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Long-term Neurobehavioral and Quality of Life Outcomes of Critically Ill Children after Glycemic Control

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Abstract

Objectives—To investigate adaptive skills, behavior, and quality health-related quality of life (HRQoL) in children from 32-centers enrolling in the Heart And Lung Failure-Pediatric INsulin Titration (HALF-PINT) randomized control trial.

Study design—This prospective longitudinal cohort study compared the effect of 2 tight glycemic control ranges [lower-target: 80–100 mg/dL vs. higher-target: 150–180 mg/dL] on one-year neurobehavioral and HRQoL outcomes. Subjects had confirmed hyperglycemia and cardiac and/or respiratory failure. Patients aged 2 to 16 years old enrolled between April 2012 and September 2016 were studied one-year post-ICU discharge. The primary outcome, adaptive skills, was assessed using the Vineland Adaptive Behavior Scale (VABS-II). Secondary behavior and HRQoL outcomes were assessed using the Pediatric Quality of Life (PedsQL) and Child Behavior Checklist (CBCL) at baseline and one-year follow-up. Group differences were evaluated using regression models adjusting for age category, baseline overall performance, and risk of mortality.

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[*]List of additional members of the HALF-PINT trial study investigators is available at www.jpeds.com (Appendix)

The authors declare no conflicts of interests.

Results—Of 369 eligible children, 358 survived post-hospital discharge and 214 (60%) completed follow-up. One-year VABS-II Composite scores were not different (mean [standard deviation], 79.9 [25.5] vs. 79.4 [26.9], lower- vs higher-target, $P = .20$). Improvement in PedsQL Total Health from baseline was greater in the higher-target group (adjusted mean difference, 8.2, [95% confidence interval, 1.1–15.3], $p=0.02$).

Conclusions—One-year adaptive behavior in critically ill children with lower- vs. higher-target glycemic control did not differ. The higher-target group demonstrated improvement from baseline in overall health. This study affirms the lack of benefit of lower glucose targeting.

Trial registration—ClinicalTrials.gov: NCT01565941

Clinical management of patients with critical illness-associated hyperglycemia has evolved, provoking questions about the outcomes of patients managed with glycemic control. After initial reports of reduced mortality[2] and morbidity,[3,4] subsequent multicenter trials demonstrated no such benefit.[5–7] Follow-up analysis of the largest trial[8] and meta-analyses[9–11] have called attention to the potential for harm from hypoglycemia. Glucose control has the potential for inducing neurologic injury. The mammalian brain is an obligate glucose user requiring a continuous supply.[12] This is especially true for the developing brain which undergoes a maturational up regulation of the glucose transporter protein.[13] Tight glycemic control presents the risk of inducing hypo-glycorrhachia and neuronal injury.[13] Because of these risks, assessment of long-term neurological function is an important outcome of these trials.

We report an *a priori* aim of the Heart And Lung Failure-Pediatric INsulin Titration trial (HALF-PINT)[1,14] of tight glycemic control in critically ill children. We studied the long-term neurobehavioral (adaptive skills and behavior) and Health Related Quality of Life (HRQoL) outcomes one-year after pediatric intensive care unit (PICU) discharge. Patients were hyperglycemic (two blood glucose measurements ≥150 mg/dL [8.3 mmol/L]) infants and children with cardiac and/or respiratory failure treated with lower-target (80–110 mg/dL [4.4–6.1 mmol/L]) vs. higher-target (150–180 mg/dL [8.3–10.0 mmol/L]) glycemic control. PICU-free days and mortality did not differ between lower- and higher-target groups. Hypoglycemia (<60 mg/dL [<3.3 mmol/L]) occurred more frequently in the lower-target group.[1] Therefore, an additional aim was to determine the effect of any hypoglycemia on outcomes.

METHODS

Institutional review and clinical conduct of the study were coordinated by the Institutional Review Board and Clinical Coordinating Center at Boston Children's Hospital.[1,14] Outcome assessments were performed by a Neurobehavioral Research Team from the Gertrude Sergievsky Center at Columbia University Medical Center. Data analysis was performed by the Data Coordinating Center at Boston Children's Hospital.[1] Appropriate reliance and data use and safe exchange of protected health information agreements were enacted.

HALF-PINT was a randomized trial (ClinicalTrials.gov: NCT01565941) that enrolled patients with confirmed hyperglycemia from April 2012 through September 2016.[1] The

glycemic control methodology of the HALF-PINT trial has been previously described in detail.[14] A total of 35 centers were approved to enroll patients but the trial was stopped early based on recommendations from the data and safety monitoring board. Three centers were not enrolling patients at stoppage. The study protocol involved the use of continuous glucose monitoring, an explicit treatment protocol, and maintenance of a minimal glucose infusion rate as safety measures.[14] Patients eligible for the follow-up study were aged 2 to 16 at the time of enrollment, received the HALF-PINT protocol, and spoke English or Spanish. Patients were excluded from follow up if they did not survive, were under the care of persons with insufficient knowledge about regular behavior to complete assessment, or for whom consent was withdrawn.

After randomization and during the first week of stay, parents or guardians were asked to complete baseline assessments when acclimated to the PICU. Assessments included age-appropriate Pediatric Quality of Life Version 4.0-Short Form (PedsQL)[15] and Child Behavior Checklist (CBCL)[16] instruments. Parents were asked to represent their child's pre-hospitalization baseline condition. Parents also completed demographic and socioeconomic questionnaires. Gross performance was assessed by bedside staff using the Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scores.[17] Severity of illness was assessed by the Pediatric Risk of Mortality (PRISM) III-12 score.[18]

The Neurobehavioral Research Team was notified of eligible patients bimonthly. Email and postcard reminders were sent to parents or guardians at nine months. At eleven months post-PICU discharge, parents were contacted to schedule a telephone interview. Outcome assessments were conducted up to thirteen months post-PICU discharge. Interviews were conducted on weekdays, weekends, and evenings at the parent's convenience. The duration of interviews was two to three hours and, for some, was accomplished over two telephone calls. Parent report forms were used for all study measures. All members of the Neurobehavioral Research Team were trained by a co-investigator and were blinded as to treatment group. Parent report forms were separately scored by two research assistants; discrepancies were adjudicated by the training co-investigator. Validated Spanish language translation forms were used and Spanish-speaking research assistants conducted all interviews with Spanish-speaking parents.

