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Model-Based Approach To Improve Clinical Outcomes In Neonates With Opioid Withdrawal Syndrome Using Real-World Data

Nadeesri Wijekoon[1], Oluwatobi Aduroja[2], Jessica M. Biggs[3], Dina El-Metwally[2], Mathangi Gopalakrishnan[4]

[1]Department of Mathematics and Statistics, University of Maryland, Baltimore County

[2]Department of Pediatrics, School of Medicine, University of Maryland, Baltimore

[3]University of Maryland Medical Center, Baltimore

[4]Center for Translational Medicine, School of Pharmacy, University of Maryland, Baltimore

Corresponding author

Mathangi Gopalakrishnan, MPharm PhD

Center for Translational Medicine

University of Maryland School of Pharmacy

20, N.Pine street

Baltimore – 21201

mgopalakrishnan@rx.umaryland.edu

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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ABSTRACT

At least 60% of the neonates with opioid withdrawal syndrome (NOWS) require morphine to control withdrawal symptoms. Currently, the morphine dosing strategies are empiric, not optimal and associated with longer hospital stay. The aim of the study was to develop a quantitative, model-based, real world data-driven approach to morphine dosing to improve clinical outcomes such as reducing time on treatment. Longitudinal morphine dose, clinical response (Modified Finnegan Score (MFS)), and baseline risk factors were collected using a retrospective cohort design from the electronic medical records of neonates with NOWS (N=177) admitted to the University of Maryland Medical Center. A dynamic linear mixed effects model was developed to describe the relationship between MFS and morphine dose adjusting for baseline risk factors using a split-sample data approach (70% training: 30% test). The training model was evaluated in the test dataset using a simulation based approach. Maternal methadone and benzodiazepine use, race were significant predictors of the MFS response. Positive autocorrelations of 0.56 and 0.12 were estimated between consecutive MFS responses. On an average, for a 1000 microgram increase in the morphine dose, the MFS decreased by 0.3 units. The model evaluation showed that observed and predicted median time on treatment were similar (13.0 vs 13.8 days). A model based framework was developed to describe the MFS–morphine dose relationship using real world data that could potentially be used to develop an adaptive, individualized morphine dosing strategy to improve clinical outcomes in infants with NOWS.

INTRODUCTION

Neonatal Opioid withdrawal syndrome (NOWS), also known as neonatal abstinence syndrome (NAS) is a drug withdrawal syndrome experienced by 55-94% of *in utero* opioid-exposed neonates shortly after birth[1]. The dramatic increase of opioid use in pregnancy has led to a five-fold increase in NOWS with an incidence of 1.5 to 8.0 per 1000 hospital births from 2004 to 2014[2–4]. On average in the United States, one infant is born every 15 minutes with NOWS, with an estimated $2.5 billion in total hospital charges between 2004 to 2014[3]. From 2004 to 2013, NOWS was responsible for a 4-fold increase in Neonatal Intensive Care (NICU) admissions causing substantial strain on the resources[5]. Based on severity of NOWS measured by well-recognized scoring methods (e.g., Modified Finnegan Neonatal Abstinence Scoring tool[6]), non-pharmacological or pharmacological treatment is recommended. Approximately 60-80% of newborns with NOWS require pharmacotherapy with an opioid[1]. Depending on the half-life of the maternal opioid, the American Academy of Pediatrics recommends observing infants with opioid exposures for NOWS symptoms for 3-7 days before hospital discharge[7].

Currently**,** diluted morphine is the most commonly used first-line pharmacologic treatment for NOWS due to the availability of a stable infant formulation[8–10]. The typical morphine treatment protocol involves titrating the dose to first stabilize the clinical symptoms of NOWS as measured by Modified Finnegan Score (MFS)[6], and then to wean the infant off morphine in a step-wise fashion. Despite the importance of pharmacotherapy to treat moderate-to-severe symptoms of NOWS, there is no universally accepted standard of care. Unstructured protocols for pharmacotherapy initiation and weaning have been associated with poor outcomes[9,11] (47% longer mean duration of opioid treatment and 33% longer mean length of stay (LOS)[11]) as compared to use of structured protocols. Though use of structured protocols is promising, there are significant gaps in knowledge concerning the optimal treatment strategy and the impact of prolonged pharmacotherapy with opioid on long-term developmental outcomes[7,12,13]. There is considerable heterogeneity regarding the dosing of morphine, clinical threshold for initiating treatment, starting doses, weaning protocol and adjunctive medications[1,14]. Therefore, morphine dosing adjustments tend to be empiric with considerable variability between hospitals potentially leading to longer times to stabilization and hence longer time

on treatment and longer hospital stays adding to the financial burden. The average length of stay (LOS) of infants affected by NOWS is estimated to be about 16 days per infant[3,15] and those that requiring pharmacotherapy stay in the hospital for an average of 22-23 days (30% increase in LOS)[15,16]. Typically, Medicaid is the primary payer for an estimated 78% of the infants with NOWS, highlighting the need for cost effective treatment in order to alleviate the burden of the already strained public health system[3,15]. With at least 30% increased LOS associated with infants requiring pharmacotherapy, there is a strong need for optimizing the pharmacotherapeutic treatment[17].

