problems, 18 had moderate problems, and 22 had one or more minor problems. In the study only one third of the children were severely ill, necessitating PICU
admission. (19) Since PICU patient survival from septic shock has increased considerably and risk factors for cognitive problems are hypoperfusion, hypoxia, sepsis and inflammation, evaluation of the cognitive function of these patients is important. (20;41) Since we did not include a control group, it is not clear whether there is an association between cognitive problems and sepsis in our patients. On the other hand, a recent follow-up study on HRQoL in a heterogeneous group of PICU survivors shows no cognitive impairment in 27 children (8-15 years) admitted for a broad range of diseases (e.g. asthma, trauma, meningococcal disease, cardiac failure). (12) These findings could suggest that children with septic shock are at risk for developing cognitive problems. Moreover, this study indicates that the younger brain is probably more vulnerable. (42) However, only 13% of the variance was explained with the linear regression model. Strong conclusions are therefore not possible. The possible risk factors (e.g. meningitis) and pathophysiologic mechanisms mediating cognitive dysfunction need to be analysed in larger populations in future studies. (20)

Cognitive function problems, as evaluated by the children themselves, is associated with more depressive moods, bullying and depression in the current study despite the fact that HRQoL and depression in the whole study group were comparable with the norm population. Children with cognitive function problems may adapt less well to stressful events and may be more vulnerable to other problems than children without cognitive function problems. Prospective follow-up studies with adequate neuropsychological testing are necessary to evaluate cognitive function and risk factors (before, during and after PICU admission) for cognitive function problems. (43;44) Awareness of long-term sequelae may result in supportive programs after discharge, as is the case for neonatal and trauma patients. (45;46)

A number of limitations to this study should be taken into account. First, this is a retrospective study in one centre with no control group. The response rate of our study was 77%. Although other follow-up studies in the PICU have had similar response rates, this may have biased our results. In addition, no statistically significant differences were found between patient characteristics of participants and non-participants. However, there is a trend (p<0.1) that the majority of the participating children were younger and admitted for a longer period of time compared to the non-participating children. This could have resulted into selection bias by excluding the older cases admitted shorter. Second, the number of studied children is relatively small, and due to different ages, gender and follow-up times, strong conclusions are difficult. However, a case control study matched on age, gender, follow-up time, and admitted to the hospital or PICU would be interesting. Third, seven children were excluded because they did not complete the Dutch questionnaire adequately due to language barrier. Our results therefore cannot be extrapolated to all ethnic and cultural groups living in the Amsterdam region. Fourth, cognitive function was evaluated by self-reporting and was not objectified by standardized neuropsychological tests; younger children (<8 years of age) were not evaluated. Future research should evaluate cognitive function in all pediatric septic shock survivors with standardized neuropsychological tests. Besides, pre-morbid health status is likely an important factor, but is difficult to assess. (47) Finally, the definition of children as being ‘at risk’ for a cognitive problem was based on the value of the 25th percentile of the domain in the norm population. Because there is no gold standard comparison, the cut-off point may seem
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quite arbitrary. This method, however, compared to contrasting means, reveals clear differences between our study group and healthy controls. Despite these limitations, this is one of the few studies that provides insight into psycho-social behaviour of pediatric septic shock survivors. The fact that the majority of these survivors matches or even surpasses the general population in HRQoL, anxiety and depression scores and the indication of cognitive problems in young survivors are noteworthy and require further discussion and research.

Suggestions for future research

Cohort case-control studies of PICU survivors evaluating patient outcomes (physical, psychological and cognitive sequelae, and quality of life) and risk factors for sequelae (before, during and after PICU admission) are essential. Awareness of long-term sequelae and their risk factors may result in changes in treatment during the acute phase and in supportive programs after discharge. (48;49) Long-term follow-up clinics of PICU survivors and rehabilitation programs comparable with follow-up care in neonatal and trauma patients should be developed to detect, support and treat children with cognitive, developmental and psychological problems. These programs are expected to improve daily life and minimize the impact on children’s well-being and future development. (45;46)

Conclusion

In this group of septic shock survivors HRQoL, anxiety and depression were better or equal compared to the age-related Dutch norm population. Apparently, children are able to overcome the stressful experience of septic shock. Children admitted at a younger age especially reported cognitive function problems. Prospective follow-up studies with adequate neuropsychological testing and information on risk factors such as meningitis are warranted to evaluate the association between septic shock, cognitive function and risk factors for cognitive problems.

References

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