Optimizing Pediatric Outcomes: Advanced Bayesian Modeling of Days Without Mechanical Ventilation in Respiratory Trials

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Introduction: Complex Outcomes in Clinical Trials

❓ **Why are complex outcomes challenging?**

Many clinical interventions affect **multiple outcome dimensions** simultaneously (e.g., duration, severity, recurrence).

Outcomes may be:

- **Composites** (combining binary, ordinal, continuous)
- **Semi-continuous** (e.g., duration with many zeros)
- **Bounded** or **non-normal**

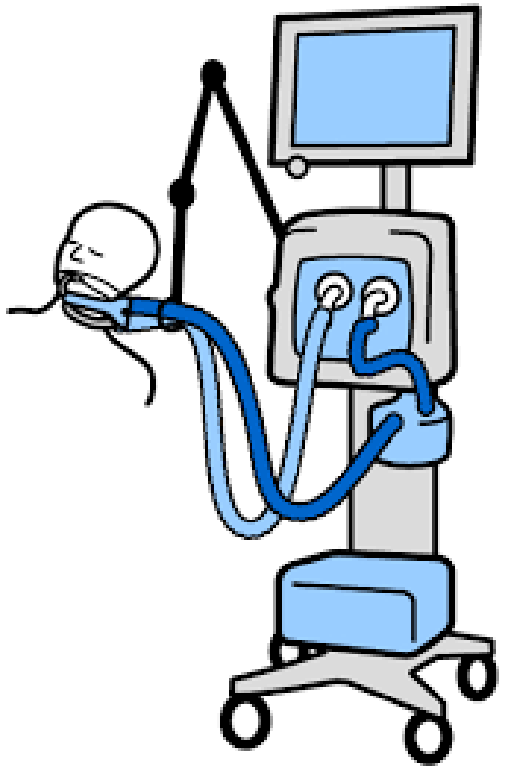
Why are outcomes complex in the PICU setting?

Pediatric ICU (PICU) patients often experience **multifaceted clinical trajectories**:

- Nonlinear recovery
- Intermittent escalation in support
- Heterogeneity in response to interventions

Common outcomes like:

- **Days of mechanical ventilation (MV)**
- **Composite escalation scores**
- **Duration-free days (e.g., ventilation-free or ICU-free)**
- are *not* normally distributed and often contain **structural zeros** or **bounded distributions**.



Case Study

- **Population**: Infants <2 years with mild to moderate respiratory distress (Wood-Downes-Ferrés ≤8).
- **Randomized trial**: NIV (n=126) vs. HFNC (n=126).
- **Primary outcome**: Need for invasive mechanical ventilation (intubation).
- **Secondary outcomes**: Sedation, nasal trauma, hospital LOS, etc.
- **Noninferiority margin**: 15% absolute risk difference.

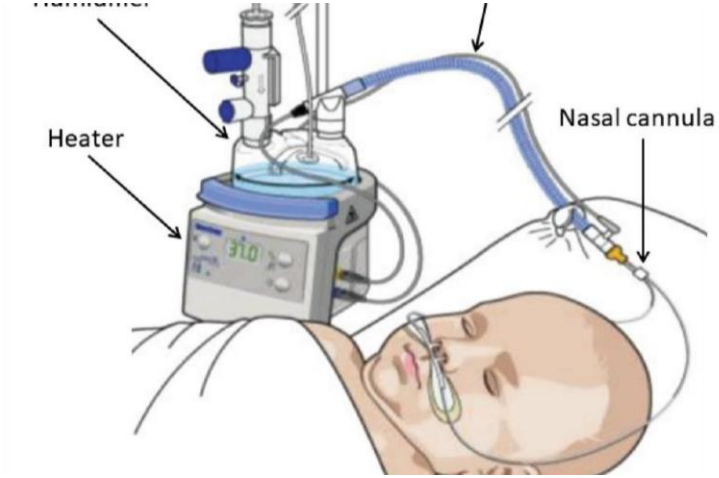
Full face mask
Ref- Intersurgical
BiTrac MaxShield Select

