The Association of Severe Pain Experienced in the PICU and Health-Related Quality of Life Post-Discharge

Mallory B. Smith

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Science

University of Washington

2021

Committee:

Noel S. Weiss

R. Scott Watson

Frederick R. Rivara

Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

The Association of Severe Pain Experienced in the PICU and Health-Related Quality of Life Post-Discharge

Mallory B. Smith

Chair of the Supervisory Committee:

Noel S. Weiss

Epidemiology

BACKGROUND: A decline in health-related quality of life (HRQL) is common after pediatric intensive care unit (PICU) admission. There are few known modifiable risk factors during PICU admission for a clinically significant decline in HRQL. Chronic pain is known to be associated with low HRQL. We hypothesized that the duration of severe pain during PICU admission is associated with low HRQL post-discharge.

METHODS: This was a retrospective cohort study of 546 patients <18 years of age admitted to a tertiary PICU in a free-standing children's hospital with follow-up data on HRQL post-discharge. Pain scores were abstracted from the electronic medical record and were documented every two hours during PICU admission. The primary exposure was days of severe pain, "severe" defined as days with ≥25% of pain scores at a level of 7 or above. The primary outcome was HRQL score at the time of follow-up at 4-6 weeks following hospital discharge. We compared patient demographic, baseline function and health, illness, and treatment characteristics for patients with zero days of severe pain in the PICU to patients

with one or more days of severe pain in the PICU with chi-square tests and Fisher exact tests (for comparisons involving < 30 in a category) for categorical variables and Student's t-test for continuous variables. We used multivariable linear regression models to evaluate a possible association between days of severe pain and HRQL post-discharge adjusting for age, baseline HRQL score, baseline cognitive function as defined by the PCPC, illness severity as defined by days with PELOD score indicating dysfunction in two or more organ systems, and PICU LOS. We did a stratified analysis of HRQL score for patients who responded with the PedsQL™ as opposed to the FS-II R by primary diagnosis category (surgical vs medical).

RESULTS: Relative to children without at least one day of severe pain, those who did experience pain were older (7.4 years vs 5.8 years), less likely to have cognitive dysfunction (10.8% versus 24.1%), more likely to be admitted for a surgical diagnosis (63.1% versus 46.4%), had a longer hospital length of stay (8.6 days vs. 6.0 days), more days of agitation (1.8 days vs. 0.9 days), and received more opiates in the PICU (2.7 mg/kg of morphine vs. 1.4 mg/kg of morphine). HRQL scores post-discharge declined in a linear pattern for each increasing day of severe pain. For children with the same baseline HRQL, each day of severe pain experienced in the PICU was associated with a lower post-discharge HRQL score by 3.9 points (95% CI -6.53 to -1.27). In multivariable linear regression, each day of pain was associated with a lower post-discharge HRQL score by 3.4 points (95% CI -6.04 to -0.73), after adjustment for baseline HRQL score, age, baseline cognitive function, days with multi-organ dysfunction, and PICU LOS. This association was stronger among surgical patients than among medical patients.

CONCLUSIONS: Children admitted to the PICU who experience relatively more severe pain have lower HRQL post-discharge, particularly among children who had undergone surgery.

BACKGROUND

Health-related quality of life (HRQL) is an important outcome after pediatric critical illness (1,2). Children admitted to the pediatric intensive care unit (PICU) for respiratory failure, sepsis, and injury may have a decline in their HRQL from baseline after discharge (3-9). A recent multi-center prospective study designed to identify characteristics of critical illness associated with a decline in HRQL post-discharge identified only three significant risk factors: the cumulative organ dysfunction score, a high vasoactive score, and the presence of a pathologic neurological sign or event (10). Of these, only the presence of a neurological abnormality had a strong association. This implies that preexisting patient factors, acute and persistent symptoms of critical illness, and psychosocial factors may explain the association between critical illness and decline or low HRQL post-discharge (2, 11).

One characteristic that may impact HRQL post-discharge that has received little attention is the presence of severe pain during hospitalization. Chronic and persistent pain are associated with lower HRQL scores in survivors of critical illness (12, 13). Acute pain may be experienced because of the underlying disease process (examples: malignancy, intrabdominal pathology) or as a result of the therapy used to treat critical illness (examples: surgery, chest tubes, endotracheal intubation). Acute pain may lead to chronic pain and complex pain syndromes that ultimately affect overall functioning and HRQL. A better understanding of this relationship is needed, given that pain is an identifiable and potentially modifiable symptom of critical illness.

METHODS

Study design & setting: This retrospective cohort study evaluated health-related quality of life among children admitted to the Seattle Children's PICU who were enrolled in the Seattle Children's Outcomes Assessment Program (OAP). Seattle Children's is a freestanding academic children's hospital with 334 inpatient beds, including 32 PICU beds. The OAP collected HRQL data for all consenting participants admitted to the PICU from December 2011 to February 2017. Children receiving treatment

for previously diagnosed oncologic conditions or not living with their legal guardian were excluded. Further exclusion criteria included active Child Protective Services involvement with the family, the family declining participation within the past 2 months or three times total, or treatment team refusal. Surveys were available in English, Spanish, Chinese, Russian, and Vietnamese. OAP staff approached parents (or non-parent legal guardians) for consent within 72 hours of admission, and parents of enrolled participants were asked to score their child's HRQL for the month prior to PICU admission, excluding the current illness, as an estimate of baseline HRQL. Families were contacted via e-mail or telephone 4-6 weeks following hospital discharge to complete a follow-up survey, referring to HRQL over the week prior to the assessment. OAP staff attempted to contact families for up to eight weeks following the initial attempt. This study was approved by the Seattle Children's Hospital Institutional Review Board and parents/guardians provided informed consent; patient assent was also obtained when possible.

