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ARTICLE

Variability of Dosing and Number of Medications Needed to Achieve Adequate Sedation in Mechanically Ventilated Pediatric Intensive Care Patients

Emma M. Tillman[1,*], Joseph Ipe[1], Kelly J. Weaver[2], Todd C. Skaar[1], Courtney M. Rowan[3] and James E. Slaven[4]

Children admitted to the pediatric intensive care unit (PICU) often require multiple medications to achieve comfort and sedation. Although starting doses are available, these medications are typically titrated to the desired effect. Both oversedation and undersedation are associated with adverse events. The aim of this retrospective study was to evaluate cumulative medication burden necessary to achieve comfort in patients in the PICU and determine relevant predictors of medication needs. In order to account for all of the sedative medications, *z*-scores were used to assess the population average dose of each medication and compare each patient day to this population average. Sedation regimens for 130 patients in the PICU were evaluated. Mean overall infusion rates of fentanyl, morphine, and hydromorphone were 1.67 ± 0.81 µg/kg/hour, 0.12 ± 0.08 mg/kg/hour, and 17.84 ± 13.4 µg/kg/hour, respectively. The mean infusion rate of dexmedetomidine was 0.59 ± 0.28 µg/kg/hour, and midazolam was 0.14 ± 0.1 mg/kg/hour. Summation *z*-sores were used to rank the amount of sedation medication needed to achieve comfort for each individual patient for his/her PICU stay in relation to the entire sample. Patient age, weight, and length of mechanical ventilation were all significant predictors of sedation requirement. This study will provide data necessary to develop a model of cumulative medication burden needed to achieve appropriate sedation in this population. This descriptive model in appropriately ranking patients based on sedative needs is the first step in exploring potential genetic factors that may provide an insight into homing in on the appropriate sedation regimen.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ The time it takes to achieve adequate sedation for children in the pediatric intensive care unit (PICU) can be agonizing for both the patients and their caregivers. Although starting doses are available for these medications, the dosing normally requires further titration to achieve the desired effect.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ There is a critical gap in knowing how to optimize pediatric comfort and sedation in a timely manner while minimizing unwanted adverse events.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ We have illustrated that sedation requirements in patients on mechanical ventilation in the PICU are highly variable. These preliminary data will allow us to identify patients that required very little or high amounts of sedation medications to achieve comfort. We are currently planning a prospective study to follow-up with the patients included in this study and obtain consent to collect DNA for whole genome sequencing in hopes of identifying genetic predictors that may be beneficial in determining sedation for patients in the PICU. Pharmacogenomics may not be able to successfully predict the exact dose, but we believe this could be a potential tool to choose the appropriate medication regimen and doses to minimize iatrogenic adverse events.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ This descriptive model in appropriately ranking patients based on sedative needs is the first step in a translational approach at exploring potential genetic factors that may provide the appropriate sedation regimen and thereby shorten the time to optimal sedation in the PICU population.

Children admitted to the pediatric intensive care unit (PICU) often require mechanical ventilation and invasive procedures. Because these procedures are uncomfortable, children are usually sedated with medications, such as opioids, benzodiazepines, and other sedatives.[1] Although starting doses are available for these medications, the dosing normally requires further titration to achieve the desired effect.[1] Some patients require a small cumulative dose

[1]Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, Indiana, USA; [2]College of Pharmacy, Purdue University, West Lafayette, Indiana, USA; [3]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana, USA; [4]Department of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana, USA. *Correspondence: Emma M. Tillman (emtillma@iu.edu)
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of these medications to achieve sedation goals, whereas other children require higher doses, or even multiple medications.[2] This dose titration often takes several hours to accomplish adequate sedation. During this time, some patients will be undersedated, in much discomfort, and at risk for unplanned extubation. Others are oversedated, further suppressing respiratory drive, hindering respiratory clearance, and overall movement; this increases the risk of increased length of time of mechanical ventilation.[3] Oversedation can also increase their risk of delirium; this is one of the most notable iatrogenic adverse events in patients in the PICU.[4] Recent studies have evaluated the effect of protocolizing sedation on length of mechanical ventilation, but these studies have shown minimal effects on length of mechanical ventilation.[5,6] The uncertainty of sedation dosing, and the potential iatrogenic effects that this can cause, demands an understanding of the inter-relationships between clinical and genetic factors that influence sedative medication needs of critically ill children. In recent years, the use of the pediatric sedation state scale has been beneficial in objectively evaluating the appropriateness of both procedural sedation and continuous sedation in the PICU.[7]