Oronasal Mask
Ref - Dragger

Nasal Mask
Ref - Resmed Pixie

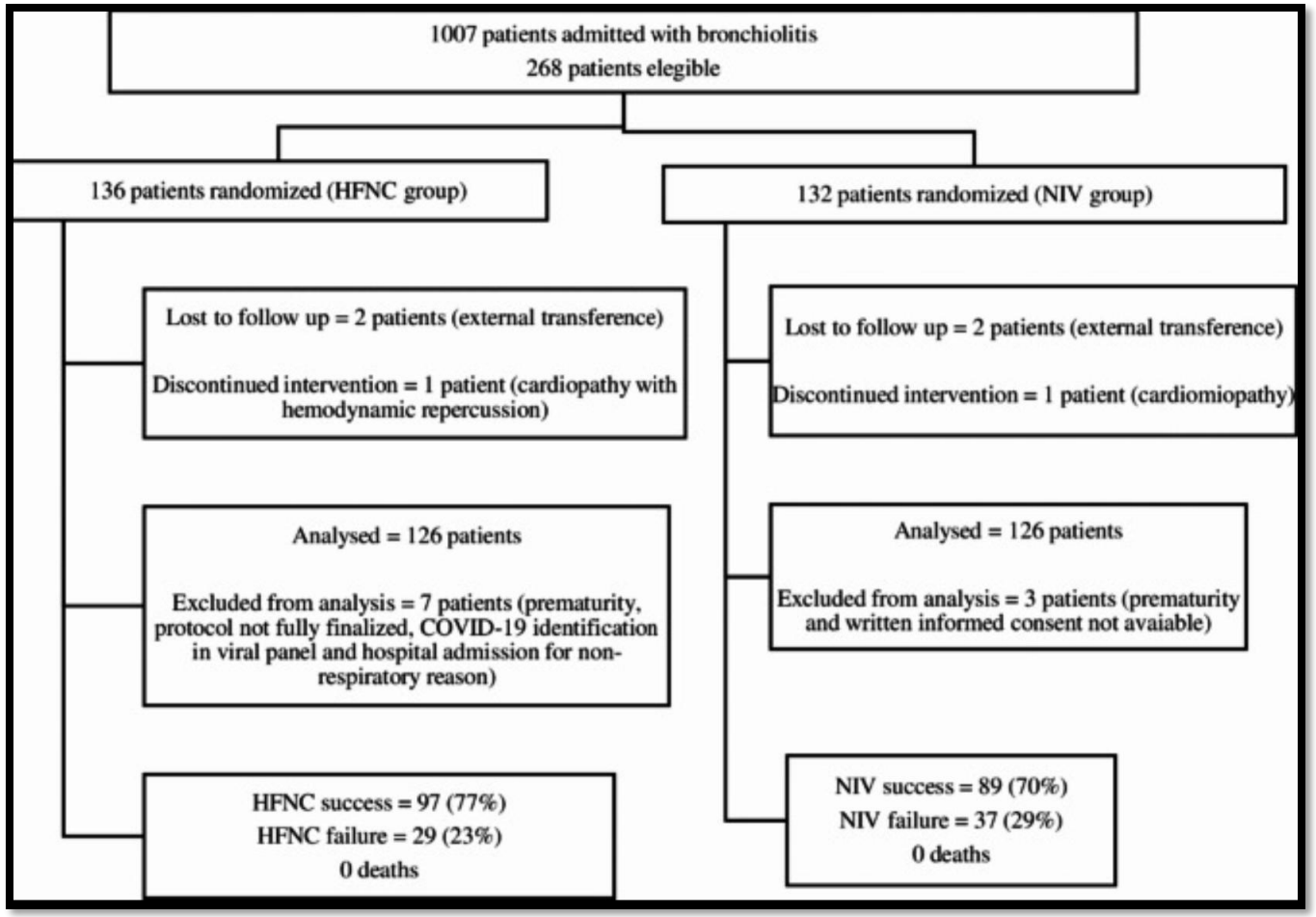
Nasal Pillow
Ref - Resmed AirFit P30i

Non-Invasive Ventilation (NIV)



HFNC High Flow Nasal Cannula

Trial Flowchart



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BMC Pediatrics

RESEARCH Open Access

"Comparison between high-flow nasal cannula (HFNC) therapy and noninvasive ventilation (NIV) in children with acute respiratory failure by bronchiolitis: a randomized controlled trial"

Ana Carolina Etrusco Zaroni Santos[1*], Carolina Marques Caiado[1], Alessandra Geisler Daud Lopes[1], Gabriela Cunha de França[1], Ana Karolina Antunes Eisen[2], Danielle Bruna Leal Oliveira[2,3], Orlei Ribeiro de Araujo[4] and Werther Brunow de Carvalho[5]

Outcomes

Primary Outcome. Assessing, in infants hospitalized for bronchiolitis with mild to moderate respiratory distress, that HFNC therapy is noninferior to NIV in terms of intubation rate (δ = 0.15)

Secondary Outcome. Sedation usage, invasive mechanical ventilation duration, the PICU LOS, the hospital LOS, and the mortality rate.