Participants: We included all children less than 18 years of age admitted to the Seattle Children's PICU from December 2011 through February 2017 for whom there were both baseline and follow-up HRQL assessments provided by their parents. We considered children with congenital cardiac disease to have a unique set of risk factors and reasons to have pain during admission. Therefore, they were excluded from this study. We also excluded PICU patients without pain data from their ICU admission (n=6).

Exposures: We abstracted data from the Seattle Children's Electronic Medical Record (EMR) and the Virtual Pediatric Systems database and combined them with the OAP database to determine patient demographic, illness, and treatment characteristics. Demographic features included age, sex, primary language, and race. Non-demographic, baseline patient characteristics included functional status

(Pediatric Cerebral Performance Category (PCPC) score and Pediatric Overall Performance Category (POPC) score) and Pediatric Medical Complexity Algorithm (PMCA) category. The POPC and the PCPC have categories from 1 to 6: 1 – normal function, 2 – mild dysfunction, 3 – moderate dysfunction, 4 – severe dysfunction, 5 – coma, 6 – death (14-15). The PMCA category classifies patients based on their medical comorbidity and complexity into three categories: no chronic illness, non-complex chronic illness (one single isolated organ system affected, e.g. asthma), or complex chronic illness (progressive or affecting multiple organ systems, e.g. cystic fibrosis) (16). Illness characteristics included admission primary diagnosis category (medical versus surgical) and days with multiple organ dysfunction defined as a Pediatric Logistic Organ Dysfunction (PELOD) score indicating dysfunction of two or more organs. Medical treatment characteristics included variables representing duration or receipt of an ICU therapy or the subsequent downstream effect of an ICU therapy. Treatment variables were receipt of non-invasive positive pressure ventilation (high-flow nasal canula, continuous positive airway pressure, and/or bi-level positive airway pressure), receipt of invasive mechanical ventilation, days of mechanical ventilation received, total opiate dose received in the PICU in milliequivalents of morphine per kilogram, total benzodiazepine dose received in the PICU in milliequivalents of lorazepam per kilogram, total dose of dexmedetomidine received in the PICU in micrograms per kilogram, and total dose of neuromuscular blockade received in the PICU in milligrams per kilogram. Downstream effect variables included PICU length of stay (LOS), hospital LOS, total PICU days of coma (defined as a Richmond Agitation-Sedation Scale (RASS) <-3 for 25% of the day or more), total days of agitation (defined as a RASS score $\geq$ 2 for 25% of the day or more), and total days of delirium (defined as a day with at least 1 Cornell Assessment for Pediatric Delirium (CAPD) score $\geq$ 9) (17, 18).

Our primary exposure of interest was days of severe pain. This information was abstracted from the Seattle Children's EMR and was defined as a pain score greater than or equal to 7 for 25% of the day or more. The standard protocol for documenting pain scores in the PICU is every 2 hours on a 0-10 pain

score (0 indicates no pain and 10 indicates the most severe pain). We chose a score of 7 as our cut-off because this score has been shown to represent severe pain in pediatric populations (19). A score of 4 or more is indicative of unacceptable pain that should be treated (20-22). However, given the pain scores used for this study are nurse reported scores rather than patient reported scores, we chose a higher cut-off to obtain a more specific (albeit less sensitive) measure of the presence of severe pain .

Outcome: The OAP assessed HRQL using the Pediatric Quality of Life Inventory (PedsQL™) 4.0 Generic Core Scales (23), the PedsQL™ Infant Scales (24) or the Functional Status II-R (FS II-R) (25). The FS II-R was suggested for children with severe developmental delay or functional disability, but families elected which survey to complete. The PedsQL™ scores range from 0-100, with higher scores indicating better HRQL. The population mean score for the PedsQL™ is 84.1 (26). A change of $\geq$4.5 points between two scores on the PedsQL™ has been considered a clinically important difference (26), and is the standard error of the mean total parent-report PedsQL™ score for healthy children. The FS II-R was designed to measure HRQL in children with chronic physical conditions by parental report of their child's physical, psychological, cognitive, and social functioning and is validated for ages 0 to 16 years (25). Items are behaviorally-based and evaluate communication, mood, energy, eating, sleep, responsiveness, and attention. The total score ranges from 0-100, with higher scores indicating better HRQL.

The primary outcome for our study was HRQL post-discharge defined as a continuous variable. Secondary outcomes were the psychologic sub-domain and the physical sub-domain of the PedsQL™.