One-Year Assessments

Neurobehavioral outcomes assessing adaptive skills, behavior, and HRQoL were examined. The primary outcome for the study was the Adaptive Behavior Composite score of the Vineland Adaptive Behavior Scales, Second Edition-Survey Interview (VABS-II).[19] The VABS-II was chosen as the primary outcome measure because it is a single validated instrument (Cronbach alpha ≥ 0.95 for Adaptive Behavior Composite across all pediatric ages) and is sensitive to detect changes in a variety of populations.[20] The VABS-II assesses adaptive behaviors in three primary domains, Communication, Daily Living Skills, and Socialization.[19] For children younger than 7 years, a Motor Skills domain is added.

Additional measures included the age-appropriate PedsQL[15] and CBCL[16] checklists. These were administered at baseline and follow-up. The PedsQL is a 15-question form that

assesses four domains (Physical, Emotional, Social, and School Functioning). Four age-appropriate forms of the PedsQL were used – ages 2 through 4, 5 through 7, 8 through 11, and 12–18 years (Cronbach alpha ≥ 0.88 for all ages for Total Score). Summary Total Health, Physical Health and Psychosocial Health scores were calculated with Psychosocial Health comprised of the last three of the above named domains. The primary outcome variable for the PedsQL was the Total Health score with higher scores indicating better HRQoL. In defining impairment, we used the findings of a previous study of HRQoL in PICU survivors[21] as PedsQL Total, Physical or Psychosocial Health scores more than 1 SD below a population mean.[22]

The CBCL is a comprehensive checklist that assesses Total Problems with behavior as well as two broad-band scores, Internalizing and Externalizing Problems comprised of multiple age-dependent subscores.[16] Two age-appropriate forms of the CBCL were used – ages 1.5 through 5 years and 6–18 years (Cronbach alpha 0.90 and 0.97 for Total Problems, respectively). For children aged 6 to 18, two questions concerned the existence of self-harming behaviors or suicidal ideation/attempts. If these questions were answered in the affirmative, site-investigators were informed and required to contact primary care physicians for referral for appropriate counseling. CBCL raw scores were converted into T-scores. At-risk behavior was defined as a T-score greater than 65.[16] The primary outcome variable was the Total Problems score.

Statistical Analyses

Our original target sample size of 378 (189 per group) provided 90% power to detect a one-third standard deviation (SD) effect size (5-point difference) between groups in the VABS-II Adaptive Behavior Composite score using a two-sided 0.05 level test. Due to early stopping of the HALF-PINT trial these calculations were revised based on our final per-protocol sample size of 698. A revised target sample size of 214 patients (107 per group) provided 80% power to detect an effect size of 0.38 SD units (6-point difference).

For patients with an age-appropriate interview at one-year post-PICU discharge, overall adaptive functioning, HRQoL, and behavioral problems were evaluated. For patients who completed both baseline and one-year post-ICU discharge PedsQL and CBCL, the change in score was calculated. Only patients with complete data sets for both time points were included in the paired analysis; whereas all data points are shown for unpaired analyses at baseline and one-year post-ICU times. Subsequent analyses also compared the outcomes between patients who experienced hypoglycemia (any blood glucose <60 mg/dL [3.3 mmol/L]) and those who did not. Group comparisons used linear and logistic regression adjusted for age group (2 to 6 years vs. 7 years and greater), baseline POPC>1 vs. POPC=1, and PRISM III-12 for continuous and binary outcomes, respectively. These adjustments were made to account for age-related differences in carbohydrate requirements, baseline overall functioning, and severity of illness, respectively. Pre- and post-randomization demographic and clinical characteristics were compared between patients with follow-up and those without and between target groups. Differences between groups were evaluated by Wilcoxon rank-sum tests and Fisher exact tests for continuous and categorical variables, respectively, except with t-tests for baseline PedsQL and CBCL T scores. All *p* values are

two-tailed and have not been adjusted for multiple comparisons. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

A total of 713 patients were randomized by the 32 participating HALF-PINT sites (Figure). Of these, 94 died prior to hospital discharge and 15 underwent randomization but were not treated per-protocol. Of the remaining patients, 358 eligible patients survived post-hospital discharge and 214 (60%) families participated in follow-up, 102 from the lower-target and 112 from the higher-target group. Reasons that follow-up was not completed are described in Table I (available at www.jpeds.com). Families that participated in follow-up had a lower proportion in the lowest income category (45 of 162 [28%]) compared with families that did not participate (46 of 106 [43%], p=0.02). Maternal education was higher for families that participated in follow-up with 129 of 192 families (67%) reporting more than a high school diploma (p=0.046). Mean CBCL Total Problems (49.2 [SD, 11.8] vs. 46.2 (12.3], p=0.03) and Internalizing Problems (50.8 [10.7] vs. 47.7 [11.2], p=0.02) T-scores differed between those who were studied and those who were not (Table 2; available at www.jpeds.com). Post-randomization clinical factors were similar between groups (Table 2).

Baseline Neurobehavioral and HRQoL Status

Pre-randomization characteristics were similar between groups with slight differences in baseline cognitive and overall performance (Table 3; available at www.jpeds.com). The lower-target group had fewer patients with poorer overall performance (POPC, 31% [95% confidence interval {CI}, 23%−41%] vs 46% [36%−55%], p=0.04) and nonsignificantly poorer cognitive performance (PCPC, 28% [20%−38%] vs 41% [32%−51%], p=0.06) compared with the higher-target group. Lower mean baseline PedsQL Total Health (69.8 [SD, 20.8] vs. 77.4 [19.3], p=0.01) and Psychosocial Health (73.0[19.8] vs. 79.3 [17.1], p=0.03) were reported for higher vs. lower-target groups, respectively. Baseline CBCL Total Problems and subscale T-scores did not differ. Baseline PedsQL and CBCL subscale scores are described in Table 4 (available at www.jpeds.com). Post-randomization factors related to tight glycemic control differed between the lower- and higher-target groups. Percent of patients treated with insulin (p<0.001) and number of episodes of any hypoglycemia (p=0.005) were greater for the lower-target group (Table 3). Median time-weighted blood glucose average (110 [interquartile range {IQR}, 105–120] vs. 124 [IQR, 111–146 mg/dL], lower- vs. higher-target group) and percent time-in-target range (54 [IQR, 42–66] vs. 91 [IQR, 82–96], lower- vs. higher-target group) were greater for the higher-target group (p<0.001 for both comparisons). More patients in the lower-target group (6 of 102 patients [6%]) experienced an episode of severe hypoglycemia (<40 mg/dL [<2.2 mmol/L]) as compared with the higher-target group (1 of 112 patients [<1%], p=0.06). Post-randomization characteristics not related to tight glycemic control (PICU-free days, ventilator-free days, or POPC) did not differ. Median time to follow-up interview was 12.3 months (IQR, 11.5–13.3 months) with no difference in time to follow-up for the lower- vs. higher-target groups (Table 3).