Trial Results

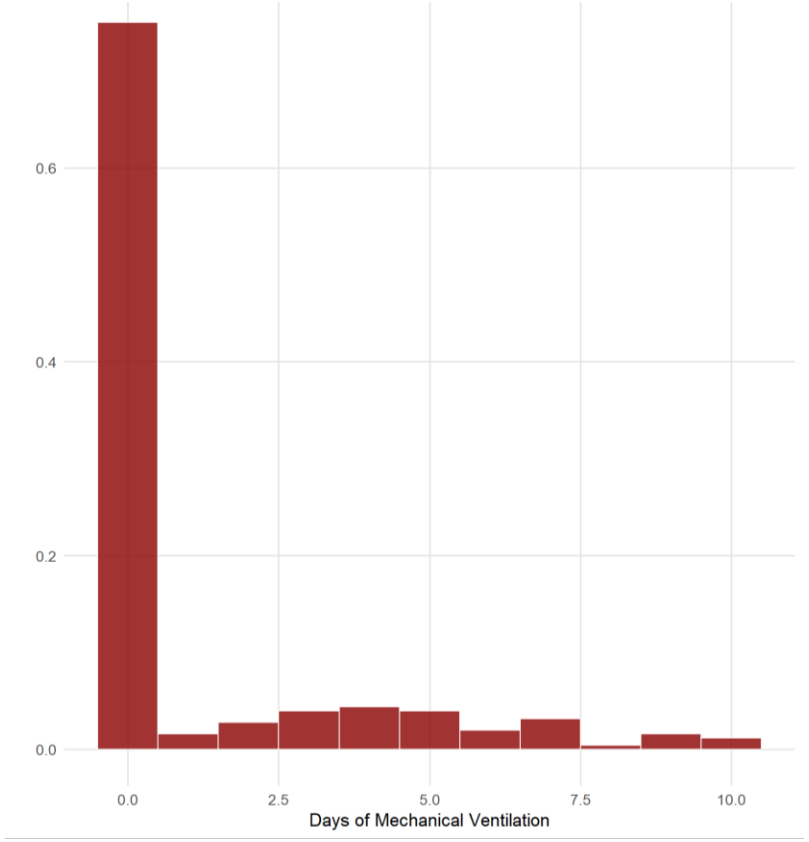
- Thirty-seven patients in the NIV group were intubated (29%), and 29 patients in the HFNC group were intubated (23%, $p = 0.25$).
- According to the Farrington-Manning test, within the noninferiority margin of 15%, the difference was 6.3% in favor of HFNC therapy (95% confidence interval: -4.5 to 17.1%, $p < 0.0001$)

	NIV	HFNC	*p*
Age (months, IQR)	2.5 (1–6)	3 (2–7)	0.07
Weight z score for age (mean, SD)	-0.18 (1.18)	-0.18 (1.11)	0.95
Female (N, %)	52 (41%)	41 (32.5%)	0.15
Previous wheezing (N, %)	39 (31%)	32 (25.3%)	0.3
Previous respiratory hospitalization (N, %)	30 (23.8%)	22 (17.4%)	0.2
NIV/HFNC duration (hours, median, IQR)	48 (24–78)	77.5 (46.5–108)	0.0003
Initial FiO_2 (mean, SD)	40.8 (10.8)	36.2 (10.6)	0.0002
Initial WDF (mean, SD)	5.9 (0.9)	5.9 (1.1)	0.9
Initial SpO_2 (mean, SD)	97.6 (1.9)	97.4 (1.9)	0.25
Sedation (N, %)	121 (96%)	54 (42.8%)	< 0.001
Sedation (days, median, IQR) Nasogastric tube (days, median, IQR)	3 (2–4) 3 (2–4)	2 (1–4) 4 (2–5)	0.08 0.012
PICU LOS (days, median, IQR)	5 (3–10)	5 (4–7)	0.3
Hospital LOS (days, median, IQR)	9 (6–14)	8 (6–10)	0.006
Invasive mechanical ventilation duration (days, median, IQR) Antibiotic use (n, %) Ventilator-associated pneumonia	5 (3.7–7) 62 (49%) 1 (2%)	4 (2.5–4.5) 49 (38%) 1 (3,4%)	0.02 < 0.001 -
PIM 2 score (mean, SD)	1.8 (1.7)	1.5 (1.4)	0.49