The sedative medications are individually and dynamically titrated and combined to achieve the phenotype of "comfort."[1] The clinical practice in this PICU is to titrate sedation to a state behavior scale (SBS) score of 0 to −1.[8] During the titration, each individual patient is assessed by bedside clinicians using a sedation scale. Because they will be on mechanical ventilators, there is a narrow therapeutic window to prevent further breathing complications. The dose and choice of medications must be carefully titrated to the sedation pharmacodynamic end point. This contrasts with the titration of many other medications that are dosed to achieve a therapeutic plasma concentration. Pharmacogenomics provides an opportunity to help predict individual patients' response to target medications.[9] In fact, there are several known genetic variants that play a role in a patient's response to both opioids and benzodiazepines; however, they are not yet used in this clinical setting. In addition, there also remain many other unknown clinical and environmental factors that contribute to the variability.[10,11] In order to more accurately identify the genetic and environmental factors that contribute to the variable dose and medication combinations, a strategy is needed to appropriately include the medications, the doses, and their combinations into an individual medication phenotype. Thus, the aim of this retrospective pragmatic study was to evaluate the individual level cumulative medication requirements necessary to achieve adequate sedation and comfort in mechanically ventilated patients in the PICU. In addition, we also identified clinical parameters associated with the variable medication requirements.

METHODS

In order to evaluate and characterize the variability of sedative medications used in patients in the PICU on mechanical ventilation, we conducted a retrospective study that included all patients < 3-years-old who were admitted to the Riley Children's Hospital PICU for at least 4 days between May 2015 and April 2019 and required mechanical ventilation. Patients were excluded if they were transferred to the PICU from the neonatal intensive care unit due to the need for training for home mechanical ventilation. Demographic data, comorbidities, home medications, PICU admitting diagnosis, critical illness severity scores: pediatric logistic organ dysfunction score and pediatric index of mortality, SBS scores, PICU length of stay (LOS), hospital LOS, laboratory data, surgical or invasive procedures, complications or adverse events, length of mechanical ventilation, hospital discharge data, and medication data, such as specific opioid and sedative medications and doses required to achieve adequate sedation, were collected from the electronic medical records. The study was approved by the Indiana University Institutional Review Board.

We chose to use *z*-scores to accurately assess the cumulative sedative agents used to achieve sedation and comfort. The *z*-scores allowed us to take into account the population average dose of each medication and compare each patient day to this population average. Briefly, a *z*-score (also called a standard score) represents how far a data point is from the mean. More specifically, it is a measure of how many SDs below or above an individual raw score is from the population mean. A *z*-score typically has a normal distribution curve.[12] We first calculated *z*-scores for each of the drugs used as continuous infusions for each patient on each day. Then all patient *z*-scores were added together for a "summation total *z*-score" and divided by the number of days of mechanical ventilation to normalize to a patient's average *z*-score per ventilator days. We used this as a measure of the sedation load. This calculation served as an objective way to compare individual patients' medication loads to the rest of the population. Each patient was given a value for every medication on each day of mechanical ventilation. If a patient did not receive that medication, a zero was recorded and used for population *z*-score calculations. Clinically, all starting drugs and doses were chosen at the preference of the attending physician with the recommendation of the clinical pharmacist. Patient factors may have influenced this medication choice, but there was not a standard dosing algorithm or decision tree for starting or changing medications.

A heatmap was created using the ComplexHeatmap package in R (version 3.6.2). Euclidian distance and Mcquitty Clustering method (Weighted Pair Group Method with Arithmetic Mean) were used to generate the heatmap. Principal component analysis (PCA) was performed and loadings were determined using the "factoextra" R package.[13]

Descriptive statistics were generated, with means (SDs) given for linear continuous variables, medians (ranges) for nonlinear continuous variables, and frequencies (percentages) for categorical variables. Bivariate analyses were performed to determine which demographic and clinical characteristics were associated with the overall summation *z*-score, using analysis of variance models for categorical variables and correlation models for continuous variables. All analytic assumptions were verified, with Spearman correlation analyses being used where necessary and checked, including histograms and QQ plots, as well as the Anderson–Darling statistic. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

We identified 130 patients who met study inclusion criteria. The mean age was 9.1 ± 8.6 months (mean ± SD; **Table 1**). The median (ranges) of hospital and PICU lengths of stays were 16 (6–268) days and 9 (5–88) days, respectively. Sedation scores were documented in 67.6% of patients and not documented in 32% of patients, and sedation goals were achieved in 70.1% of these patients.