Statistical analyses: We compared patient demographic, baseline function and health, illness, and treatment characteristics for patients with zero days of severe pain in the PICU to patients with one or more days of severe pain in the PICU. For univariate analyses, we used chi-square tests and Fisher exact tests (for comparisons involving < 30 in a category) for categorical variables and Student's t-test

for continuous variables. We used multivariable linear regression models to evaluate a possible association between days of severe pain and HRQL post-discharge. Covariates were selected *a priori* included age, baseline HRQL score, baseline cognitive function as defined by the PCPC, illness severity as defined by days with PELOD score indicating dysfunction in two or more organ systems, and PICU LOS. We selected to use days of multiple organ dysfunction defined by PELOD scores as our marker for illness severity rather than PRISM scores, because the PELOD score represents illness severity throughout PICU admission and not just on day one. The presence or absence of a surgical diagnosis was selected as an effect modifier *a priori* given pain in this population may be due to a surgery that improves their function and quality of life post-discharge. Days of opiates and days of agitation were collinear with days of severe pain and were potentially on the causal pathway, and therefore, we did not adjust for these variables. The same multivariable linear regression models were used to evaluate an association between days of severe pain in the PICU and psychologic HRQL and physical HRQL subdomain scores post-discharge for patients who had PedsQL™ score data (n=390).

RESULTS

A total of 546 children admitted to the PICU had both baseline and post-discharge HRQL data and pain data from their PICU admission and were included in the study. (Figure 1) The six patients without pain data all had PICU LOS less than one day. Three were medical patients and three were surgical patients. Their ages ranged from 0.75 – 13.3 years old, and four were male. Only one patient required mechanical ventilation after her scheduled surgery. (Supplemental Table 1)

Relative to children without at least one day of severe pain, those who did experience pain were relatively older (7.4 years vs 5.8 years), less likely to have cognitive dysfunction (10.8% versus 24.1%), and more likely to be admitted for a surgical diagnosis (63.1% versus 46.4%). There was no difference in other demographic, baseline medical complexity, or illness severity between the two groups. Baseline

HRQL score was similar in children with severe pain days versus those without severe pain days (78.9 versus 82.0). (Table 1) Children with one or more day of severe pain had a longer hospital length of stay (8.6 days versus 6.0 days), more days of agitation (1.8 days versus 0.9 days), and received higher total opiate doses in the PICU (2.7 mg/kg of morphine equivalents versus 1.4 mq/kg of morphine equivalents). There were no differences in other treatment factors between groups. (Table 2)

Association between Severe Pain and HRQL Post-Discharge: Health-related quality of life scores declined in a linear pattern for each increasing day of severe pain. In unadjusted linear regression analysis, each day of severe pain experienced in the PICU was associated with a lower post-discharge HRQL score by 5.5 points (95% CI -8.50 to -2.46). For children with the same baseline HRQL, each day of severe pain experienced in the PICU was associated with a lower post-discharge HRQL score by 3.9 points (95% CI -6.53 to -1.27). (Table 3) In multivariable linear regression, each day of pain was associated with a lower post-discharge HRQL score by 3.4 points (95% CI -6.04 to -0.73), after adjustment for baseline HRQL score, age, baseline cognitive function, days with multi-organ dysfunction, and PICU LOS. (Table 4)

Each day of severe pain experienced in the PICU by surgical patients was associated with a lower post-discharge HRQL score by 5.1 points (95% CI -9.40 to -0.73) after adjustment for baseline HRQL, age, baseline cognitive function, days of multi-organ dysfunction, and PICU LOS. The association between severe pain and HRQL post-discharge was weaker for medical patients, who had a lower HRQL score by 2.5 points (95% CI -5.67 to 0.72) for every day more of severe pain. (Table 5)

PedsQL™ Sub-domain scores: There was an association between days of severe pain in the PICU and a lower PedsQL™ psychological score post-discharge for surgical patients, but not for medical patients. Each day of severe pain experienced was associated with a lower psychological score by 8.8 points (95% CI -13.32 to -4.27) for surgical patients after adjustment for baseline PedsQL™ psychological

score, age, baseline cognitive function, days of multi-organ dysfunction and PICU LOS. Compared to patients without any days of severe pain, patients with one or more days of severe pain had more clinically significant declines in HRQL score for the following symptoms on the PedsQL™ and the Infant PedsQL™: excessive worry, difficulty sleeping, anger, increased crankiness, poor sleep, ability to fall asleep, and fussiness. Days of severe pain experienced in the PICU was also significantly associated with post-discharge PedsQL™ physical HRQL sub-domain score for surgical patients, but not for medical patients. Each day of severe pain experienced was associated with a lower physical score by 6.1 points (95% CI -12.11 to -0.09) for surgical patients after adjustment for baseline PedsQL™ physical score, age, baseline cognitive function, days of multi-organ dysfunction and PICU LOS.

DISCUSSION

The results of this cohort study from a tertiary PICU in a free standing children's hospital suggest that severe pain experienced in the PICU is associated with lower HRQL scores post-discharge, and this association is more pronounced for surgical patients compared to medical patients. Furthermore, both the psychological and physical components of HRQL are affected and the psychological component is affected to a greater degree. For the surgical patients, each day of severe pain experienced in the PICU was associated with a lower HRQL score in both domains by a magnitude greater than what is regarded as clinically significant (4.5 points).