Why dicotomize and split the outcome? 🤔

What Next

Outcomes are **bounded, skewed, and include zeros!**



👩 **Case in point: Bronchiolitis trial (Santos et al., 2024)**

- Many infants **never intubated** → excess zeros
- Others have **long durations** → right-skew
- Outcomes are **semi-continuous** and **bounded**

📉 **Challenges for standard models:**

- **Linear regression** assumes normality and unbounded support
- **GLMs** often fail to capture **zero-inflation** or **ceiling effects**
- Loss of statistical Power.
- 📉 Example: Converting "days of mechanical ventilation" into "prolonged MV: yes/no" ignores the difference between 3 and 10 days.

Reframe the outcome modelling

📉 Outcome model

- **Hurdle models:** separate zero/non-zero parts
- **Zero-One Inflated Beta (ZOIB):** for bounded [0,1] data with mass at extremes
- **Cumulative logistic regression:** for ordinal duration categories

🧠 Bayesian Modelling

- Incorporation of prior knowledge.
- Full posterior uncertainty quantification.
- Probability statements (noninferiority, superiority).

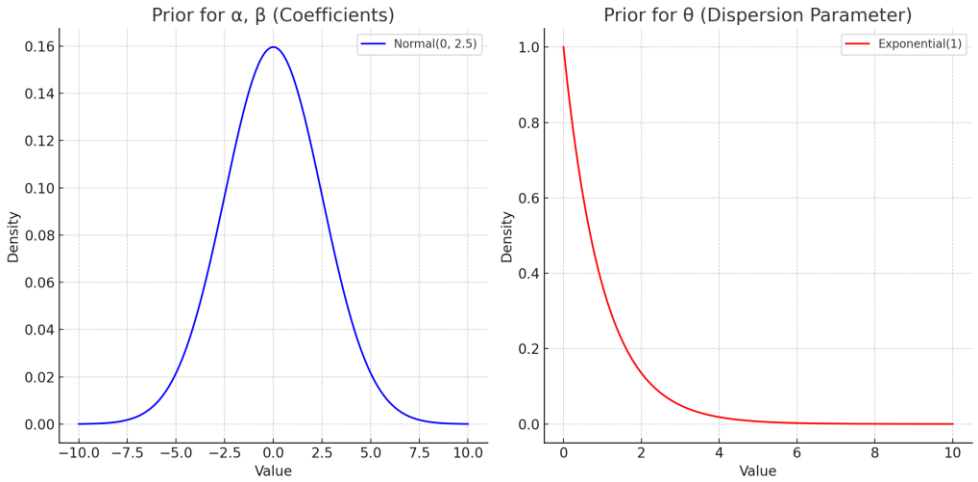
Hurdle Model

- Two-part model for count data with many zeros:
- **Part 1**: Binary outcome for whether $Y_i > 0$

$$\Pr(Y_i > 0) = \text{logit}^{-1}(\alpha_0 + \alpha_1 \cdot \text{HFNC}_i)$$

- **Part 2**: Count model for $Y_i \mid Y_i > 0$

$$Y_i \sim \text{NegBin}(\mu_i, \theta), \log(\mu_i) = \beta_0 + \beta_1 \cdot \text{HFNC}_i$$



Priors:

- $\alpha_j, \beta_j \sim \text{Normal}(0, 2.5)$
- $\theta \sim \text{Exponential}(1)$ or $\text{Gamma}(0.01, 0.01)$ (for overdispersion)

Zero-One Inflated Beta (ZOIB) Model

- Models in 3 part $Y_i \in [0,1]$ with excess 0 and 1 values
- Probability of zero or one:

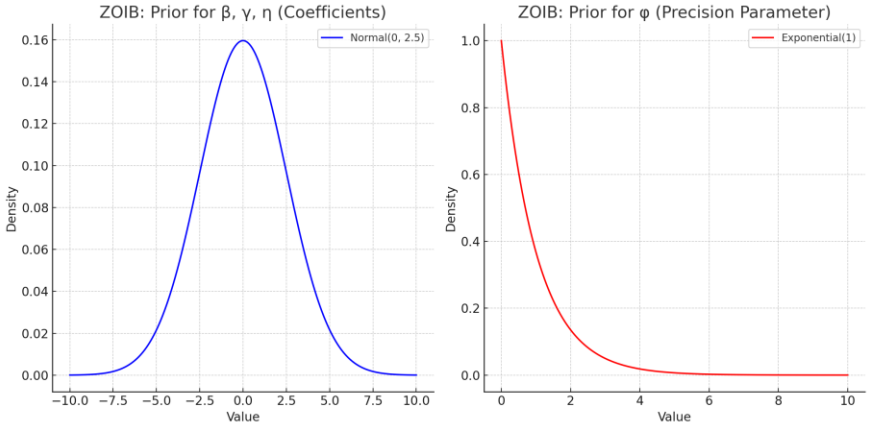
$$\Pr(Y_i \in \{0,1\}) = \text{logit}^{-1}(\gamma_0 + \gamma_1 \cdot \text{HFNC}_i)$$

- Probability of one given boundary:

$$\Pr(Y_i = 1 \mid Y_i \in \{0,1\}) = \text{logit}^{-1}(\eta_0 + \eta_1 \cdot \text{HFNC}_i)$$

- Beta-distributed component for $Y_i \in \{0,1\}$

$$\text{logit}(\mu_i) = \beta_0 + \beta_1 \cdot \text{HFNC}_i, Y_i \sim \text{Beta}(\mu_i, \phi)$$



Priors

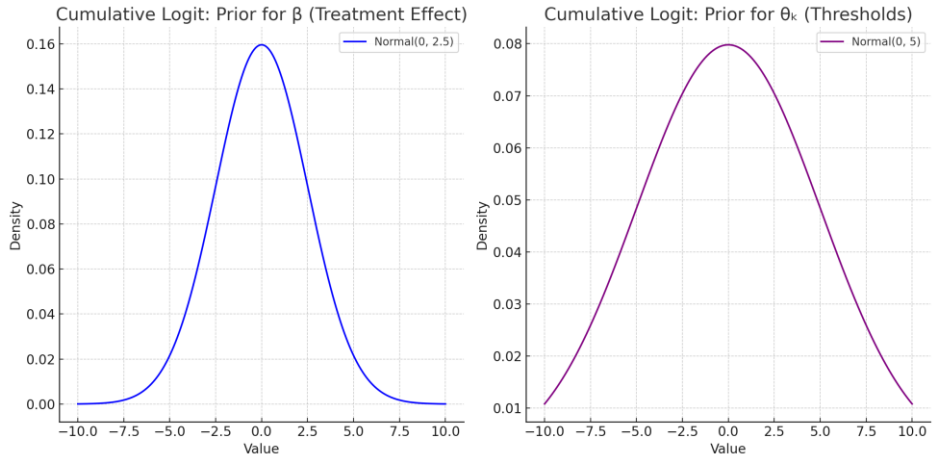
$$\beta_j, \gamma_j, \eta_j \sim \text{Normal}(0, 2.5)$$
$$\phi \sim \text{Exponential}(1) \text{ (precision)}$$

Cumulative Logistic Regression

- For ordinal outcome with categories *1,2,…,K*:

$$\Pr(Y_i \leq k) = \text{logit}^{-1}(\theta_k - \beta \cdot \text{HFNC}_i), k = 1, \ldots, K-1$$

- θ_k Threshold Parameter
- β Treatment Effect

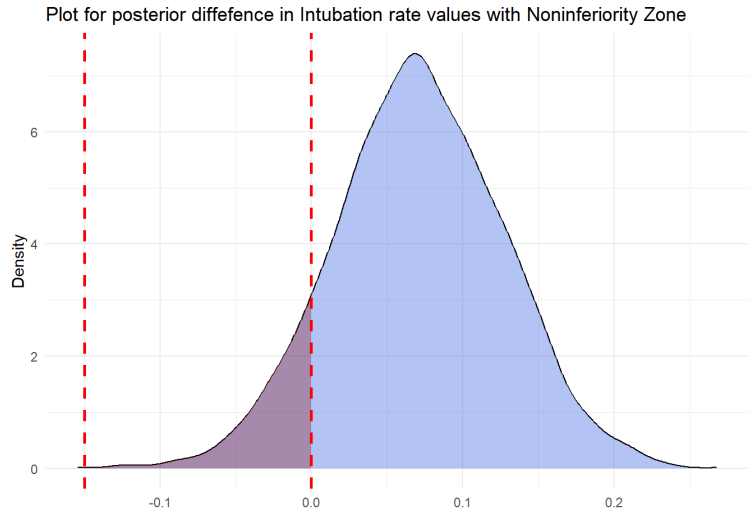


Priors:

- $\beta \sim \text{Normal}(0, 2.5)$
- $\theta_k \sim \text{Normal}(0, 5)$, ordered for identifiability

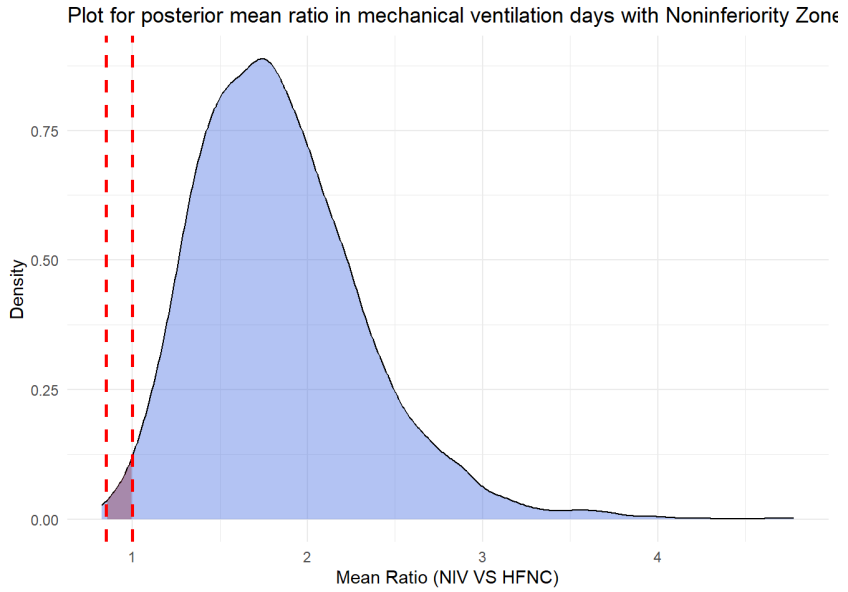
Classical approaches

- Bayesian logistic regression on Intubation Risk



HFNC	NIV	Rate Difference (RD)	1-Probability of Noninferiority	1-Probability of Superiority
0.21 (0.15; 0.29)	0.29 (0.21; 0.37)	0.07 (-0.04; 0.18)	<0.001	0.102

- Bayesian Linear Model



HFNC MV Days	NIV MV Days	Mean Ratio (MR)	1-Probability of Noninferiority	1-Probability of Superiority
0.86 (0.42; 1.27)	1.52 (1.1; 1.95)	0.67 (0.08; 1.28)	0.00225	0.00025