Understanding the relationship between morphine dose and MFS, while adjusting for subject specific factors using quantitative model-based approaches will enable optimization of dose and dosing regimen for morphine that in turn, can potentially improve NOWS outcomes. Additionally, given that there are several barriers to performing clinical pharmacokinetic studies in pediatrics, utilizing real world data from electronic medical records from hospitals to generate real world evidence could lead to improved care in the pediatric population[18]. Electronic medical records, which include routinely collected longitudinal clinical care data are increasingly used for clinical research and optimizing therapeutics[19–22]. A combination of real-world data and quantitative model-based approaches will enable conversion of the empirical evidence to usable and actionable knowledge that can potentially lead to improvements in NOWS related patient care.

The main objectives of the study are to (i) develop and validate a morphine dose - MFS relationship using routinely collected clinical care data from electronic medical records of infants with NOWS adjusting for maternal and infant baseline factors and (ii) evaluate the utility of the developed morphine dose-response model by Bayesian forecasting of the clinical response.

METHODS

Study Design and Patients

The study data was collected using a retrospective cohort design, by review of medical records of infants admitted to the level IV Neonatal Intensive Care Unit (NICU) of the University of Maryland Medical Center (UMMC) between January 2013 to December 2017. The retrospective cohort was

identified using the diagnostic codes, "Neonatal Abstinence Syndrome", "drug exposure" and "drug withdrawal" from the hospital electronic medical records and charts. The inclusion criteria was all infants with gestation greater than or equal to 35 0/7 weeks with *in utero* exposure to opioids that were determined by maternal history, toxicology reports during pregnancy and/or at the time of delivery, and/or infant urine toxicology reports and symptoms of NOWS requiring pharmacological treatment. Infants who were < 34 6/7 weeks gestation or with major congenital anomalies or diagnosed with iatrogenic NOWS (i.e., withdrawal due to postnatal extended period of use of opioids for treating other ailments not related to prenatal substance exposure) were excluded to avoid complications related to prematurity or other abnormalities. Baseline infant characteristics collected included gestational age, race, gender, birth weight, and receipt of breast milk. The maternal demographics included age and race (maternal self-identified). In addition, maternal opioid use (methadone, buprenorphine, morphine, heroin, codeine and hydropmorphone, oxycodone) and other substance use (cocaine, benzodiazepine, barbiturate, marijuana smoking, amphetamine, selective serotonin reuptake inhibitor (SSRI), antipsychotics, tobacco and alcohol) data were collected. Longitudinal information on morphine dose and the 21 sub-scores of MFS, along with total MFS were obtained. The UMMC NOWS protocol included monitoring of infants using MFS every 3-4 hours. Infants with two consecutive MFS > 9 were started on first-line therapy using neonatal diluted morphine (0.2ml (0.08mg) 0.4mg/ml) every 3 hours. If the MFS continued to remain elevated > 9, clonidine (1ug/kg) was added as a second line agent[23]. All providers and nurses are trained on MFS scoring and NOWS protocol to ensure consistency in scoring and protocol adherence. The study protocol was approved by the Institutional Review Board of the University of Maryland, Baltimore.

Data Analysis

The data analysis included exploratory graphical and descriptive analysis of baseline characteristics of infants and mothers, morphine dosing and MFS trends. The MFS consisted of 21 items representing signs and symptoms of withdrawal in NOWS infants for the three systems namely, central nervous system, metabolic/vasomotor/respiratory and gastro-intestinal system[6,24]. For each of the items, scores were recorded by a trained clinician every 3 hours. The MFS was the cumulative score of the 21 items (typical range: 0 to 15) and was treated as a continuous response variable in the analysis. A

split-sample approach comprising of training (70%) and test (30%) dataset was used in the morphine dose-MFS model development and validation respectively. The data analysis included the following three steps: (i) morphine dose-MFS response model development using training dataset (ii) model evaluation using training and test dataset and (iii) Bayesian forecasting to assess model performance. All analysis was performed using R (version 3.6.1)[25] and the RStudio Interface[26].