Most patients required a combination of multiple medications to achieve adequate sedation with a mean of 2.58 ± 1.18 medications per patient during the PICU stay. Only 17% of patients received only a single medication, 36% received 2 medications, 29% received 3 medications, 12% received 4 medications, and 6% required 5 or 6 medications during the PICU stay. These included continuous infusions of fentanyl, morphine, hydromorphone, dexmedetomidine, midazolam, and propofol, as well as intermittent doses of all of the aforementioned medications and also ketamine, methadone, lorazepam, and chloral hydrate. The dosing ranges of medications were also highly variable. The median *z*-scores for each of the medications are shown in **Table 2**.

Patient age, weight, and hospital LOS were all significant predictors of sedation requirements (**Table 1**). Older, heavier patients required more medication (mg/kg) to achieve desired sedation. Additionally, longer duration of mechanical ventilation was also associated with higher medication requirements. However, PICU LOS, critical illness severity scores, neurological status, and history of critical care admission were not predictors of sedation medication requirements.

Summation *z*-scores were used to rank the amount of sedation medication needed (sedative load) to achieve comfort for each individual patient. This was the sum of the *z*-scores for each medication on each day of his/her PICU stay divided by the number of days of stay. Although doses of propofol and ketamine were collected, these were not included in this analysis because their use was so infrequent for < 24 hours as additional procedural sedation and not as a long-term sedative. This resulted in an overall *z*-score that described their average sedative load per day in relation to the entire sample population (**Figure 1**).

In addition, this was also graphically represented using a heatmap where patients in each of the four quartiles of sedative load mostly clustered together (see the quartiles column

Table 1 Study population (*n* = 130)

	Mean (SD)[a], Number (%)[b] median (range)[c]	Parameter estimates	*P* value
Age, months	9.30 (8.84)[a]	0.3762	< 0.0001*
Weight, kg	7.50 (3.47)[a]	0.3457	< 0.0001*
Sex, % male			
Male	75 (57.7)[b]	−0.04	0.1611
Female	55 (42.3)[b]	0.36	
Race			0.2303
White	99 (76.2)[b]	0.10	
Black	23 (17.7)[b]	0.54	
Asian	5 (3.9)[b]	−0.19	
Multi	2 (1.5)[b]	−1.22	
Unknown	1 (0.8)[b]	−1.05	
PICU LOS, days	9 (5–66)[c]	0.1591	0.0729
Hospital LOS, days	16 (6–268)[c]	0.1884	0.0066*
Length of mechanical ventilation, days	7 (1–80)[c]	0.1316	0.0889
PELOD	4.66 (7.03)[a]	0.0675	0.5116
PIM	−4.04 (1.62)[a]	−0.0421	0.6401
Neurological status			0.1038
Normal	113 (86.9)[b]	0.22	
Delayed	17 (13.1)[b]	−0.46	
Prior NICU or PICU admission			0.5009
Confirmed	52 (40.0)[b]	0.25	
Not confirmed	78 (60.0)[b]	0.05	

Values are means (SDs) or medians (ranges) for continuous variables depending on linearity, and frequencies (percentages) for categorical variables. The parameter estimates show the correlation with *z*-scores. A positive parameter estimate reflects that variable is associated with a higher summative z-score, and a negative parameter estimate is reflective of a lower *z*-score.
LOS, length of stay; NICU, neonatal intensive care unit; PELOD, pediatric logistic organ dysfunction score; PICU, pediatric intensive care unit; PIM, pediatric index of mortality.
[a]Mean (SD).
[b]Number (%).
[c]Median (range).
*Statistically significant.