One-year Neurobehavioral and HRQoL Status

Table 5 describes the long-term outcomes. Mean one-year VABS-II Adaptive Behavior Composite scores were not significantly different for lower- vs. higher-target patients (79.9 [SD, 25.5] vs. 79.4 [26.9], p=0.20). Moreover, percent of patients in each adaptive level did not differ. Total, Psychosocial, or Physical Health scores were similar between groups. CBCL T-scores did not differ between groups for the Total Problems or broad-band scores. Percent of patients at risk did not differ (Table 5). Between group comparisons for the PedsQL and CBCL subscale scores did not differ with the exception of one CBCL subscale score in one age category (Table 6; available at www.jpeds.com).

In the higher-target group, mean PedsQL Total Health improved from 69.7 (SD, 20.9) at baseline to 76.4 (20.5) at one-year. The change from baseline was greater in the higher- as compared with the lower-target group (adjusted mean difference, 8.2 [95% CI, 1.1–15.3, p=0.02). This improvement in Total Health could be ascribed to improvement in mean Psychosocial Health which changed from 72.8 (SD, 19.9) at baseline to 81.9 (18.3) at one-year for the higher-target group [adjusted mean difference of 8.5 (95% CI, 1.7–5.3, p=0.01)] between higher-target and lower-target groups. No differences in the change from baseline performance in the CBCL Total Problems T-score or the two broad-band scores were observed between target groups (Table 7).

Status by Hypoglycemia Experience

Table 8 describe the outcomes for patients who experienced any hypoglycemia in the trial and those who did not. VABS-II Adaptive Behavior Composite, VABS-II subscale scores, or CBCL Total Problems or broad-band T-scores were similar between groups. However, PedsQL Physical Health scores were lower for those with any hypoglycemia (adjusted mean difference, −13.9 [95% CI, −27.9–0.1], p=0.05). The proportion with impairment on the PedsQL Psychosocial subscale was greater in those who experienced any hypoglycemic event (p=0.04). Only seven patients in the follow-up cohort experienced severe hypoglycemia (<40 mg/dL [<2.2 mmol/L]). These numbers are insufficient to make comparisons concerning severity of hypoglycemia.

DISCUSSION

In this study of lower- vs. higher-target tight glycemic control in children 2 years of age and older, one-year neurobehavioral (adaptive skills and behavior) and HRQoL outcomes were not significantly different. These results support the safety of glycemic control, especially with the use of explicit protocols, close glucose monitoring, and provision of minimal carbohydrate supply.[14] Improvement in psychosocial performance was noted at one-year in the higher-target group suggesting that higher-targeting may be the preferred range. However, these results should be interpreted cautiously given differences noted in baseline functioning. Finally, deleterious effects in physical health and incidence of psychosocial impairment were associated with any episode of hypoglycemia underscoring the possibility of long-term dysfunction with glucose deprivation of the brain during critical illness. The HALF-PINT trial had a lower rate of hypoglycemia than found in other trials[2,3,5,7,23] or than occurs spontaneously in a similar PICU population.[24] Viewed from a wider context, these

results affirm the lack of benefit of lower-target tight glycemic control and underscore the potential for harm with hypoglycemia.

To date, there have been over 20 observational and randomized trials of tight glycemic control in children and adults. Meta-analyses of these differ slightly in that some suggest no mortality benefit for adults[10] or children,[9,25] whereas another demonstrates higher mortality with lower targets in adult subpopulations.[11] These studies are in agreement, however, that targeted glycemic control confers a risk of hypoglycemia.[9,11,25] Outcomes of critically ill infants and children managed with tight glycemic control have been studied in limited fashion. One-year follow-up of children in a multi-center United Kingdom study demonstrated no difference in mortality between lower- and higher-target groups.[23] In the single-center Leuven study of largely postoperative cardiac surgical patients, intelligence and visual-motor skills were lower than normal children but did not differ between those with lower target glucose control vs. usual therapy.[4,26] We previously reported neurodevelopmental outcomes at one-year of age in a neonatal cardiac surgical population and noted compromised intelligence and visual motor-skill levels similar to the Leuven study only among those who had an episode of moderate or severe hypoglycemia. Those without moderate or severe hypoglycemia had substantially higher scores and were, in fact, indistinguishable from normal children.[27]

Our current results are in agreement with the mortality rates of the U.K. study and with our prior results in pediatric cardiac surgery patients. In the current study we found no decrement in behavior or adaptive skills. Glycemic control can be performed safely. Moreover, these results add to the growing body of knowledge on the deleterious effects of hypoglycemia during critical illness. HRQoL may be negatively impacted by such events. Yet, it is not reasonable to conclude that glycemic control should be abandoned altogether, rather only that the low target range (80–110 mg/dL) should be avoided. Hyperglycemia has direct neurotoxic effects, exaggerating brain injury as demonstrated in animal models,[28] and children.[29] Our results support intensive glucose monitoring and provision of minimal carbohydrate supply during insulin therapy and suggest a safer range of glucose targeting in the 150–180 mg/dL range.