Morphine dose – MFS response model

The morphine dose-MFS response model was developed using the training dataset (70% of the data). In the electronic medical data used in the study, the MFS was recorded every 3 hours throughout the treatment period in the NOWS infant. The morphine dosing started once the MFS score in the infant crossed a particular threshold as mentioned in the NOWS UMMC protocol (Figure S1). The morphine dose was administered every 3 hours and the next dose of morphine was changed based on the feedback from the previous MFS response. In this setting, the MFS response can be considered as an intermediate variable, while the morphine dose followed a stochastic process that was interdependent with the MFS response. Secondly, the effect of morphine dose on MFS response was considered as a direct linear effect. Thus, a first-order dynamic linear mixed effect model (DLME)[27–31] was used to model the current MFS response as a function of previous MFS response (representing past dose history) and the morphine dose as a time-varying covariate. The DLME model relating the MFS response and the morphine dose for the i^{th} infant and the j^{th} time was specified as (Equation 1):

$$MFS_i(t_j) = f(\boldsymbol{\beta}, x(t_j)) + \sum_k \rho_k \cdot MFS(t_{j-k}) + \eta_i + \epsilon_{ij} \qquad (1)$$

Where β is the vector of coefficients for the different subject-specific covariates, x is the vector of covariates, which included a time effect (certain infants did not need pharmacotherapy and improved over time), time-varying morphine dose and the time-varying need of clonidine, ρ_k is the autocorrelation coefficient at time t_{j-k}, η_i is the random intercept assumed to follow a normal distribution with mean 0 and variance ω^2 and ϵ_{ij} is the residual error assumed to follow a normal distribution with mean 0 and variance σ^2. The number of auto-correlation terms (i.e., linking MFS response at t_j to t_{j-1}, t_{j-2} etc) added to the model was determined based on the magnitude of the

correlation coefficient. Prior knowledge and clinically meaningful subject specific factors were considered as covariates and the final model was determined by step-wise regression procedure using Akaike Information Criteria (AIC). An independent covariance structure was assumed for the residual error model.

Model evaluation

The morphine dose-MFS model evaluation was performed in three steps: (i) Model evaluation in the training dataset (ii) External validation using the test dataset and (iii) Simulation based model evaluation using clinically meaningful metrics (i.e., total time on morphine treatment) for both training and test dataset.

The training model was evaluated using observed versus predicted MFS responses split by different time intervals at both population and individual level and standard residual plots. The external validation of the morphine dose-MFS response model was performed using the test dataset (30% of the data). Using the training model, the MFS responses were predicted for the test dataset and graphically assessed by plotting the observed versus predicted MFS responses split by different time intervals at both population and individual level. The percent mean absolute relative error ($\% MAE = \frac{1}{n}\sum|\frac{MFS_{observed,i} - MFS_{predicted,i}}{MFS_{observed,i}}|$); an indicator of prediction accuracy and standard deviation of prediction error ($RMSE = \sqrt{\frac{1}{n}\sum(MFS_{observed,i} - MFS_{predicted,i})^2}$); an indicator of precision of the predictions were determined.

A simulation based approach was used to evaluate the training model by deriving the clinically meaningful metrics such as total time on morphine treatment, time to maximum morphine dose and number of infants requiring clonidine in both training and test datasets. Utilizing the UMMC hospital morphine dosing protocol (Figure S1), longitudinal MFS responses were simulated ($N_{sim} = 100$) for each infant in both the training and test dataset using the training model. Then, from the simulated longitudinal MFS responses, time on morphine treatment, time to reach maximum morphine dose and number of infants requiring clonidine were calculated. The observed and simulated clinically

meaningful metrics as mentioned above were compared to assess the predictive ability of the morphine-MFS model (similar to a quantitative predictive check approach[32]).

Bayesian Forecasting

To additionally evaluate the morphine-MFS model performance, Bayesian forecasting of the MFS responses was performed for the NOWS infants in the test dataset. The Bayesian forecasting approach[33] considered the training model as prior information and individual observed MFS response to forecast future MFS responses in an infant for subsequent time intervals. The forecasting procedure for an infant started after monitoring the infant for the first 36 hours. Then, using the population morphine dose-MFS model, longitudinal MFS responses were forecasted for the next 24 hours by considering the UMMC morphine dosing protocol. The forecasting was then updated for the subsequent 24-hour time intervals (36-60hrs, 60-84hrs, 84-108hrs, 108-132hrs, 132-156hrs,156-180hrs, 156-180hrs, 180-204hrs, 204-228hrs, 228-252hrs, 252-276hrs) by refitting the model at an individual level and the cycle was repeated. The uncertainty (confidence bands) in the forecasting was obtained by repeating the simulations at each 24-hour forecasting cycle for 200 iterations. The forecasting ability of the model was assessed by comparing the observed and forecasted MFS responses graphically.