The findings of this study suggest that acute pain could be a preceding factor in the relationship between chronic and persistent pain and low HRQL. Pediatric chronic pain is quite difficult to treat (27), and it is possible that more aggressive treatment of acute pain during hospitalization may be a more effective way to impact HRQL outcomes.

Patients with one or more day of pain had longer hospital lengths of stay compared to patients without a day of severe pain. This may be due to side effects from the higher opiate doses patients with pain received and the time it takes to wean off these medications. It could also be due to the underlying

disease process although patients with pain had similar severity of illness and baseline health markers. Even in the absence of complete data to explain the association between severe pain and longer LOS, patients that experience severe pain in the PICU utilized more healthcare resources.

The psychological domain scores were more strongly associated with acute, severe pain for surgical patients compared to the physical domain scores. Children with pain in our study reported the most difficulty with sleeping and increased crankiness and anger. These symptoms are similar to the hyperarousal and reexperiencing symptoms of post-traumatic stress disorder (PTSD) (28). This is consistent with studies in trauma survivors that show a correlation between acute pain and the later development of PTSD (29-32). There is a known inverse association with PTSD and HRQL (33-38). Post-discharge symptoms of PTSD were not collected in this study, but could potentially mediate the association between acute pain and low HRQL for surgical patients.

Our study has potential implications for the management of pain in the pediatric intensive care setting. Pain is treatable, but not without risks. Opiates are the primary analgesic medication for treating severe pain and can cause respiratory depression, bowl ileus, and dependency (39). There has been an increase in the utilization of regional nerve blocks for treating pain in adult patients in the ICU, but this practice has not been adopted widely by pediatric providers (40). Non-pharmacologic methods for controlling pain like music therapy and distraction have not been well studied in the pediatric critically ill population, but they show limited value in treating severe pain in other pediatric populations (41-49). Virtual reality has been shown to be effective for reducing pain in pediatric patients with burn injuries (50-51) and has recently been shown to be acceptable in non-intubated patients in the PICU (52). More efforts to treat severe pain the PICU using a multi-modal approach may impact long-term outcomes.

This study was limited due to its limited size, and to a lack of data on the other potential factors that could explain the relationship between acute pain and the outcome. Additionally, the pain scores

utilized in this study were mostly nurse-reported pain scores and therefore subject to misclassification, especially in young children and in those with cognitive impairment.

CONCLUSION

Our results suggest that children admitted to the PICU who experience relatively more severe pain have lower HRQL post-discharge. . Further studies examining the relationship between acute pain in the general PICU population in relation to post-discharge PTSD and HRQL are warranted, given there are effective treatments for both pain and PTSD.

REFERENCES:

1. Fink EL, Maddux AB, Pinto N, et al. A Core Outcome Set for Pediatric Critical Care. *Crit Care Med*. 2020;48(12):1819-1828. doi:10.1097/CCM.0000000000004660
2. Aspesberro F, Mangione-Smith R, Zimmerman JJ. Health-related quality of life following pediatric critical illness. *Intensive Care Med*. 2015;41(7):1235-1246. doi:10.1007/s00134-015-3780-7
3. Meert KL, Reeder R, Maddux AB, et al. Trajectories and Risk Factors for Altered Physical and Psychosocial Health-Related Quality of Life After Pediatric Community-Acquired Septic Shock. Pediatr Crit Care Med. 2020;21(10):869-878. doi:10.1097/PCC.0000000000002374
4. Taylor A, Butt W, Ciardulli M. The functional outcome and quality of life of children after admission to an intensive care unit. *Intensive Care Med*. 2003;29(5):795-800. doi:10.1007/s00134-003-1690-6
5. Pinto NP, Rhinesmith EW, Kim TY, Ladner PH, Pollack MM. Long-Term Function After Pediatric Critical Illness: Results From the Survivor Outcomes Study. *Pediatr Crit Care Med*. 2017;18(3):e122-e130. doi:10.1097/PCC.0000000000001070
6. Watson RS, Asaro LA, Hutchins L, et al. Risk Factors for Functional Decline and Impaired Quality of Life after Pediatric Respiratory Failure. *Am J Respir Crit Care Med*. 2019;200(7):900-909. doi:10.1164/rccm.201810-1881OC
7. Zimmerman JJ, Banks R, Berg RA, et al. Trajectory of Mortality and Health-Related Quality of Life Morbidity Following Community-Acquired Pediatric Septic Shock. *Crit Care Med*. 2020;48(3):329-337. doi:10.1097/CCM.0000000000004123
8. Starr MC, Banks R, Reeder RW, et al. Severe Acute Kidney Injury Is Associated With Increased Risk of Death and New Morbidity After Pediatric Septic Shock. *Pediatr Crit Care Med*. 2020;21(9):e686-e695. doi:10.1097/PCC.0000000000002418
9. Killien EY, Farris RWD, Watson RS, Dervan LA, Zimmerman JJ. Health-Related Quality of Life Among Survivors of Pediatric Sepsis. *Pediatr Crit Care Med*. 2019;20(6):501-509. doi:10.1097/PCC.0000000000001886
10. Zimmerman JJ, Banks R, Berg RA, et al. Critical Illness Factors Associated With Long-Term Mortality and Health-Related Quality of Life Morbidity Following Community-Acquired Pediatric Septic Shock. *Crit Care Med*. 2020;48(3):319-328. doi:10.1097/CCM.0000000000004122
11. Colville GA, Pierce CM. Children's self-reported quality of life after intensive care treatment [published correction appears in Pediatr Crit Care Med. 2013 May;14(4):446]. *Pediatr Crit Care Med*. 2013;14(2):e85-e92. doi:10.1097/PCC.0b013e3182712997
12. Estrup S, Kjer CK, Vilhelmsen F, et al. Health-related quality of life, anxiety and depression and physical recovery after critical illness - a prospective cohort study [published online ahead of print, 2021 Aug 23]. *Acta Anaesthesiol Scand*. 2021;10.1111/aas.13976. doi:10.1111/aas.13976
13. Rabbitts JA, Palermo TM, Zhou C, Mangione-Smith R. Pain and Health-Related Quality of Life After Pediatric Inpatient Surgery. *J Pain*. 2015;16(12):1334-1341. doi:10.1016/j.jpain.2015.09.005
14. Pollack MM, Holubkov R, Funai T, et al. Relationship between the functional status scale and the pediatric overall performance category and pediatric cerebral performance category scales. *JAMA Pediatr*. 2014;168(7):671-676. doi:10.1001/jamapediatrics.2013.5316
15. Fiser DH. Assessing the outcome of pediatric intensive care. *J Pediatr*. 1992;121(1):68-74. doi:10.1016/s0022-3476(05)82544-2