Table 2 Sedation medication doses and *z*-scores

Medication (dosing units)	Doses (mean, SD)[a] (only including doses when drug was given)	Doses (mean, SD)[b] (including zeros when drugs were not given)	Sedation *z*-scores (mean, SD; median, range) summation *z*-score/ day of mechanical ventilation
Fentanyl, μg/kg/hour	1.67 (0.81)	0.41 (0.82)	0 (0.99); −0.32 (−1.05, 3.73)
Morphine, mg/kg/hour	0.12 (0.08)	0.02 (0.05)	0 (0.99); −0.44 (−0.72, 4.32)
Hydromorphone, μg/kg/hour	17.84 (13.40)	1.79 (6.80)	0 (0.99); −0.30 (−0.59, 8.12)
Dexmedetomidine, μg/kg/hour	0.59 (0.28)	0.18 (0.31)	0 (0.99); −0.65 (−1.09, 3.03)
Midazolam, mg/kg/hour	0.14 (0.10)	0.04 (0.08)	0 (0.99); −0.54 (−0.88, 5.40)
Ketamine, mg/kg/hour	0.96 (0.52)	0.005 (0.08)	0 (0.99); −0.11 (−0.20, 10.77)
Propofol, mg/kg/minute	32.37 (17.58)	0.66 (5.20)	0 (0.99); −0.13 (−0.44, 10.77)
Total/summation, all 7			0 (2.89); −0.48 (−3.72, 20.14)
Total/summation (excludes ketamine/propofol)			0 (2.31); −0.30 (−3.33, 11.54)

[a]*Z*-scores were calculated excluding days that a patient did not receive the medication, therefore, these doses reflect typical doses.
[b]*Z*-scores include a value for each patient for each day, with zeros included if a patient did not receive that medication on a given day. The *z*-scores were calculated using the zero values and normalized per days of mechanical ventilation.

of **Figure 2**). Using the individual *z*-scores of the five medications, hierarchical clustering also identified several groups of patients that had similar medication regimens. For example, one group required high doses of hydromorphone in combination with dexmedetomidine; another group received primarily only morphine but low levels of other medications; another group received moderate levels of fentanyl and midazolam; and another group did not receive high doses of any of the five medications.

The principle component analysis also demonstrated clustering of patients with similar sedative load (**Figure 3**). For example, the Q1 patients (pink circles) tended to cluster in the upper right portion of the plot; the Q2 patients (green triangles) formed a partial ring surrounding the Q1 patients; the Q3 patients (blue squares) formed a partial ring further out from the Q2 patients; and the Q4 (purple crosshatches) were furthest out from the Q1 and had the most scatter. Each principle component (PC) is a dimension that is made up of a combination of the *z*-scores of all five variables (drugs). Although a PCA in of itself cannot determine if one variable is the driver of the observed data, we can determine the loadings of each principle component and calculate the percentage of influence that each variable has on each principle component. Loadings from the PCA analysis show that no one medication alone was responsible for impacting the overall model (**Table S1**); however, we do see that PC1 (horizontal spread) is primarily driven by fentanyl, morphine, and midazolam, whereas PC2 (vertical spread) is driven by hydromorphone and dexmedetomidine (**Figure 3**).