RESULTS

Out of the 242 infants admitted to the NICU for NOWS diagnosis, complete electronic medical records which included morphine dosing information were available for 177 infants over the 5-year time period. Out of the 177 infants, 152 infants (85.9%) received pharmacotherapy. Of those who received pharmacotherapy, 38.2% (58/152) received morphine monotherapy and 61.8% (94/152) needed morphine and clonidine. The median gestational age of the infants was 38.5 weeks. Majority of the infants (80%) were full term (≥ 37 weeks gestational age) and 58% of the full-term infants required morphine+clonidine as compared to 31% of the pre-term infants (< 37 weeks gestational age). Baseline infant demographics and maternal drug use characteristics are summarized in Table 1. The flow diagram depicting the analysis data construction is provided in Figure 1. The median length of stay (range) in the hospital for all infants with NOWS was 13 (3-59) days. The median length of

stay for NOWS infants requiring pharmacotherapy was 14.5 (4-59) days. On average, each infant had at least 200 observations of MFS responses and representative individual profiles of longitudinal MFS and morphine dose are shown in Supplementary Figure S2. The median (range) daily morphine dose administrated orally was 120µg (8-880ug) or 42ug/kg (2.8-314µg/kg).

Morphine dose-MFS model

The training model was developed using the training data set (70% of entire data: 123 infants, 28039 observations) based on the DLME modeling approach (Equation 1). The longitudinal mean MFS response as a function of time varying morphine dose was best described by the following model (Equation 2) and the parameter estimates are provided in Table 2: $MFS_{\{i\}(t_{\{j\}})} = \beta_0 + \rho_1 . MFS_{\{i\}(t_{\{j-1\}})} + \rho_2 . MFS_{\{i\}(t_{\{j-2\}})} + \beta_1 Morphine_{\{i\}(t_{\{j-1\}})} + \beta_2 PNA_{\{i\}} + + \beta_3 (is.Clonidine_{\{i,t_j\}}) + \beta_4 (is.Methadone_{\{i\}}) + \beta_5 (is.Benzodiazepine_{\{i\}}) + \beta_6 (is.Race_{\{i\}} == "Caucasian") + b_{\{0i\}} + \epsilon\_ij$ (2)

The base model included post-natal age and time-varying clonidine use as predictors. Significant clinically meaningful covariates were in utero methadone exposure (methadone vs other opioids), maternal benzodiazepine use (yes or no) and race of the infant (Caucasian vs African American). Significant positive autocorrelations of the previous two MFS with the current MFS response were observed with correlation coefficients of ρ_1=0.56 and ρ_2=0.12 respectively. On average, for a 1000μg increase in morphine dose, the mean MFS decreased by 0.3 units adjusting for other factors. A significant negative time effect (captured by the 24-hour post-natal age) indicated that some infants do improve over time without the need for pharmacotherapy. On average, methadone only exposed infant had a 42% higher mean MFS compared to an infant exposed to other opioids (for e.g., heroin, buprenorphine, hydrocodone, unspecified opiates). Maternal benzodiazepine use along with opioids also showed a 32% increase in mean MFS score as compared no benzodiazepine use. Moreover, on average, it was expected to see an approximate 30% increase in MFS score in Caucasian infants compared to African-American infants when other factors remain constant.

Model Evaluation

Figure S3 and Figure 2 show the population and individual predicted vs observed MFS response in the training (A) and the test (B) datasets (30% of the data: 54 infants) captured in 24-hour intervals. The goodness of fit plot demonstrates that the model was able to adequately describe the observed MFS responses at both the population and the individual level at all the time intervals evaluated. Figure S4 depicts the individual predicted longitudinal MFS response trajectory in representative