That HRQoL deficits at one-year post-PICU discharge are associated with hypoglycemia may be anticipated from the pathology of glucose deprivation. Glucose is an obligatory neuronal fuel and is provided through action of facilitated transporters called GLUTs.[12,13] Consequences of hypoglycemia are neuronal energy run-down, autophagy, and death.[11] The brain can burn alternative fuels, ketone bodies and lactate,[13] and in critical illness elevated catecholamine levels can drive additional fuel provision.[13] However, the use of insulin to achieve tight glycemic control suppresses serum glucose and ketone concentrations and may deprive the brain of both fuels.[30]

A shortcoming of our study is the limited sample size. This was the result of early stoppage of enrollment and difficulties experienced with follow-up contact. We were, however, able to achieve 97% (208/214) of our revised sample size estimate for the primary outcome. The difference in our primary outcome variable observed between groups was very small and not of a clinically relevant magnitude. Concerning recruitment, we attribute the difficulties

experienced in following up subjects to the two to three hour duration of telephone interviews, as well as changed personal contact information. Similar rates of follow-up have been reported in a European[31] population, but higher rates have been achieved with briefer intervals from the index hospitalization,[32] shorter interviews,[32] and with assistance of state-sponsored health care registries.[26] In our study, significant findings were demonstrated despite the fact that the group studied had a higher socioeconomic status implying that the study was biased against finding a difference (Table 2). Finally, although patients who were studied had higher baseline CBCL T-scores, mean scores were normal suggesting that the studied group was representative.

Another shortcoming of this study was the limitation of the study group to children between the ages 2 and 17. This age range was chosen to facilitate the interpretation of the before and after results. We deliberately chose a single study instrument that would remain valid across the entire age range for both baseline and follow up measures. The PedsQL is one of the most widely used measures but it is valid only for children between the ages of two and 18. Similarly, the CBCL is widely used but is limited to children between the ages of 18 months and 18 years. In order to study children less than two, other measures of quality of life and behavior would have been required. This would have limited interpretation of the paired results. We acknowledge that these results cannot be readily extrapolated to infants less than two.

A strength of this study is the variety of outcomes examined. Although no differences were noted between target groups on the VABS-II composite or subscales, a large variance was noted. The proportion with low or moderately low adaptive behavior exceeded 50% of the group, confirming the wide variety of neurobehavioral complications found in PICU populations, and supporting the need for broad-based assessments. Another study strength is the baseline assessment, which enabled a paired analysis essential to detect the protective effect of targeting the higher glycemic range of 150–180 mg/dL.

We found no significant between-group differences in one-year neurobehavioral and HRQoL outcomes in critically ill children randomized to lower- vs. higher-target glycemic control in this multicenter, randomized trial. Improvement from baseline in the psychosocial domain was noted with a higher-target. Deleterious effects in physical health were associated with any episode of hypoglycemia. This study affirms the lack of benefit of lower target glycemic control, upholds the safety of higher targeting, and underscores the potential for harm with hypoglycemia.

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Appendix

HALF-PINT Study Investigator List

The following investigators contributed subjects to the analyses presented in this manuscript.

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The following investigators were instrumental in trial design, oversight, and preparation of this manuscript.

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Study Organization List	
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Other Study Performance Sites	
The following sites obtained approval from their inst itutional ethics review board to conduct the trial, screened patients for eligibility, but did not contribute subjects to the analyses presented in this manuscript.	
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PALISI (http://www.palisi.org) is a network of clinical researchers from more than 90 pediatric intensive care units across the world that develops multicenter trials to improve interventions and outcomes in the care of critically ill children. PALISI provided the HALF-PINT trial with meeting space and support at biannual national meetings for protocol training, trial management, and site recruitment.

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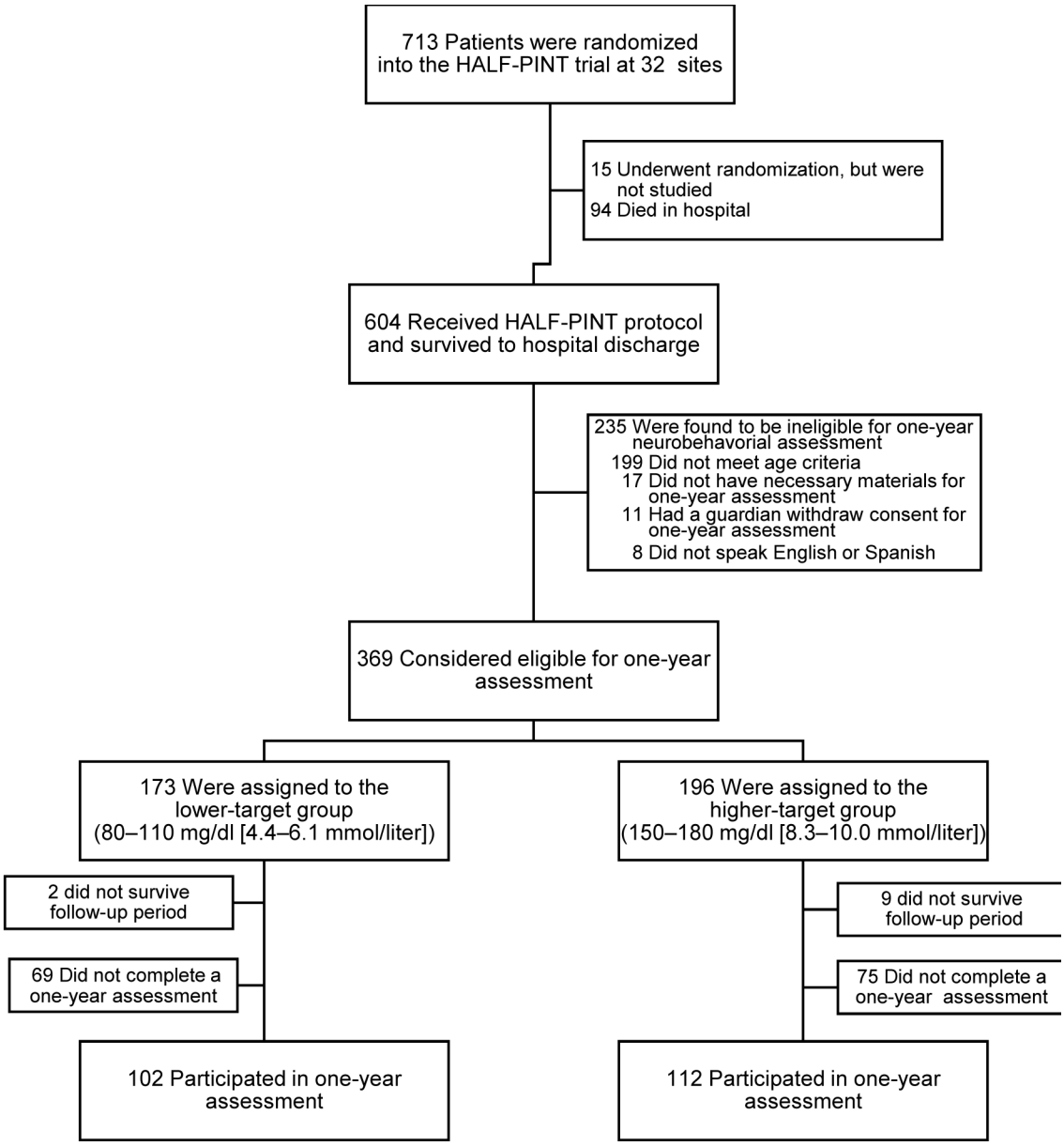

