Supplementary Material for "ASSOCIATION OF THE PATTERN OF TRANSITION BETWEEN AROUSAL STATES IN NEONATES WITH THE CORD BLOOD LEAD LEVEL" by Mamtani et al.

1. Results of multinomial logistic regression analysis demonstrating the concordance between two schemes of categorization of CBL

Using cut-off values of 1 and 10 μg/dL for categorization of the CBL levels, while clinically useful, created three groups in our dataset with substantially different number of subjects in each group (58, 96 and 13). To ensure that the results shown in Figure A to E of the main text are not an artifact of this scheme of categorization, we also assessed if similar trends hold if the data are categorized using criteria that lead to more comparable groups with respect to size.

For this, we categorized the study subjects into three groups based on the tertiles of CBL level. The 33rd and 67th tertiles were observed to be 0.9688 and 2.3384 μg/dL, respectively. These cut-offs resulted in three groups of sizes 55 (CBL ≤0.9688 μg/dL), 58 (CBL 0.9688 – 2.3384 μg/dL) and 55 (CBL >2.3384 μg/dL). The total number of arousal state transitions (and the average number of transitions per neonate) observed in the subjects within each of these groups were 318 (5.78), 364 (6.28) and 328 (5.96), respectively.

The following table compares the likelihood of being in the second or third tertile for CBL level to the likelihood of being the first tertile for each of observed state transition using multinomial logistic regression analysis. The results are adjusted for same confounders as those shown in Table 2 of main text. The most common transition (4→6) is used here as the reference transition. These results: i) compare very well with the results shown in Table 2 of the mains text, and ii) demonstrate that our results shown in the main text are unlikely to be artifactual.

Transition	Middle Tertile			Upper Tertile		
	OR	95% CI	P	OR	95% CI	P
Reference transition						
4 → 6	1.00	---	---	1.00	---	---
Transitions with less likelihood						
2 → 3	0.24	0.06 – 0.88	0.032	0.29	0.08 – 1.10	0.068
6 → 3	0.37	0.14 – 1.02	0.054	0.15	0.03 – 0.70	0.016
Transitions with more likelihood						
2 → 5	1.73	0.42 – 7.19	0.447	3.58	0.94 – 13.6	0.061
6 → 5	2.05	1.10 – 3.83	0.023	3.05	1.64 – 5.68	<0.001
5 → 6	2.39	1.24 – 4.59	0.009	3.76	1.97 – 7.19	<0.001

2. Markov modeling specifications to predict the transition between arousal states

To characterize and predict a sequence of transition between arousal states in a given neonate, we used Markov modeling. For this purpose we used the software DATA 3.51 (Decision Analysis by TreeAge,). We first generated state transition matrices based on the data shown in Fig A to C of the main text. These matrices summarize the probability of transition from a previous state (rows of the state transition matrix) to the next state (columns of the state transition matrix). These matrices are as follows:

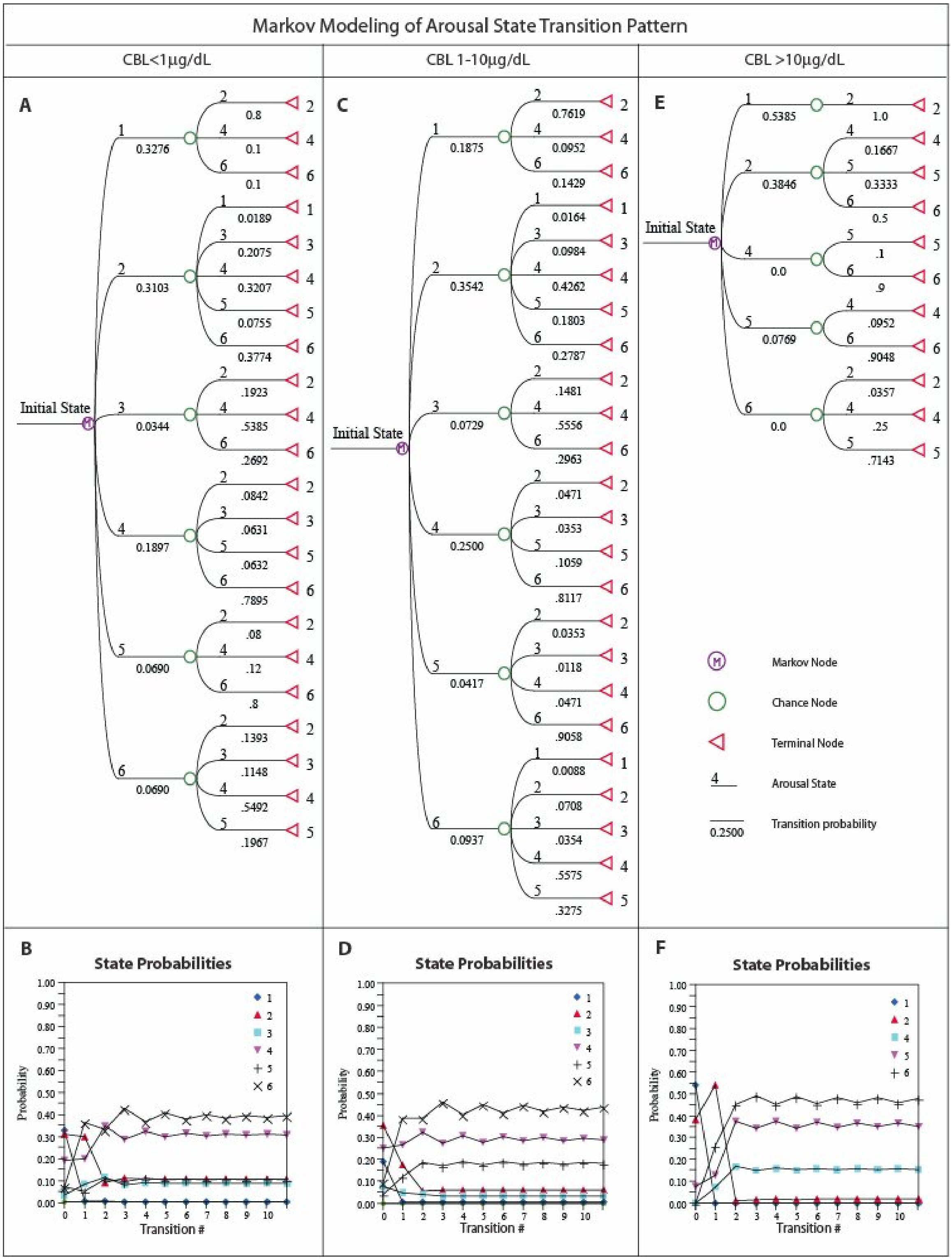
$$\text{CBL} <1\mu\text{g/dL} \quad \begin{bmatrix} 0 & 0.8 & 0 & 0.1 & 0 & 0.1 \\ 0.0189 & 0 & 0.2075 & 0.3207 & 0.0755 & 0.3774 \\ 0 & 0.1923 & 0 & 0.5385 & 0 & 0.2692 \\ 0 & 0.0842 & 0.0631 & 0 & 0.0632 & 0.7895 \\ 0 & 0.08 & 0 & 0.12 & 0 & 0.8 \\ 0 & 0.1393 & 0.1148 & 0.5492 & 0.1967 & 0 \end{bmatrix}$$

$$\text{CBL 1-10 } \mu\text{g/dL} \quad \begin{bmatrix} 0 & 0.7619 & 0 & 0.0952 & 0 & 0.1429 \\ 0.0164 & 0 & 0.0984 & 0.4262 & 0.1803 & 0.2787 \\ 0 & 0.1481 & 0 & 0.5556 & 0 & 0.2963 \\ 0 & 0.0471 & 0.0353 & 0 & 0.1059 & 0.8117 \\ 0 & 0.0353 & 0.0118 & 0.0471 & 0 & 0.9058 \\ 0.0088 & 0.0708 & 0.0354 & 0.5575 & 0.3275 & 0 \end{bmatrix}$$

$$\text{CBL} >10\ \mu\text{g/dL} \quad \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0.1667 & 0.3333 & 0.5 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0.1 & 0.9 \\ 0 & 0 & 0 & 0.0952 & 0 & 0.9048 \\ 0 & 0.0357 & 0 & 0.25 & 0.7143 & 0 \end{bmatrix}$$

We then used the observed probabilities of initial states within each of these categories of CBL as the initial probabilities (shown along the branches of the Markov node in the Supplementary Figure 1, A, C and E) and modeled the probabilities of each state in the first 10 transitions (Supplementary Figure 1, B, D and F).

Supplementary Figure 1



3. Results of Markov Modeling to predict transition between arousal states

Shown below are the results of Markov modeling derived from the results shown in Supplementary Figure 1, B, D and F. Here, we compare the probability of being in a specified arousal state based on the CBL level. We observed that (as can be expected from the dynamics of state transitions shown in Figure A to C in the main text) the strongest association of CBL levels was with the probability of being in arousal state 5. In the table below we show the range of odds ratios for being in a CBL category given a specified arousal state after transition #2 (when the probabilities become stabilized as shown in Supplementary Figure 1, B, D and F. The odds ratio was for being in a specified for a given category of CBL levels was calculated as follows. Let us assume that p1,p2 and p3 are probabilities of being in state X at transition # Y. Then the odds ratio for being in the category of 1-10 μg/dL compared to being in category <1 μg/dL was calculated as [p2 (1 – p1)]/[p1 (1-p2)]. Similarly, the odds ratio for being in CBL category of >10 μg/dL compared to the category of <1 μg/dL was calculated as [p3 (1-p1)]/[p1 (1-p3)]. The odds ratios were estimated for all states and all transitions and shown in the following table is the range of the odds ratios for each state after transition #2.

Arousal State	CBL 1-10 μg/dL	CBL >10 μg/dL
1	1.10 – 2.49	0
2	0.51 – 0.59	0.09 – 0.15
3	0.33 – 0.40	0
4	0.89 – 0.94	0.38 – 0.44
5	1.89 – 1.99	4.64 – 5.00
6	1.14 – 1.27	1.31 – 1.65