infants from the test dataset. The %MAE and RMSE in the test dataset were 44% and 1.92 indicating a reasonable performance of the training model. Figure 3 and Figure S5 show the Kaplan-Meier curve for observed and predicted proportion of NOWS infants on morphine treatment and time to maximum morphine dose respectively for the training and test dataset. The clinically meaningful metrics presented in Table 3 were derived from simulations using the training model based on the existing UMMC hospital morphine dosing protocol. The model predicted and observed time on morphine treatment for the entire group in the training dataset was 12.8 (95% CI: 11.4, 14.8) and 15.1 (95% CI: 13.4, 16.9) days, respectively (Table 3). In the test dataset, model predicted and observed time on morphine treatment for the entire group was 13.8 (95% CI: 11.5,17.2) and 13.0 (95% CI: 12.5, 14.8) days respectively (Table 3). Table 3 also shows the observed and model predicted time to maximum morphine dose and number of infants requiring clonidine or not in the training and test dataset. The observed and model predicted time to maximum morphine dose in infants who required both morphine and clonidine in the test dataset was 2.9 (95% CI: 2.5, 5.2) and 2.8 (95% CI: 2.4, 3.6) respectively. The model predicted number of infants requiring clonidine in the test dataset was 38 in comparison to 29 infants in the observed data. It can be seen from Table 3 that the model predicted metrics were within $\pm 30\%$ deviation for all the clinically meaningful metrics with overlapping confidence intervals. Overall, the simulation based model evaluation has indicated that the morphine dose-MFS model was able to capture the observed clinically meaningful metrics reasonably.

Forecasting

Figure 4 depicts the observed and forecasted MFS observations with uncertainty in representative infants from the test dataset. It can be seen that the observed longitudinal trend of MFS response was reasonably captured by the forecasted MFS responses in certain infants over the various 24-hour time intervals as described in the methods section. At least 50% of the observed MFS responses were within the uncertainty (95% confidence bands) of forecasting in each of the 24- hour forecasting intervals (Figure S6).

DISCUSSION

Despite a majority of NOWS infants (at least 60-80%) requiring pharmacotherapy and with morphine being the most commonly used opioid, there are currently no standardized or universally accepted morphine dosing protocols. Till date, there is no FDA approved drug indicated for NOWS. The lack of standardized dosing protocols has led to individual hospitals using their own protocol which may not be optimized potentially leading to longer time to stabilize withdrawal symptoms, longer time on treatment and hence longer hospital stays. Secondly, it is not practically feasible to conduct dedicated studies to evaluate different morphine dosing protocols in the neonatal population, thus leading, to pediatricians routinely making dosing decisions based on minimal empirical evidence[34]. Pharmaceutical companies have no incentive to invest in optimizing therapeutics for generic drugs like morphine, and academic research utilizing real world data can play an important role in filling the gap. The current study utilized routinely collected electronic medical records (real-world data) of infants suffering from NOWS to develop and validate a morphine dose-MFS model with the ultimate goal to optimize and individualize morphine dosing in infants with NOWS.

The routine clinical practice for pharmacotherapy with morphine in NOWS infants include titrating the dose of morphine according to the severity of MFS score to control the withdrawal, stabilizing the withdrawal symptoms and then weaning off morphine. Adjunct treatment with clonidine or other agents may be used if the symptoms are not controlled with morphine alone. Currently, the MFS is the predominant tool used in the United States for quantifying the severity of neonatal withdrawal. The withdrawal state assessment using the MFS is the main driver for pharmacotherapy in neonatal drug withdrawal[35]. Though at UMMC, the morphine dosing protocol as shown in Figure S1 is routinely used, often subjectivity is involved in morphine dosing decisions to control and stabilize the withdrawal symptoms. A quantitative understanding of the morphine dose and MFS response could assist in an objective and data-driven clinical decision making with potentially improved clinical outcomes (i.e., lesser time on treatment).

In the current study, using electronic medical records, a longitudinal morphine dose-MFS model was developed using a DLME approach, where the morphine dose was treated as a time-varying predictor linearly related to MFS response incorporating a feedback from the response process to the dosing process. Inherently, the decision on the next morphine dose was based on the previous outcome of

the MFS response. Thus, using the DLME modeling framework, the current MFS response was regressed on the previous MFS responses, which accounts for the past dosing history. Morphine dose was considered as the drug exposure variable as it is not regular clinical practice to measure morphine blood concentrations. The usual starting dose of morphine at UMMC was 80ug and is titrated upwards based on the NOWS severity in the respective infant as measured by MFS response. The DLME models have been previously reported to assess dose-response relationship in flexible dose clinical trials and provide an unbiased and efficient estimator to recover the exposure-response relationship[27,30]. The morphine dose-MFS model also incorporated the time effect as some infants exhibit mild withdrawal signs and improve without pharmacotherapy and a time-varying clonidine effect to include infants who received adjunct clonidine treatment.