Figure. Eligibility and One-year Follow-up of the Study Patients.

A neurobehavioral or health-related quality of life assessment was available for 60% (214 of 358 eligible patients) of the HALF-PINT study population. Only patients aged 2 to 16 years at the time of randomization were eligible for follow-up. Of the 369 eligible for one-year assessment, 11 (3%) patients did not survive one-year follow-up period.

TABLE 1.

Reasons Patients did not Complete a One-year Assessment According to Study Group *

Reason	Lower Target (*n* = 69)	Higher Target (*n* = 75)
Unsuccessful contact attempts	46 (67)	57 (76)
Parent refusal	18 (26)	14 (19)
Guardianship changed or could not be determined	4 (6)	2 (3)
Staff or procedural error	1 (1)	2 (3)

* Data are *n* (%)

TABLE 2.

Patient Characteristics According to One-year Participation Status

Characteristics	Participated	Did Not Participate	*P* Value *
Pre-randomization	**(*n* = 214)**	**(*n* = 144)**	
Age at ICU admission (yr), median (IQR)	10.1 (5.1–14.1)	8.3 (4.6–13.4)	0.09
Female sex, *n* (%)	106 (50)	73 (51)	0.91
Black race, *n*/ *n* total (%)	46/204 (23)	44/142 (31)	0.08
Hispanic ethnic group, *n*/ *n* total (%)	50/213 (23)	33/144 (23)	1.0
Cognitive performance (PCPC>1), *n* (%)	75 (35)	50 (35)	1.0
Overall performance (POPC>1), *n* (%)	83 (39)	58 (40)	0.83
Any known genetic syndrome, *n* (%)	39 (18)	23 (16)	0.67
Primary reason for ICU admission, *n* (%)			0.40
Respiratory (including infections)	95 (44)	73 (51)	
Cardiovascular (including shock)	36 (17)	22 (15)	
Trauma	24 (11)	19 (13)	
Neurologic	22 (10)	13 (9)	
Following procedure	16 (7)	10 (7)	
Gastrointestinal or liver	12 (6)	6 (4)	
Other	9 (4)	1 (<1)	
PRISM III-12 score, median (IQR)	12 (7–17)	12 (7–19.5)	0.50
Mother's education: High school diploma or lower, *n*/ *n* total (%)	63/192 (33)	57/129 (44)	0.046
Household income, *n*/ *n* total (%)			0.02
<$25,000	45/162 (28)	46/106 (43)	
$25,000-$65,000	55/162 (34)	34/106 (32)	
>$65,000	62/162 (38)	26/106 (25)	
Spanish as primary language, *n*/ *n* total (%)	29/190 (15)	12/128 (9)	0.17
Baseline PedsQL, mean (SD) †			
Total Health	73.6 (20.4)	72.1 (22.1)	0.56
Physical Health	68.6 (34.4)	60.8 (37.9)	0.07
Psychosocial Health	76.1 (18.8)	77.6 (19.0)	0.50
Baseline CBCL T-scores, mean (SD) ≠			
Total Problems	49.2 (11.8)	46.2 (12.3)	0.03
Internalizing Problems	50.8 (10.7)	47.7 (11.2)	0.02
Externalizing Problems	46.6 (10.8)	44.9 (10.0)	0.18
Post-randomization			
Treated with insulin therapy, *n* (%)	169 (79)	113 (78)	1.0
Time-weighted blood glucose average (mg/dL), median (IQR)	115 (107–130)	116 (105–130)	0.66
Time in the target range (% of time), median (IQR)	73.8 (53.8–91.8)	77.4 (58.6–93.5)	0.22
Any hypoglycemia (<60 mg/dL), *n* (%)	24 (11)	20 (14)	0.51
Severe hypoglycemia (<40 mg/dl), *n* (%)	7 (3)	4 (3)	1.0
New seizure, *n* (%)	4 (2)	1 (<1)	0.65

Characteristics	Participated	Did Not Participate	*P* Value *
Pre-randomization	**(*n* = 214)**	**(*n* = 144)**	
Any CPR, *n* (%)	3 (1)	2 (1)	1.0
N ICU-free days through day 28, median (IQR)	21.2 (14.8–25.0)	21.4 (15.3–24.1)	0.91
N ventilator-free days through day 28, median (IQR)	22.2 (17.0–25.3)	22.9 (18.0–25.4)	0.44
N hospital-free days through day 28, median (IQR)	9 (0–17)	12 (0–19)	0.13
Cognitive performance at discharge (PCPC>1), *n*/ *n* total (%)	106/209 (51)	70/134 (52)	0.83
Overall performance at discharge (POPC>1), *n*/ *n* total (%)	127/209 (61)	89/134 (66)	0.30

Abbreviations: CBCL, Child Behavior Checklist; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; IQR, interquartile range; PCPC, Pediatric Cerebral Performance Category; PedsQL, Pediatric Quality of Life Version 4.0 Short Form; POPC, Pediatric Overall Performance Category; PRISM-III 12, Pediatric Risk of Mortality Score III from the first 12 hours of ICU admission; SD, standard deviation.