16. Simon TD, Haaland W, Hawley K, Lambka K, Mangione-Smith R. Development and Validation of the Pediatric Medical Complexity Algorithm (PMCA) Version 3.0. *Acad Pediatr*. 2018;18(5):577-580. doi:10.1016/j.acap.2018.02.010
17. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA*. 2003;289(22):2983-2991. doi:10.1001/jama.289.22.2983
18. Silver G, Kearney J, Traube C, Hertzig M. Delirium screening anchored in child development: The Cornell Assessment for Pediatric Delirium. *Palliat Support Care*. 2015;13(4):1005-1011. doi:10.1017/S1478951514000947
19. Zieliński J, Morawska-Kochman M, Zatoński T. Pain assessment and management in children in the postoperative period: A review of the most commonly used postoperative pain assessment tools, new diagnostic methods and the latest guidelines for postoperative pain therapy in children. *Adv Clin Exp Med*. 2020;29(3):365-374. doi:10.17219/acem/112600
20. Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain. 1995;61(2):277-84
21. Hirschfeld G, Zernikow B. Cut points for mild, moderate, and severe pain on the VAS for children and adolescents: what can be learned from 10 million ANOVAs? Pain. 2013;154(12):2626-32.
22. Hirschfeld G, Zernikow B. Variability of "optimal" cut points for mild, moderate, and severe pain: neglected problems when comparing groups. Pain. 2013;154(1):154-9.
23. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Medical care.* 2001;39(8):800-812.
24. Varni JW, Limbers CA, Neighbors K, et al. The PedsQL Infant Scales: feasibility, internal consistency reliability, and validity in healthy and ill infants. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2011;20(1):45-55.
25. Stein RE, Jessop DJ. Functional status II(R). A measure of child health status. *Medical care.* 1990;28(11):1041-1055.
26. Varni, James W, Burwinkle, Tasha M, Seid, Michael, Skarr, Douglas. The PedsQL™ 4.0 as a Pediatric Population Health Measure: Feasibility, Reliability, and Validity. *Ambulatory pediatrics : the official journal of the Ambulatory Pediatric Association*. 2003;3(6):329-341. doi:10.1367/1539-4409(2003)003<0329:TPAAPP>2.0.CO;2
27. Landry BW, Fischer PR, Driscoll SW, et al. Managing Chronic Pain in Children and Adolescents: A Clinical Review. *PM R*. 2015;7(11 Suppl):S295-S315. doi:10.1016/j.pmrj.2015.09.006
28. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders : DSM-5.* Fifth edition. American Psychiatric Association; 2013.
29. Giannoni-Pastor A, Eiroa-Orosa FJ, Fidel Kinori SG, Arguello JM, Casas M. Prevalence and Predictors of Posttraumatic Stress Symptomatology Among Burn Survivors: A Systematic Review and Meta-Analysis. *J Burn Care Res*. 2016;37(1):e79-e89. doi:10.1097/BCR.0000000000000226
30. McGhee LL, Slater TM, Garza TH, Fowler M, DeSocio PA, Maani CV. The relationship of early pain scores and posttraumatic stress disorder in burned soldiers. *J Burn Care Res*. 2011;32(1):46-51. doi:10.1097/BCR.0b013e318204b359
31. Saxe GN, Stoddard F, Hall E, et al. Pathways to PTSD, part I: Children with burns. *Am J Psychiatry*. 2005;162(7):1299-1304. doi:10.1176/appi.ajp.162.7.1299