Maternal methadone use, benzodiazepine use and race of the infant were found to be significant covariates based on the data and were associated with higher MFS response. Methadone maintenance is recommended as standard of care for opioid dependent pregnant women as it is associated with improved fetal growth, stabilized maternal lifestyle and reduced risk-taking behaviours[36,37]. Withdrawal in infants with prenatal exposure to methadone has been shown to be more prolonged than that from other illicit opioids[38] (i.e., heroin use), which could be attributed to longer pharmacokinetic half-life of methadone (mean ~22 hours)[39]. The current data also demonstrated that *in utero* exposure to methadone is associated with 42% higher mean MFS response as compared to infants who were exposed to other opioids. Use of benzodiazepines with opioids have been associated with longer length of hospital stays from multiple studies[40,41] and is consistent with this analysis, as maternal benzodiazepine use was associated with a 32% increase in mean MFS response. Benzodiazepines augment the action of the central nervous inhibitory neurotransmitter; g-aminobutyric acid receptor[42]. In the current study, Caucasian infants were associated with a 30% increase in mean MFS score compared to African-American infants, which is consistent with our previous finding that Caucasian infants are 2.2 times more likely to require pharmacotherapy than African-American infants[23].

The analysis used a split-sample approach, where the developed morphine dose-MFS model was externally validated in a test dataset (30% of the data not used in model development). The predicted

mean MFS scores were in close agreement with the predicted MFS scores in the test dataset indicating adequate model performance (Figure 2B). In addition, the clinically meaningful metrics such as time on morphine treatment, time to maximum morphine dose and proportion of infants requiring clonidine simulated by using the existing UMMC protocol were within 30% deviation of the observed values in the test dataset suggesting robustness of the model (Table 3). The Bayesian forecasting was able to capture the individual trajectories reasonably well, indicating the model has the potential to derive individualized dosing for NOWS infants.

One of the primary limitations of the study was that the data was obtained from the electronic medical records from a single hospital with a specific morphine dosing protocol, limiting generalizability of the results. Other limitations include not considering non-pharmacological interventions (NPI) such as the effect of environment, use of soothing techniques, cuddling, parental presence and/or rooming - in on the MFS response, as the information was not collected or not available due to retrospective nature of the data. In addition, another clinically meaningful predictor such as breast feeding rate was not adjusted in the model, as the rates of breast feeding during the study period were less than 5%. The impact of the factors could not be assessed in the analysis due to non-availability of the information. In the future, it is expected to collect the information to further refine the MFS-morphine dose model that could potentially improve the forecasting capabilities. Finally, though MFS is the standard tool used for assessing the severity of NOWS, Finnegan scoring system (comprising of 21 items) itself contains both objective and subjective items. There are certain highly subjective ones, such as the excessiveness of sucking or crying, degree of briskness of Moro reflex, hypertonia or nasal stuffiness, and other items that are difficult to measure such as the number of yawns and sneezes[43]. However, the inter-rater variability in the MFS scoring was assumed to be minimal.

In summary, a comprehensive morphine dose- MFS model was successfully developed adjusting for infant and maternal baseline factors using routinely collected data from electronic medical records and was internally and externally validated. Further, Bayesian forecasting of individual MFS trajectory reasonably described the observed MFS profile. Optimizing NOWS treatment and morphine dosing is a priority, given the nationwide opioid epidemic and the unknown effects of early

exposure to opioids on infant and child development. Reports have suggested that infants exposed to prenatal opioids are born small for gestational age, have smaller head circumference and reduced neurocognitive performance in childhood[44–46]. Further more, the impact of prolonged pharmacotherapy with opioid on long-term developmental outcomes are not clearly understood[7,12,13]. As future work, the developed model will be utilized to explore alternate morphine dosing protocols to reduce the overall time on pharmacological treatment thereby decreasing the burden of opioids on the developing brains of the newborn leading to improved clinical outcomes. The work could potentially pave way for a unified and standardized morphine dosing protocols in hospitals/medical centers nationwide in the distant future. The quantitative model based framework can assist clinicians in performing evidence-based, adaptive, individualized, dosing of morphine in real-time.

STUDY HIGHLIGHTS

What is the current knowledge on the topic?

At least 60% of the newborns with neonatal opioid withdrawal syndrome (NOWS) require morphine, the commonly used opioid, to control withdrawal symptoms. However, the current morphine dosing protocols are not optimal leading to longer time to stabilize the symptoms and hence longer hospital stays. Till date, a quantitative model to describe the relationship between morphine dose and the clinical response (Modified Finnegan Score (MFS)) is not reported.