*P values for comparison between participation status groups were determined using Fisher's exact tests for categorical variables, *t*-tests for PedsQL and CBCLT-scores, and Wilcoxon rank-sum tests for other continuous variables.

†Age-appropriate PedsQL scores available for 173 patients with follow-up interview and 121 patients without follow-up interview.

ǂAge-appropriate CBCL T-scores available for 188 patients with a follow-up interview and 123 patients without a follow-up interview.

TABLE 3.

Characteristics of Study Patients By Study Group [*]

Characteristics	Lower Target (n = 102)	Higher Target (n = 112)
Pre-randomization		
Age at ICU admission (yr), median (IQR)	9.2 (4.8–14.3)	10.6 (6.4–14.0)
Female sex, n (%)	46 (45)	60 (54)
Black race, n/n total (%) [†]	27/99 (27)	19/105 (18)
Hispanic ethnic group, n/n total (%) [†]	24/102 (24)	26/111 (23)
Cognitive performance (PCPC>1), n (%) [‡]	29 (28)	46 (41)
Overall performance (POPC>1), n (%) [‡,§]	32 (31)	51 (46)
Any known genetic syndrome, n (%)	16 (16)	23 (21)
Primary reason for ICU admission, n (%)		
Respiratory (including infections)	48 (47)	47 (42)
Cardiovascular (including shock)	16 (16)	20 (18)
Trauma	14 (14)	10 (9)
Neurologic	10 (10)	12 (11)
Following procedure	4 (4)	12 (11)
Gastrointestinal or liver	6 (6)	6 (5)
Other [¶]	4 (4)	5 (4)
PRISM III-12 score, median (IQR) [**]	12 (7–18)	11 (7–16.5)
Mother's education: High school diploma or lower, n/n total (%)	29/89 (33)	34/103 (33)
Household income, n/n total (%)		
<$25,000	22/75 (29)	23/87 (26)
$25,000-$65,000	25/75 (33)	30/87 (34)
>$65,000	28/75 (37)	34/87 (39)
Spanish as primary language, n/n total (%)	14/88 (16)	15/102 (15)
Baseline PedsQL, mean (SD) [††]		
Total Health [§]	77.4 (19.3)	69.8 (20.8)
Physical Health	73.1 (32.4)	64.3 (35.9)
Psychosocial Health [§]	79.3 (17.1)	73.0 (19.8)
Baseline CBCL T-scores, mean (SD) [‡‡]		
Total Problems	47.8 (12.3)	50.4 (11.2)
Internalizing Problems	49.9 (10.6)	51.6 (10.9)
Externalizing Problems	46.3 (10.6)	46.8 (10.9)
Post-randomization		
Treated with insulin therapy, n (%) [§]	101 (99)	68 (61)
Time-weighted blood glucose average (mg/dl), median (IQR) [§]	110 (105–120)	124 (111–146)
Time in the target range (% of time), median (IQR) [§]	54 (42–66)	91 (82–96)

Characteristics	Lower Target (n = 102)	Higher Target (n = 112)
Any hypoglycemia (<60 mg/dl), n (%)[§]	18 (18)	6 (5)
Severe hypoglycemia (<40 mg/dl), n (%)	6 (6)	1 (<1)
New seizure, n (%)	2 (2)	2 (2)
Any CPR, n (%)	2 (2)	1 (<1)
N ICU-free days through day 28, median (IQR)	22.6 (17.2–25.2)	20.1 (13.7–24.3)
N ventilator-free days through day 28, median (IQR)	23.1 (18.6–25.3)	21.4 (15.2–25.1)
N hospital-free days through day 28, median (IQR)	11 (0–19)	7 (0–16)
Cognitive performance at discharge (PCPC>1), n/ n total (%)[‡]	47/100 (47)	59/109 (54)
Overall performance at discharge (POPC>1), n / n total (%)[‡]	54/100 (54)	73/109 (67)
Time to follow-up interview (mo.), median (IQR)	12.1 (11.5–13.2)	12.3 (11.4–13.4)

Abbreviations: CBCL, Child Behavior Checklist; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; IQR, interquartile range; PCPC, Pediatric Cerebral Performance Category; PedsQL, Pediatric Quality of Life Version 4.0 Short Form; POPC, Pediatric Overall Performance Category; PRISM-III 12, Pediatric Risk of Mortality Score III from the first 12 hours of ICU admission; SD, standard deviation.

[*] Patients in the lower-target group had their blood glucose level controlled to a target range of 80 to 110 mg per deciliter (4.4 to 6.1 mmol per liter), and those in the higher-target group to a target range of 150 to 180 mg per deciliter (8.3 to 10.0 mmol per liter) during their critical care stay. To convert values for glucose to millimoles per liter, divide by 18.

[†] Race and ethnic group were as reported in the medical record.

[‡] The scales for the Pediatric Cerebral Performance Category and Pediatric Overall Performance Category range from 1 to 6, with lower scores indicating less disability.

[§] Denotes a significant difference between target groups at the 0.05 significance level. For PedsQL and CBCL T-scores, *p* values for comparison between target groups were determined using *t*-tests. For other variables, *p* values for comparison between target groups were determined using Fisher's exact tests and Wilcoxon rank-sum tests for categorical and continuous variables, respectively.

[¶] Other includes oncologic, renal, metabolic, and hematologic reasons.

[**] The scale for the Pediatric Risk of Mortality III score from the first 12 hours in the ICU (the PRISM III-12 score) ranges from 0 to 74, with higher scores indicating a higher risk of death.

[††] PedsQL scores range from 0 to 100, with higher scores indicating higher quality of life. Age-appropriate PedsQL scores were available for 85 lower-target patients and 88 higher-target patients.

[‡‡] CBCL T-scores range from 20 to 100, with lower scores indicating the absence of behavioral problems. Age-appropriate CBCL T-scores were available for 89 lower-target patients and 99 higher-target patients.

TABLE 4.