32. Saxe G, Stoddard F, Courtney D, et al. Relationship between acute morphine and the course of PTSD in children with burns. *J Am Acad Child Adolesc Psychiatry*. 2001;40(8):915-921. doi:10.1097/00004583-200108000-00013
33. Colville G, Pierce C. Patterns of post-traumatic stress symptoms in families after paediatric intensive care. *Intensive Care Med*. 2012;38(9):1523-1531. doi:10.1007/s00134-012-2612-2
34. Rees G, Gledhill J, Garralda ME, Nadel S. Psychiatric outcome following paediatric intensive care unit (PICU) admission: a cohort study. *Intensive Care Med*. 2004;30(8):1607-1614. doi:10.1007/s00134-004-2310-9
35. Rennick JE, Johnston CC, Dougherty G, Platt R, Ritchie JA. Children's psychological responses after critical illness and exposure to invasive technology. *J Dev Behav Pediatr*. 2002;23(3):133-144. doi:10.1097/00004703-200206000-00002
36. Holbrook TL, Hoyt DB, Coimbra R, Potenza B, Sise M, Anderson JP. Long-term posttraumatic stress disorder persists after major trauma in adolescents: new data on risk factors and functional outcome. *J Trauma*. 2005;58(4):764-771. doi:10.1097/01.ta.0000159247.48547.7d
37. Landolt MA, Vollrath ME, Gnehm HE, Sennhauser FH. Post-traumatic stress impacts on quality of life in children after road traffic accidents: prospective study. *Aust N Z J Psychiatry*. 2009;43(8):746-753. doi:10.1080/00048670903001919
38. Zatzick DF, Jurkovich GJ, Fan MY, et al. Association between posttraumatic stress and depressive symptoms and functional outcomes in adolescents followed up longitudinally after injury hospitalization [published correction appears in Arch Pediatr Adolesc Med. 2009 Mar;163(3):282]. *Arch Pediatr Adolesc Med*. 2008;162(7):642-648. doi:10.1001/archpedi.162.7.642
39. Dancel R, Liles EA, Fiore D. Acute Pain Management in Hospitalized Children. *Rev Recent Clin Trials*. 2017;12(4):277-283. doi:10.2174/1574887112666170816151232
40. Kaushal B, Chauhan S, Saini K, et al. Comparison of the Efficacy of Ultrasound-Guided Serratus Anterior Plane Block, Pectoral Nerves II Block, and Intercostal Nerve Block for the Management of Postoperative Thoracotomy Pain After Pediatric Cardiac Surgery. *J Cardiothorac Vasc Anesth*. 2019;33(2):418-425. doi:10.1053/j.jvca.2018.08.209
41. Harrison D, Reszel J, Bueno M, et al. Breastfeeding for procedural pain in infants beyond the neonatal period. *Cochrane Database Syst Rev*. 2016;10(10):CD011248. Published 2016 Oct 28. doi:10.1002/14651858.CD011248.pub2
42. Trottier ED, Doré-Bergeron MJ, Chauvin-Kimoff L, Baerg K, Ali S. Managing pain and distress in children undergoing brief diagnostic and therapeutic procedures. *Paediatr Child Health*. 2019;24(8):509-535. doi:10.1093/pch/pxz026
43. Aydin D, Sahiner NC. Effects of music therapy and distraction cards on pain relief during phlebotomy in children. *Appl Nurs Res*. 2017;33:164-168. doi:10.1016/j.apnr.2016.11.011
44. Caprilli S, Anastasi F, Grotto RP, Scollo Abeti M, Messeri A. Interactive music as a treatment for pain and stress in children during venipuncture: a randomized prospective study [published correction appears in J Dev Behav Pediatr. 2009 Jun;30(3):254. Abeti, Mariana Scollo [corrected to Scollo Abeti, Marianna]]. *J Dev Behav Pediatr*. 2007;28(5):399-403. doi:10.1097/DBP.0b013e31811ff8a7
45. Newell A, Keane J, McGuire BE, et al. Interactive Versus Passive Distraction and Parent Psychoeducation as Pain Management Techniques During Pediatric Venepuncture: A Randomized Controlled Trial. *Clin J Pain*. 2018;34(11):1008-1016. doi:10.1097/AJP.0000000000000628
46. Miller K, Tan X, Hobson AD, et al. A Prospective Randomized Controlled Trial of Nonpharmacological Pain Management During Intravenous Cannulation in a Pediatric

Emergency Department. *Pediatr Emerg Care*. 2016;32(7):444-451. doi:10.1097/PEC.0000000000000778
47. Wohlheiter KA, Dahlquist LM. Interactive versus passive distraction for acute pain management in young children: the role of selective attention and development. *J Pediatr Psychol*. 2013;38(2):202-212. doi:10.1093/jpepsy/jss108
48. Sanchez Cristal N, Staab J, Chatham R, Ryan S, Mcnair B, Grubenhoff JA. Child Life Reduces Distress and Pain and Improves Family Satisfaction in the Pediatric Emergency Department. *Clin Pediatr (Phila)*. 2018;57(13):1567-1575. doi:10.1177/0009922818798386
49. Hall JE, Patel DP, Thomas JW, Richards CA, Rogers PE, Pruitt CM. Certified Child Life Specialists Lessen Emotional Distress of Children Undergoing Laceration Repair in the Emergency Department. *Pediatr Emerg Care*. 2018;34(9):603-606. doi:10.1097/PEC.0000000000001559
50. Scapin S, Echevarría-Guanilo ME, Boeira Fuculo Junior PR, Gonçalves N, Rocha PK, Coimbra R. Virtual Reality in the treatment of burn patients: A systematic review. *Burns*. 2018;44(6):1403-1416. doi:10.1016/j.burns.2017.11.002
51. Das DA, Grimmer KA, Sparnon AL, McRae SE, Thomas BH. The efficacy of playing a virtual reality game in modulating pain for children with acute burn injuries: a randomized controlled trial [ISRCTN87413556]. *BMC Pediatr*. 2005;5(1):1. Published 2005 Mar 3. doi:10.1186/1471-2431-5-1
52. Badke CM, Essner BS, O'Connell M, Malakooti MR. An Innovative Virtual Reality Experience in the PICU: A Pilot Study. *Pediatr Crit Care Med*. 2019;20(6):e283-e286. doi:10.1097/PCC.0000000000001917