What question did the study address?

The current study utilized electronic medical records of infants with NOWS to develop and validate a quantitative morphine dose-MFS model adjusted for baseline maternal and infant risk factors.

What does this study add to our knowledge?

The quantitative model developed can be used to explore alternate morphine dosing regimens and is the first step to optimally deliver morphine treatment to newborns with NOWS.

How might this change clinical pharmacology or translational science?

The quantitative morphine-MFS framework can assist clinicians with data-driven and informed clinical decision making that could lead to optimal pharmacological care for newborns suffering with NOWS.

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AUTHOR CONTRIBUTIONS

N.W., O.A., J.B., D.E., and M.G. wrote the manuscript. J.B., D.E. and M.G designed the research. N.W., O.A., J.B., and M.G. performed the research. N.W. and M.G. analyzed the data.

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FIGURE LEGENDS

Figure 1: Schematic of the analysis dataset preparation from the electronic medical records

Figure 2: Model predicted **i**ndividual Modified Finnegan Score in training (A) and test (B) dataset during the different time intervals in representative infants

Figure 3: Kaplan-Meier curves for **o**bserved and model predicted time on morphine treatment for all NOWS infants, infants on morphine and infants on morphine+clonidine in training (A) and test (B) dataset

Figure 4: Bayesian forecasting of longitudinal MFS scores in representative infants using the UMMC hospital morphine dosing protocol

Supplemental Files

1. Supplemental Material.docx

Table 1: Baseline characteristics of infants with NOWS

Infant Characteristics	Number of subjects (N= 177)
Birth weight, median (range), g	2895 (1600, 4665)
Gestational age, median (range), week	38.5 (35.0, 42.2)
Gender, n (%)	
Female	73 (41.2)
Male	104 (58.8)
Race or ethnic group, n (%)	
African American	57 (32.2)
Caucasian	120 (67.8)
Prenatal Exposure, n (%)	
Methadone	91 (51.4)
Heroin	35 (19.8)
Buprenorphine	20 (11.3)
Other opioids (hydrocodone, codeine, oxycodone)	31 (17.5)
Poly-opioid use[#]	61 (34.5)
Opioid + Benzodiazepines	37 (20.9)
Opioid + Marijuana	29 (16.4)
Opioid + Tobacco	33(18.6)
Opioid + Cocaine	52 (29.4)
Need for Pharmacotherapy, n (%)	152 (85.9)
Morphine	58 (38.2)
Morphine + Clonidine	94 (61.8)

[#] Poly-opioid use refers to use of more than one opioid by the mother.

Table 2: Mean parameter estimates (95% confidence interval) based on the training dataset