Hurdle and ZOIB model

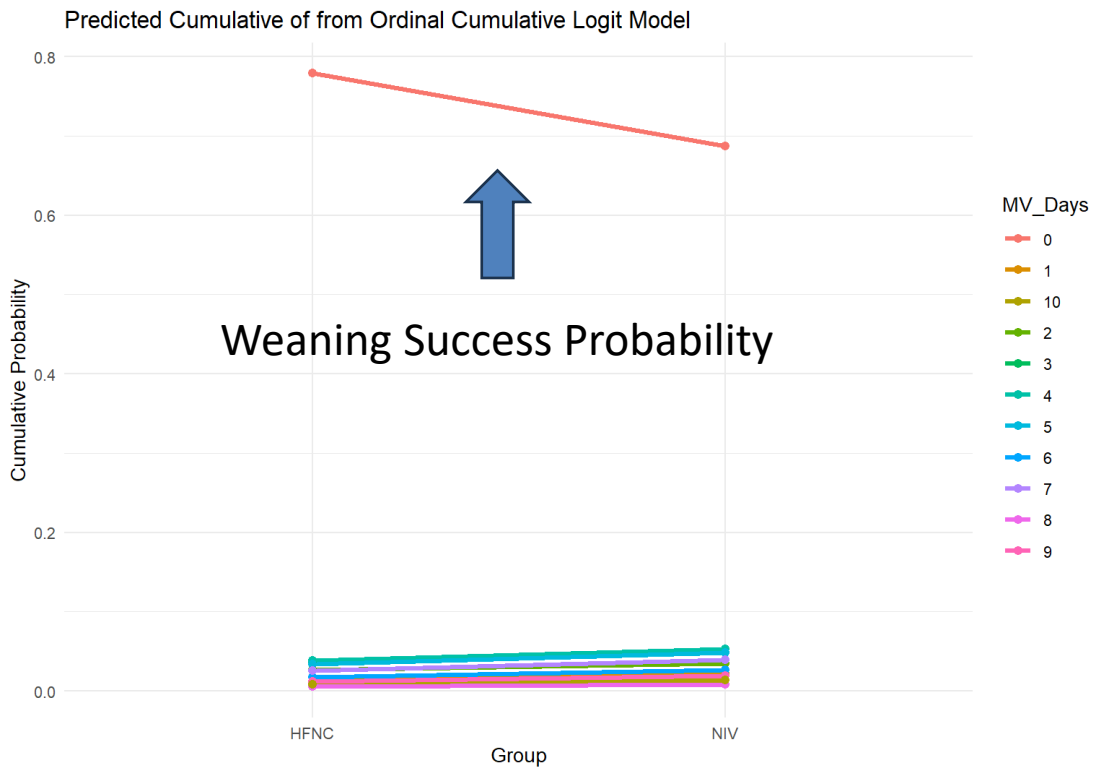
- Hurdle

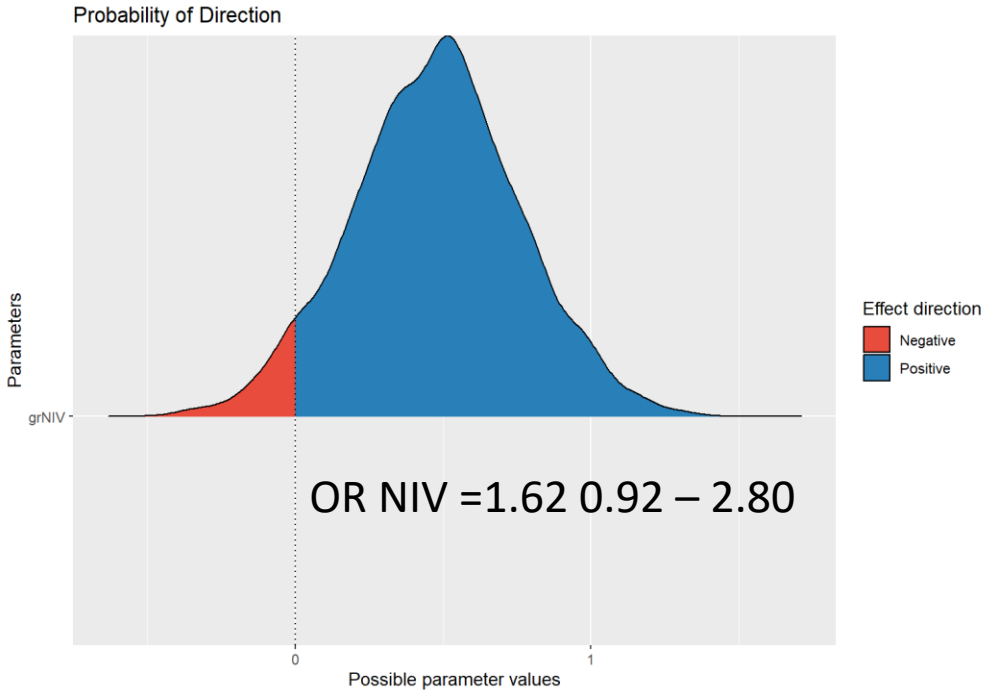
HFNC MV Days	NIV MV Days	Mean Difference in MV Days	Rate Difference (RD)	1-Probability of Noninferiority	1-Probability of Superiority (MV Days)	1-Probability of Superiority (Intubation Risk)
0.86 (0.58; 1.24)	1.52 (1.09; 2.08)	0.67 (0.1; 1.28)	-0.07 (-0.18; 0.03)	0.00075	<0.001	0.0795