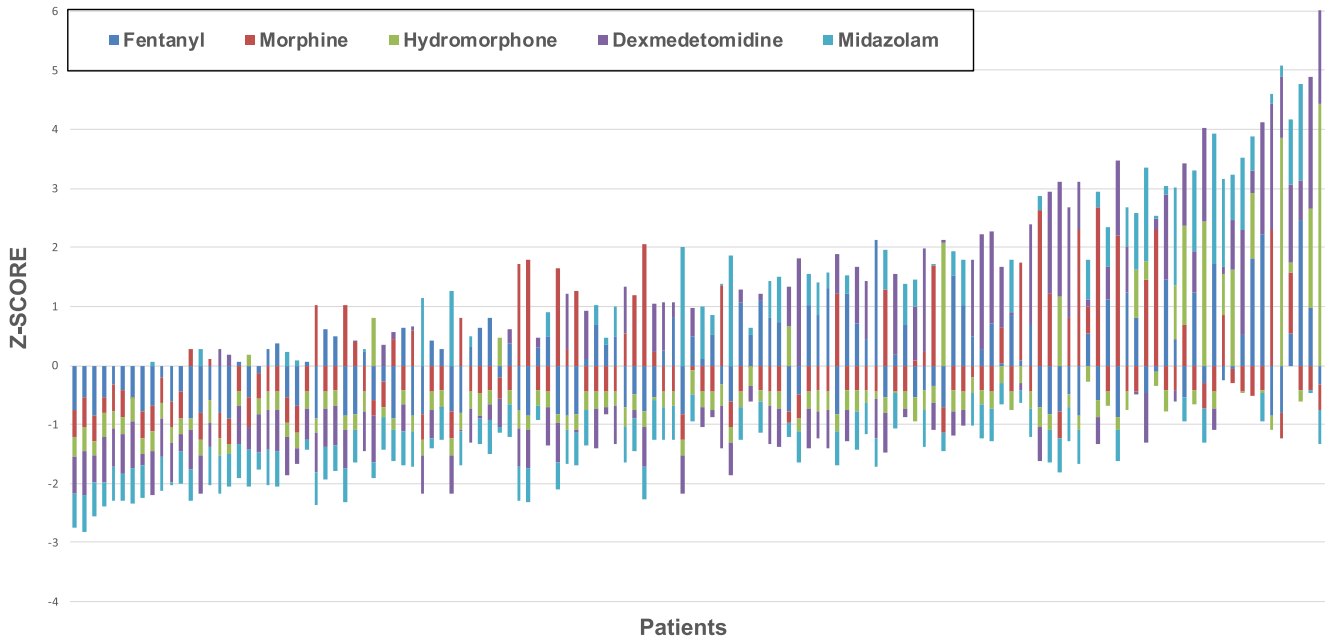

Figure 1 Waterfall plot of the medication *z*-scores for individual patients. Each bar is an individual patient. Within each bar, the different colors represent the *z*-scores for each drug. Subjects are in order by lowest to highest summation *z*-score from left to right. Bars below 0 are *z*-scores for doses below the average and bars above are *z*-scores that were above the average.

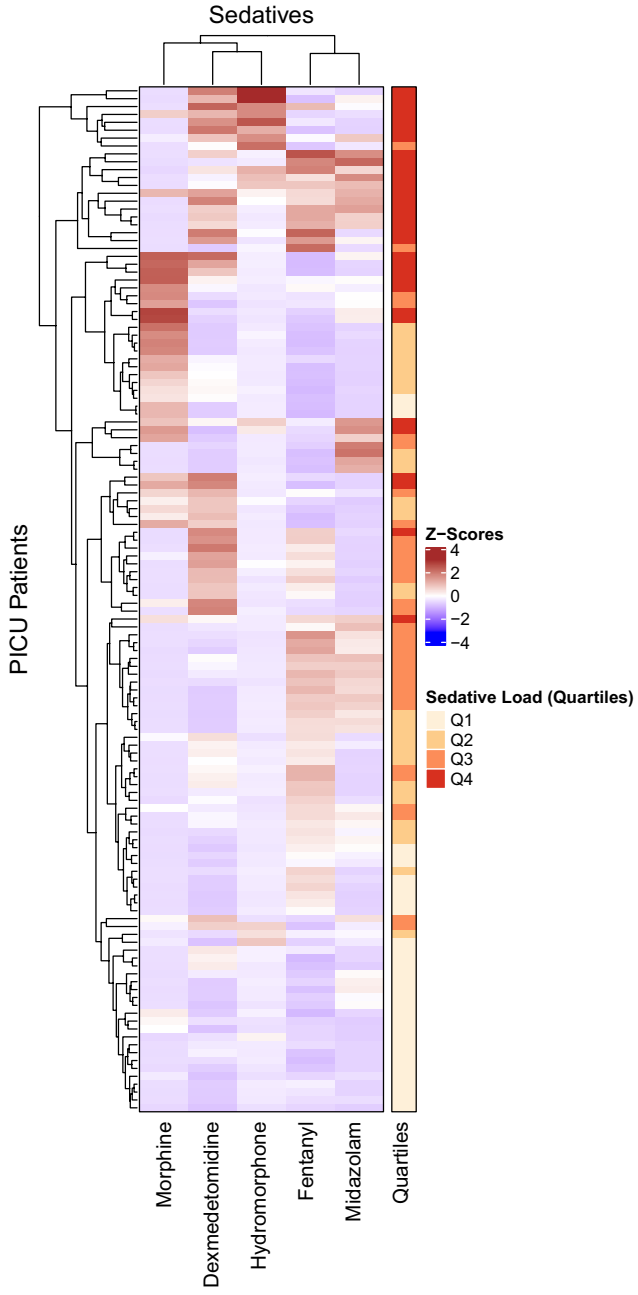

Figure 2 Heatmap of patients in the pediatric intensive care unit (PICU) clustered using *z*-scores of individual medications. Summation *z*-scores (sedative load) were divided into quartiles and annotated using color labels on the right side of each row.