Figure 1: Study Flow Diagram

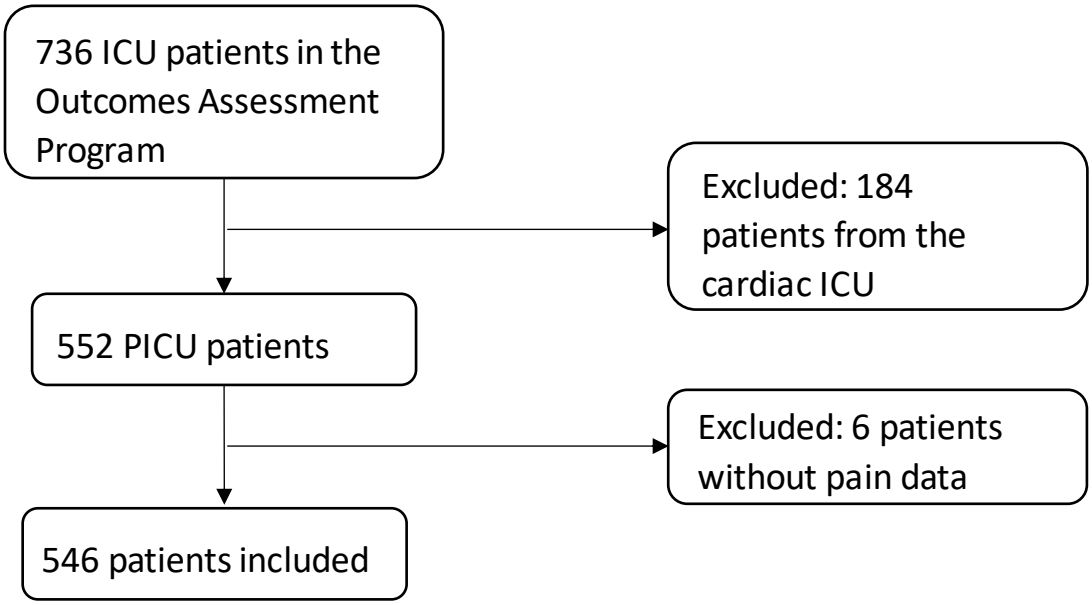

Table 1: Demographic, Baseline, and Illness Characteristics

	0 PICU Days of Severe Pain	1+ PICU Days of Severe Pain
*Age, mean (SD)	5.8 years (0.3)	7.4 years (0.8)
Female %	44.5	50.8
Race %		
White	55.9	50.8
Black	3.7	6.2
Hispanic	17.7	9.2
Asian	7.9	12.3
Other	14.8	21.5
[1]Primary Language %		
English	89.2	93.8
Spanish	9.8	3.1
Other	1.0	3.1
PMCA Category %		
Non-chronic	15.4	15.4
Non-complex chronic	31.2	21.5
Complex-chronic	53.4	63.1
Baseline HRQL score, mean (SD)	82.0 (0.7)	78.9 (2.0)
Baseline Normal Function %	50.1	41.5
*Baseline PCPC $\geq$2 %	24.1	10.8
*Surgical Diagnosis %	46.4	63.1
PRISM, mean (SD)	2.0 (0.2)	1.9 (0.4)
Days 2+ Organ System Dysfunction, mean (SD)	0.8 (0.1)	1.2 (0.4)

[1]Other languages were Amharic, Cantonese, Vietnamese, and American Sign Language.
Statistically significant differences between groups ($p<0.05$) are indicated with an asterisk.