Baseline Subscale Scores According to Study Group

Assessments*	Lower Target	Higher Target	*P value*†
PedsQL	**(*n* = 85)**	**(*n* = 88)**	
Emotional Functioning	82.1 (18.8)	74.6 (23.5)	0.02
Social Functioning	83.7 (18.6)	80.6 (23.6)	0.33
School Functioning‡	70.1 (28.1)	61.4 (32.2)	0.07
CBCL T-scores			
Ages 2 to 5 years old	**(*n* = 31)**	**(*n* = 25)**	
Emotionally Reactive	53.4 (5.4)	52.6 (4.7)	0.57
Anxious/Depressed	53.1 (4.8)	52.2 (3.7)	0.46
Withdrawn	55.0 (6.9)	55.8 (8.7)	0.68
Somatic Complaints	54.1 (5.6)	54.7 (6.2)	0.69
Attention Problems	54.6 (6.9)	52.9 (6.0)	0.32
Aggressive Behavior	52.2 (4.3)	52.1 (3.9)	0.92
Sleep Problems	54.2 (5.5)	54.6 (5.7)	0.82
Ages 6 to 18 years old	**(*n* = 58)**	**(*n* = 74)**	
Anxious/Depressed	52.3 (4.6)	54.3 (8.0)	0.08
Withdrawn/Depressed	55.1 (6.8)	55.9 (8.0)	0.50
Somatic Complaints	57.8 (7.9)	58.0 (8.8)	0.90
Rule-breaking Behavior	53.2 (4.9)	53.3 (5.0)	0.88
Aggressive Behavior	52.9 (5.2)	54.2 (7.2)	0.23
Social Problems	54.5 (5.8)	56.4 (8.3)	0.11
Thought Problems	54.3 (6.5)	56.5 (7.4)	0.07
Attention Problems	54.9 (6.1)	57.2 (9.9)	0.11

Abbreviations: CBCL, Child Behavior Checklist; PedsQL, Pediatric Quality of Life Version 4.0 Short Form.

*Data are mean (standard deviation) unless otherwise noted.

†*P* values for comparison between target groups were determined using *t*-tests.

‡School Functioning scores were not available for 6 (7%) lower-target and 10 (11%) higher-target patients at baseline.

TABLE 5.

One-year Neurobehavioral and Health-related Quality of Life Outcomes By Study Group

Assessments	Lower Target	Higher Target	*P* value*
VABS-II†	**(n = 97)**	**(n = 111)**	
Adaptive Behavior Composite, mean (SD)	79.9 (25.5)	79.4 (26.9)	0.20
Communication	81.5 (25.3)	80.8 (27.5)	0.17
Daily Living Skills	81.2 (27.9)	79.7 (28.2)	0.35
Socialization	83.3 (23.9)	83.1 (24.8)	0.16
Motor Skills	76.1 (28.0)	75.7 (24.9)	0.93
Adaptive Level, n (%)			0.59
High (≥130)	0	1 (<1)	
Moderately High (115–129)	5 (5)	7 (6)	
Adequate (86–114)	41 (42)	44 (40)	
Moderately Low (71–85)	22 (23)	22 (20)	
Low (≤70)	29 (30)	37 (33)	
PedsQLǂ	**(n = 98)**	**(n = 110)**	
Total Health, mean (SD)	74.4 (21.5)	75.6 (20.7)	0.20
Impaired (≤65) n (%)	34 (35)	37 (34)	0.41
Physical Health, mean (SD)	65.8 (36.9)	64.7 (37.3)	0.46
Impaired (≤64) n (%)	39 (40)	47 (43)	0.75
Psychosocial Health, mean (SD)	78.9 (20.2)	81.3 (18.4)	0.16
Impaired (≤63) n (%)	23 (23)	20 (18)	0.16
CBCL T-scores§	**(n = 101)**	**(n = 110)**	
Total Problems, mean (SD)	51.5 (12.0)	51.9 (12.5)	0.96
At risk, n (%)	17 (17)	15 (14)	0.38
Internalizing Problems, mean (SD)	52.2 (11.4)	51.6 (11.8)	0.60
At risk, n (%)	16 (16)	17 (15)	0.86
Externalizing Problems, mean (SD)	49.6 (11.6)	48.9 (10.9)	0.74
At risk, n (%)	11 (11)	11 (10)	0.86

Abbreviations: CBCL, Child Behavior Checklist; PedsQL, Pediatric Quality of Life Version 4.0 Short Form; SD, standard deviation; VABS-II, Vineland Adaptive Behavior Scales-Second Edition.

**P* values for the comparison between target groups were determined using logistic and linear regression adjusting for age category, baseline overall performance (POPC>1), and PRISM-III 12 score for categorical and continuous variables, respectively.

†VABS-II standard scores range from 20 to 160 with mean 100 and SD 15. Motor Skills scores are only available for patients less than 7 years old (32 lower-target, 26 higher-target).

ǂPedsQL scores range from 0 to 100. Patients were considered impaired if they were >1 SD below healthy pediatric population mean scores.

§Child Behavior Checklist T-scores range from 20 to 100. A T-score ≥65 indicates a child is at risk for a clinically relevant problem for the associated syndrome scale.

TABLE 6.

One-year Subscale Scores According to Study Group

Assessments*	Lower Target	Higher Target	*P* Vaue†
PedsQL	**(*n* = 98)**	**(*n* = 110)**	
Emotional Functioning	79.6 (21.8)	82.8 (20.7)	0.16
Social Functioning	82.3 (24.8)	86.1 (22.5)	0.12
School Functioning‡	73.1 (28.8)	73.9 (28.5)	0.57
CBCL T-scores			
Ages 2 to 5 years old	**(*n* = 29)**	**(*n* = 17)**	
Emotionally Reactive	56.9 (8.6)	51.7 (3.2)	0.01
Anxious/Depressed	56.6 (9.2)	53.4 (4.3)	0.14
Withdrawn	58.0 (9.8)	56.4 (9.6)	0.53
Somatic Complaints	56.0 (7.1)	55.8 (6.8)	0.76
Attention Problems	57.8 (8.2)	54.1 (6.8)	0.16
Aggressive Behavior	55.6 (9.4)	52.4 (3.9)	0.16
Sleep Problems	54.5 (7.4)	53.8 (5.3)	0.69
Ages 6 to 18 years old	**(*n* = 72)**	**(*n* = 93)**	
Anxious/Depressed	54.1 (6.8)	54.8 (7.6)	0.35
Withdrawn/Depressed	57.2 (8.8)	57.5 (9.3)	0.84
Somatic Complaints	54.9 (5.9)	56.3 (6.3)	0.15
Rule-breaking Behavior	54.0 (5.9)	53.5 (5.1)	0.64
Aggressive Behavior	54.3 (6.6)	55.0 (6.9)	0.49
Social Problems	57.3 (7.5)	58.3 (8.2)	0.95
Thought Problems	55.3 (7.4)	57.3 (8.2)	0.26
Attention Problems	56.3 (7.7)	58.3 (9.0)	0.23

Abbreviations: CBCL, Child Behavior Checklist; PedsQL, Pediatric Quality of Life Version 4.0 Short Form.