DISCUSSION

Our results illustrate the highly variable medication requirements to adequately sedate children on mechanical ventilation. The patients in our retrospective, real-world, observational study received various combinations of opioids (morphine, hydromorphone, or fentanyl), anesthetics (propofol or ketamine), a benzodiazepine (midazolam), and an alpha-2 agonist (dexmedetomidine). Although doses of medications within classes can be combined using "equivalents," such as morphine equivalents for opioids, combining medications of different classes is more challenging. By creating a z-score for each of the sedation medications, we were able to combine the doses of the four classes of medications to calculate a total sedation load (summation *z*-score). This enabled us to determine the variability in total sedation requirements, even in the setting of different classes of medications. By assigning a summation sedative score to each patient, we were also able to identify characteristics that were associated with the total sedative medication requirements.

As medical treatments advance and more PICU interventions are available, critical care patients are at higher risk of iatrogenic events.[14,15] For example, one of the major iatrogenic adverse events associated with the use of sedation in the PICU is delirium.[4,16,17] Delirium is a burden to the patients and is associated with increased hospital costs and LOS.[16,17] The prevalence of delirium is higher in patients < 2-years-old, on mechanical ventilation, use of physical restraints, and receiving benzodiazepines, opioids, vasopressors, and anti-epileptic medications.[16] Minimizing the use of medication and optimizing comfort is the goal for reducing the risk of delirium; however, there are currently no good strategies for predicting the optimal medication regimens for individual patients. The identification of clinical and genetic factors that predict the right sedative regimen may not only bring the patient more comfort, but also reduce the risk of PICU-associated delirium.

Achieving optimal sedation during PICU admission has been challenging. Several approaches have been attempted to minimize the LOS and adverse events. Keogh *et al*. evaluated using guidelines to direct sedation in two Australian PICUs. These guidelines impacted dose and duration of sedative agents but had no effect on length of mechanical ventilation.[6] Additionally, Curley *et al*. evaluated the impact of a nurse-implemented goal-directed sedation protocol, including daily multidisciplinary discussions of titrating and weaning medications, use of various sedation scales, including the SBS, and extubation readiness test. Unfortunately, this did not improve sedation-related adverse events or length of mechanical ventilation; however, an exploratory secondary analysis suggested that this protocol may have an impact on wakefulness, pain, and agitation.[5,8,18]

In this study, older and larger patients in our cohort had higher *z*-scores even when medication doses were corrected for weight-based dosing. One possible explanation for this could be that younger infants were less active/agitated compared with toddlers (the upper age range of our cohort) were more active/agitated and needed more medication. This is consistent with developmental norms for age. For example, a 3-month-old healthy child would be content to lay in a bed with minimal movement, whereas a 3-year-old healthy toddler would be less compliant at staying still.

This study was limited by the retrospective nature of data collection. Although medications were titrated to provide sedation during mechanical ventilation, sedation scores were not available in the electronic medical records for all patients because this was not standard documentation during the study time period. Based on clinical experience