Table 2: PICU Treatment Characteristics

	0 PICU Days of Severe Pain	1+ PICU Days of Severe Pain
Received NIPPV %	13.5	16.9
Received Mechanical Ventilation %	20.6	23.1
Mechanical Ventilation Duration[1], mean (SD)	3.1 (0.4)	2.7 (0.8)
PICU Length of Stay, mean (SD)	2.6 (0.2)	3.2 (0.5)
*Hospital Length of Stay, mean (SD)	6.0 (6.3)	8.6 (1.0)
*Days of Agitation[2], mean (SD)	0.9 (0.9)	1.8 (0.3)
Days of Coma, mean (SD)	0.2 (0.03)	0.2 (0.1)
Days of Delirium, mean (SD)	1.2 (0.2)	1.8 (0.5)
*Total PICU opiate dose[3], mean (SD)	1.4 (0.2)	2.7 (0.7)
Total PICU benzodiazepine dose[4], mean (SD)	0.3 (0.1)	0.7 (0.5)
Total PICU dexmedetomidine dose[5], mean (SD)	8.5 (1.8)	12.1 (6.6)
Total PICU paralytic dose[6], mean (SD)	0.1 (0.1)	0.4 (0.4)

[1]Mechanical ventilation duration is measured in days. [2]One day of agitation is defined as a day with >25% of the day with a RASS score of 2 or more. [3]Total opiate dose in milliequivalents of morphine per kilogram. [4]Total benzodiazepine dose in milliequivalents of lorazepam per kilogram. [5]Total dexmedetomidine dose in micrograms per kilogram. [6]Total paralytic dose in milligrams per kilogram. Statistically significant differences between groups ($p<0.05$) are indicated with an asterisk.

Table 3: Association of Severe Pain in the Pediatric Intensive Care Unit and HRQL at Follow-up

	Zero Days of Severe Pain	One Day of Severe Pain	Two Days of Severe Pain	Three Days of Severe Pain
N	481	53	9	3
Mean HRQL at Follow-up, (SD)	84.4 (0.7)	79.7 (2.4)	74.0 (8.5)	65.6 (4.3)
Linear Regression: Association of HRQL score at Follow-up (categorical pain exposure)				
Beta Coefficient	Ref	- 4.7 (-9.17 to -0.24)	- 10.3 (-20.7 to 0.1)	-21. 8 (-39.7 to -3.9)
Linear Regression: Association of HRQL score at Follow-up (categorical pain exposure) adjusted for baseline HRQL				
Beta Coefficient	Ref	-3.7 (-7.6 to 0.2)	-8.3 (-17.3 to 0.7)	-11.8 (-27.4 to 3.8)

This table shows the health-related quality of life (HRQL) score post-discharge across groups defined by days of severe pain. The unadjusted linear regression and linear regression after adjustment for baseline HRQL coefficients are presented.

Table 4: Association Between Days of Severe Pain in the PICU and HRQL Score Post-Discharge: Multivariable Linear Regression

	β Coefficient (95% CI)	p-value
Days of Severe Pain in PICU	-3.39 (-6.04 to -0.73)	0.013
Baseline HRQL Score	0.47 (0.39 to 0.54)	<0.005
Age	-0.45 (-0.67 to -0.24)	<0.005
Baseline PCPC $\geq$ 2	-1.59 (-4.45 to 1.26)	0.274
Days with MODS[1]	0.03 (-0.76 to 0.82)	0.942
PICU LOS	-0.13 (-0.65 to 0.39)	0.617

Represents the association between days of severe pain in the PICU and HRQL score post-discharge adjusted for baseline HRQL score, age, baseline abnormal cognitive function, days with multiorgan dysfunction, and PICU length of stay. [1]Defined as days with a Pediatric Logistic Organ Dysfunction (PELOD) score indicative of two or more organ dysfunctions.

Table 5: Association of Severe Pain in the PICU and HRQL Post-Discharge Stratified by Diagnosis Type

	β Coefficient (95% CI)	p-value
Surgical Patients, n=264		
Days of Severe Pain in PICU	-5.07 (-9.40 to -0.73)	0.022
Baseline HRQL Score	0.35 (0.23 to 0.48)	<0.005
Age	-0.64 (-0.98 to -0.31)	<0.005
Baseline PCPC ≥ 2	0.08 (-4.32 to 4.48)	0.971
Days of MODs	1.41 (-0.59 to 3.41)	0.166
PICU LOS	0.03 (-1.27 to 1.33)	0.967
Medical Patients, n=282		
Days of Severe Pain in PICU	-2.48 (-5.67 to 0.72)	0.128
Baseline HRQL Score	0.55 (0.46 to 0.65)	<0.005
Age	-0.30 (-0.57 to -0.03)	0.029
Baseline PCPC ≥ 2	-3.58 (-7.29 to 0.14)	0.059
Days of MODs[1]	-0.24 (-1.01 to 0.52)	0.529
PICU LOS	0.01 (-0.52 to 0.55)	0.961

Represents the association between days of severe pain in the PICU and HRQL score post-discharge stratified by primary diagnosis type and adjusted for baseline HRQL score, age, baseline abnormal cognitive function, days with multiorgan dysfunction, and PICU length of stay. [1]Defined as days with a Pediatric Logistic Organ Dysfunction (PELOD) score indicative of two or more organ dysfunctions.

Supplemental Table 1: Characteristics of Patients with Missing PICU Pain Data

Age	Gender	Race	Baseline PCPC	PRISM	Diagnosis Category	Mechanical Ventilation Days	PICU LOS
13.3	Male	Hispanic	1	7	Medical	0	0.62
9.5	Male	White	1	8	Medical	0	0.91
9.6	Female	White	1	3	Medical	0	0.64
5.8	Female	White	3	0	Scheduled Surgery	0.65	0.99
3.6	Male	White	2	0	Scheduled Surgery	0	0.99
0.75	Male	White	1	0	Acute Surgery	0	0.57