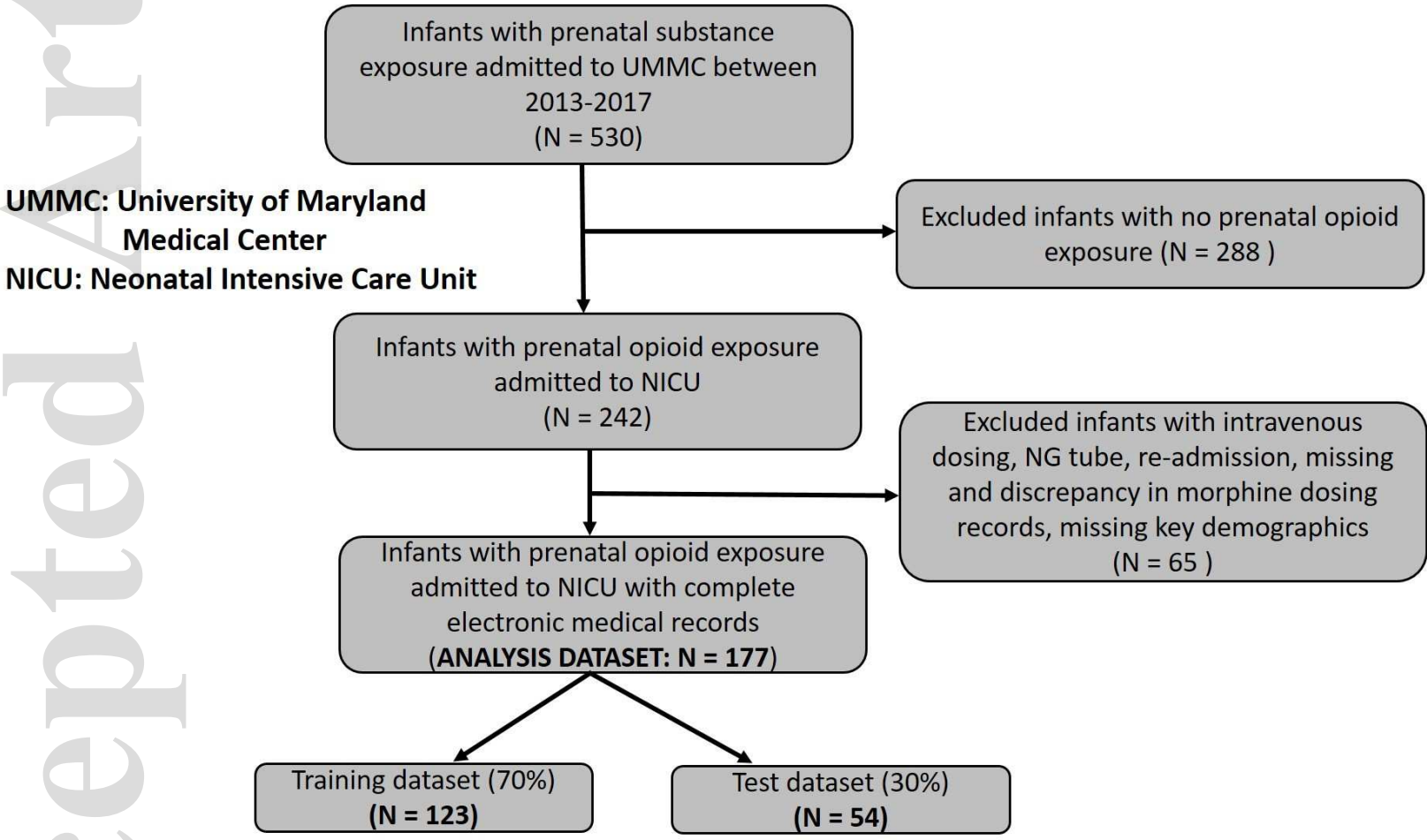
Predictor Variable	Estimate	95% Confidence Interval	
Intercept	1.6740	1.4542	1.8938
MFS (t-1)	0.5605	0.5394	0.5816
MFS (t-2)	0.1161	0.0950	0.1373
Morphine dose, ug	-0.0003	-0.00070	0.00049
Post-natal age, hours	-0.0009	-0.00212	-0.00067
Clonidine use: Yes	-0.1983	-0.3251	-0.0071
Methadone use: Yes	0.4245	0.2089	0.6402
Benzodiazepine use: Yes	0.3118	0.0447	0.5789
Race: Caucasian	0.3015	0.0724	0.5307
Residual error (SD)	1.93		
Random intercept (SD)	0.56		

MFS (t-1) - Modified Finnegan Score at time t-1, MFS (t-2) –Modified Finnegan Score at t-2

Table 3: Morphine-MFS model internal (training dataset) and external validation (test dataset) using clinically meaningful outcomes

Clinical metric		Entire Group		Morphine Group		Morphine+Clonidine Group	
		Training data	**Test data**	**Training data**	**Test data**	**Training data**	**Test data**
Median time on treatment, days	Observed	15.1 (13.4,16.9	13.0 (12.5, 14.8)	10.7 (9.1,15.1)	13.0 (8.4, 17.1)	17.0 (15.2, 20.4)	12.9 (12.3, 15.8)
	Predicted	12.8 (11.4,14.8)	13.8 (11.5, 17.2)	9.3 (8.2,10.5)	10.6 (9.2, 15.3)	18.9 (15.7,22.9)	15.6 (12.7, 19.2)
	% deviation	15.2%	-6.2%	13.5%	18.5%	-11.2%	-21%
Median time to maximum morphine dose, days	Observed	3.2 (2.9, 4.3)	2.6 (1.7, 3.9)	2.4 (1.7, 3.6)	1.7 (1.3, 3.7)	4.3 (3.2, 6.0)	2.9 (2.5, 5.2)
	Predicted	3.1 (2.6, 3.5)	2.7 (2.0,3.3)	2.5 (2.1, 2.9)	1.8 (1.5,3.2)	3.8 (3.0, 5.1)	2.8 (2.4, 3.6)
	% deviation	3.2%	-3.8%	-4.2%	-5.9%	11.6%	3.4%
Number of infants requiring only morphine and	Observed			42	16	65	29
	Predicted			44	17	79	38

morphine+clonidine					



UMMC: University of Maryland Medical Center
NICU: Neonatal Intensive Care Unit