- ZOIB

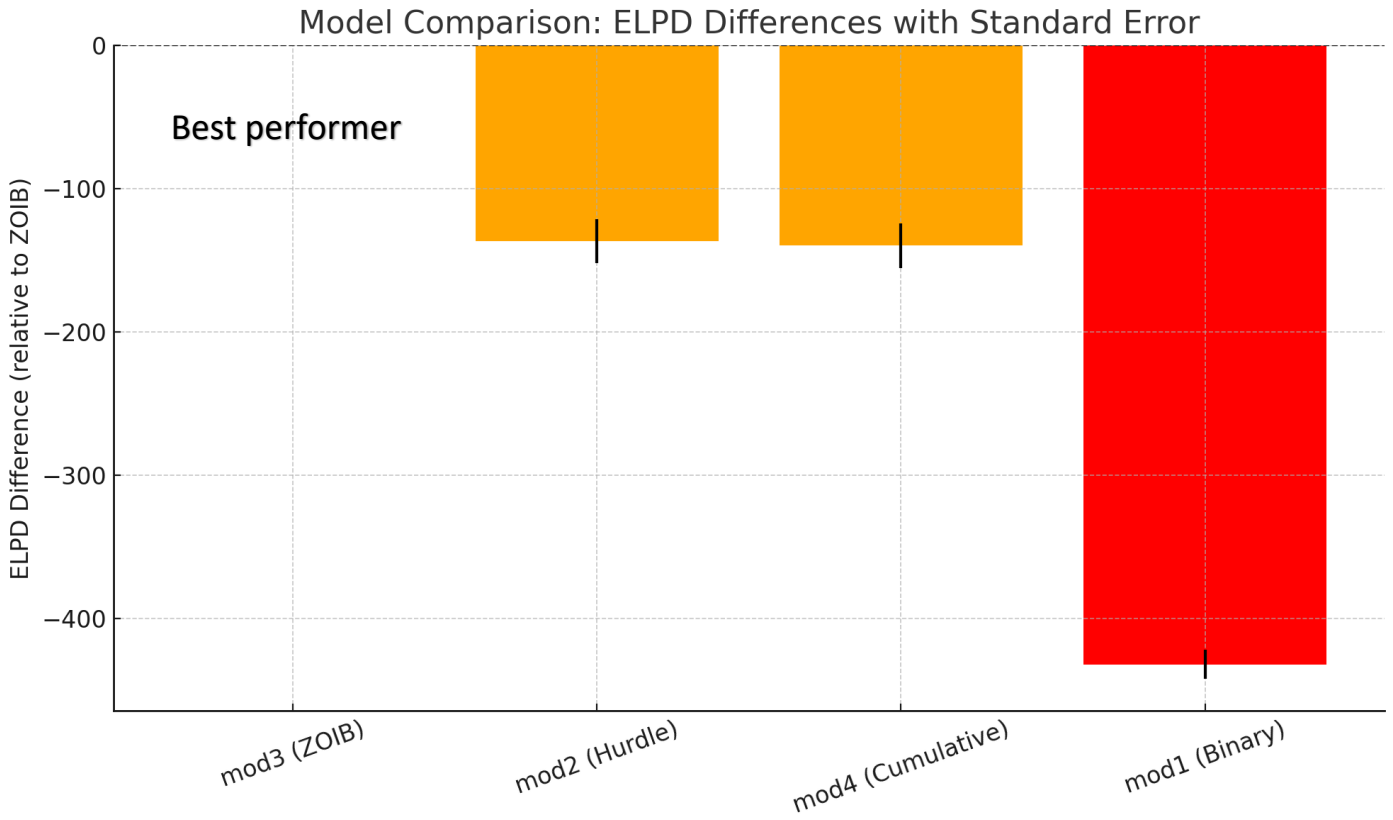
HFNC MV Days	NIV MV Days	Mean Difference in MV Days	Rate Difference (RD)	1-Probability of Noninferiority	1-Probability of Superiority (MV Days)	1-Probability of Superiority (Intubation Risk)	Worst Outcome Rate Difference	1-Probability of Worst outcome Effect
0.89 (0.6; 1.3)	1.6 (1.1; 2.1)	0.7 (0.1; 1.3)	-0.06 (-0.17; 0.04)	0.0015	<0.001	0.1168	0.01 (-0.02; 0.05)	0.251

Cumulative Logistic Regression





Leave One Out Comparison



Conclusions

Noninferiority confirmed: HFNC did not increase intubation risk compared to NIV (margin δ = 0.15).

Duration: Average MV duration was **lower in HFNC** (0.86 vs. 1.52 days).

Advanced Bayesian models (Hurdle, ZOIB, Ordinal) reflect the **real clinical outcome shape**:

- Bounded
- Skewed
- Zero-inflated

These models support **clinical interpretability** and help move beyond dichotomized thinking.

Bayesian modeling reveals that **HFNC is a safe and effective alternative** for managing pediatric respiratory distress.

Thank You for the attention!!!