*Data are mean (standard deviation) unless otherwise noted.

†*P* values for the comparison between target groups were determined using linear regression adjusting for age category, baseline overall performance (POPC>1), and PRISM-III 12 score.

‡School Functioning scores were not available for 8 (8%) lower-target and 5 (5%) higher-target patients at the one-year assessment.

TABLE 7.

Baseline and One-year Neurobehavioral and Health-related Quality of Life Outcomes By Study Group *

	Lower Target			Higher Target			
Assessments	**Baseline**	**One-year follow-up**	**Average change in score**	**Baseline**	**One-year follow-up**	**Average change in score**	***P* value†**
PedsQL‡		**(n = 82)**			**(n = 87)**		
Total Health	78.0 (19.0)	75.9 (20.5)	−2.0 (23.5)	69.7 (20.9)	76.4 (20.5)	6.7 (23.9)	0.02
Physical Health	73.3 (32.2)	67.8 (35.6)	−4.7 (39.1)	64.3 (36.1)	65.9 (37.7)	1.6 (38.9)	0.31
Psychosocial Health	80.2 (16.5)	80.0 (18.5)	−0.2 (22.3)	72.8 (19.9)	81.9 (18.3)	9.1 (23.0)	0.01
CBCLT-scores		**(n = 83)**			**(n = 91)**		
Total Problems	48.3 (12.3)	52.0 (11.4)	3.6 (11.6)	50.8 (11.4)	51.7 (13.1)	0.9 (11.0)	0.07
Internalizing Problems	50.3 (10.6)	52.8 (11.1)	2.6 (12.5)	51.6 (11.2)	52.1 (12.5)	0.5 (11.8)	0.18
Externalizing Problems	46.9 (10.5)	49.7 (10.9)	2.8 (11.0)	47.3 (11.2)	48.5 (11.1)	1.2 (9.1)	0.19

Abbreviations: CBCL, Child Behavior Checklist; PedsQL, Pediatric Quality of Life Version 4.0 Short Form.

* Data are mean (standard deviation) unless otherwise noted.

P values for comparing the average change in scores from baseline to one-year follow-up interviews between target groups were determined by linear regression adjusting for age category, baseline overall performance (POPC>1), and PRISM-III-12 score.

‡ Total Health and Physical Health scores are missing for one lower-target patient (n = 81).

TABLE 8.

One-year Neurobehavioral and Health-related Quality of Life Outcomes According to Hypoglycemia Status

Assessments	Any hypoglycemia	No hypoglycemia	P value *
VABS-II †	**(n = 24)**	**(n = 185)**	
Adaptive Behavior Composite, mean (SD)	71.5 (26.8)	80.6 (26.0)	0.42
Communication	74.7 (26.3)	82.2 (26.5)	0.45
Daily Living Skills	71.8 (28.5)	81.6 (27.8)	0.33
Socialization	82.0 (25.6)	83.5 (24.3)	0.68
Motor Skills	72.3 (25.3)	76.9 (26.9)	0.57
Adaptive Level, n (%)			0.62
High (≥130)	0	1 (<1)	
Moderately High (115–129)	1 (4)	11 (6)	
Adequate (86–114)	8 (35)	77 (42)	
Moderately Low (71–85)	3 (13)	41 (22)	
Low (≤70)	11 (48)	55 (30)	
PedsQ ǂ	**(n = 24)**	**(n = 184)**	
Total Health, mean (SD)	67.0 (22.3)	76.1 (20.7)	0.08
Impaired (≤65) n (%)	13 (54)	58 (32)	0.07
Physical Health, mean (SD)	49.2 (38.8)	67.3 (36.4)	0.05
Impaired (≤64) n (%)	14 (58)	72 (39)	0.14
Psychosocial Health, mean (SD)	76.0 (21.9)	80.7 (18.8)	0.30
Impaired (≤63) n (%)	9 (38)	34 (18)	0.04
CBCL T-scores §	**(n = 24)**	**(n = 187)**	
Total Problems, mean (SD)	51.0 (13.3)	51.8 (12.1)	0.65
At risk, n (%)	5 (21)	27 (14)	0.63
Internalizing Problems, mean (SD)	51.5 (14.1)	51.9 (11.3)	0.90
At risk, n (%)	5 (21)	28 (15)	0.47
Externalizing Problems, mean (SD)	46.9 (11.2)	49.5 (11.2)	0.28
At risk, n (%)	2 (8)	20 (11)	0.85

Abbreviations: CBCL, Child Behavior Checklist; PedsQL, Pediatric Quality of Life Version 4.0 Short Form; SD, standard deviation; VABS-II, Vineland Adaptive Behavior Scales-Second Edition.

*P values for the comparison between target groups were determined using logistic and linear regression adjusting for age category, baseline overall performance (POPC>1), and PRISM-III 12 score for categorical and continuous variables, respectively.

†VABS-II standard scores range from 20 to 160 with mean 100 and SD 15. Motor Skills scores are only available for patients less than 7 years old (any hypoglycemia, n = 12; no hypoglycemia, n = 46). Adaptive Behavior Composite was not available for one patient with hypoglycemia (n = 23).

ǂPedsQL scores range from 0 to 100. Patients were considered impaired if they were >1 SD below healthy pediatric population mean scores.

§Child Behavior Checklist T-scores range from 20 to 100. A T-score ≥65 indicates a child is at risk for a clinically relevant problem for the associated syndrome scale.