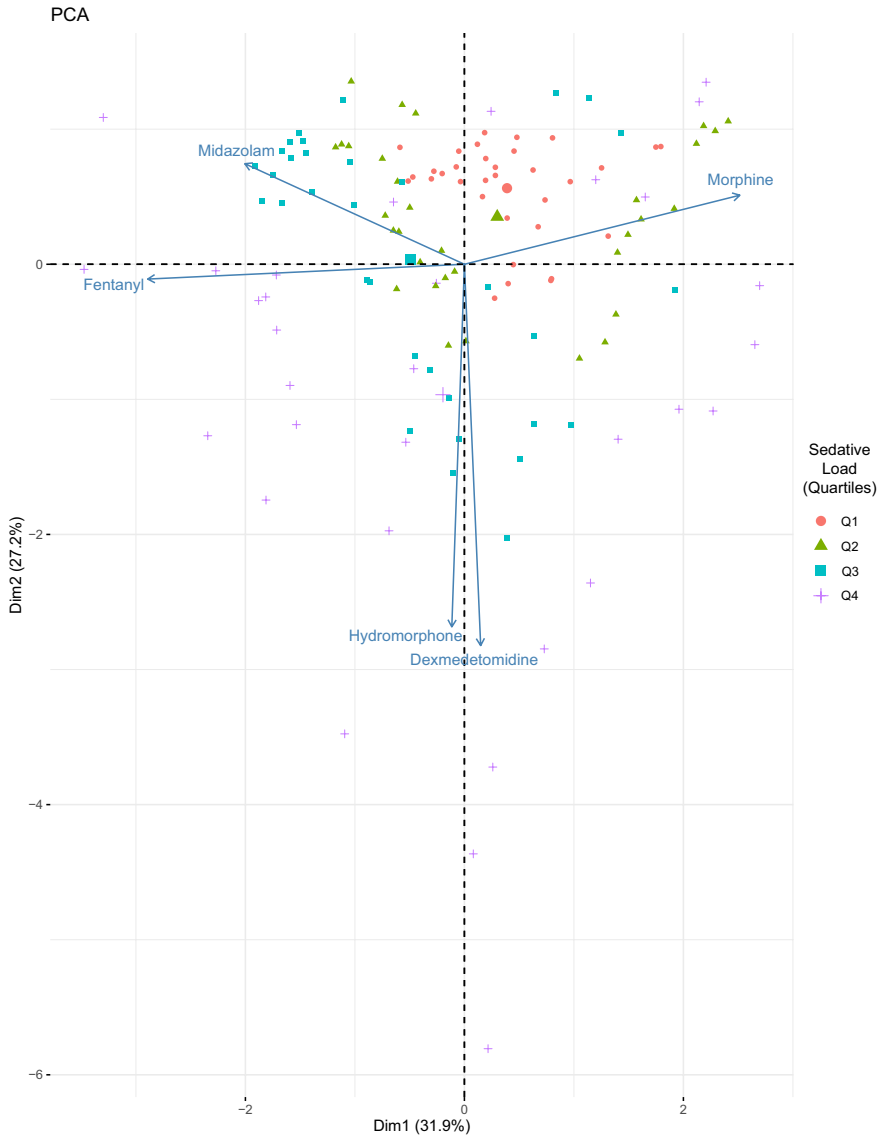

Figure 3 Principal component analysis (PCA) plot of patients in the pediatric intensive care unit using *z*-scores of individual medications. Different shapes represent the four quartiles of sedative load. The larger point of each shape indicates the center of the respective cluster. Arrows indicate the correlation of variables, and arrows in the same direction indicate positive correlation.

in the PICU, it was assumed that medication was titrated to the desired goal of 0 to −1, but unfortunately this was not confirmed. Prospective recording sedation scores would provide better outcome data for establishing predictive algorithms, but that was not available in this retrospective study. We believe that the *z*-score methods are an innovative way to capture the cumulative medication load for each patient compared with the total population; however, it has limitations. For example, medications have unique dose-response, pharmacokinetic parameters, degree of drug tolerance, and tachyphylaxis, and may be used and/or changed due to physician preference and medication shortages, as well as patient medication tolerance. A prospective study collecting detailed changes in medication doses and sedation scores would provide useful data to further validate this method.

Our long-term goal is to identify genetic, environmental, and demographic factors that predict sedation requirements and guide the therapeutic management of patients in the PICU. The *z*-score approach appears to be useful in identifying patients that require varying amounts of sedation. The *z*-scores could be used to objectively classify sedation norms for this population and identify patients with extreme phenotypes (e.g., patients needing minimal or extremely high amounts of sedation medications). The *z*-score model used here allowed us to compare each patient's daily *z*-score for every medication to the mean *z*-score of the population for that medication. This approach allowed for normalizing to the population and provided an objective comparison of the cumulative medication burden across multiple classes of medications. This normalizing within a given population will be valuable in selecting

the upper and lower 10–20% of the population for whole genome sequencing to identify potential genetic factors influencing response to sedation. We expect that the *z*-scores will be useful in future studies focused on identifying additional genomic, demographic, and environmental factors that predict sedative medication requirements of these children.

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