Supplemental information

A data-driven health

index for neonatal morbidities

Davide De Francesco, Yair J. Blumenfeld, Ivana Marić, Jonathan A. Mayo, Alan L. Chang, Ramin Fallahzadeh, Thanaphong Phongpreecha, Alex J. Butwick, Maria Xenochristou, Ciaran S. Phibbs, Neda H. Bidoki, Martin Becker, Anthony Culos, Camilo Espinosa, Qun Liu, Karl G. Sylvester, Brice Gaudilliere, Martin S. Angst, David K. Stevenson, Gary M. Shaw, and Nima Aghaeepour

Supplementary Table 1. [List of neonatal morbidities and corresponding ICD-9-CM codes, Related to STAR Methods]

Neonatal morbidity	Abbreviation	ICD-9-CM code(s)
Respiratory distress syndrome	RDS	769
Intraventricular hemorrhage	IVH	772.1
Necrotizing enterocolitis	NEC	777.5
Retinopathy of Prematurity	ROP	362.2
Bronchopulmonary dysplasia	BDP	770.7
Patent ductus arteriosus	PDA	747.0
Periventricular leukomalacia	PVL	779.7
Sepsis		771.81
Pulmonary Hemorrhage		770.3
Cerebral palsy	CP	343
Pulmonary hypertension	Pulmonary HTN	416.0
Jaundice		774; 277.4

Supplementary Table 2. [Clinical variables used to predict neonatal morbidities, Related to STAR Methods]

Variable	Source(s)	Median (IQR) or n (%)	n (%) of missing
Maternal demographics			
Age [years]	Birth certificate	28 (23, 32)	402 (<1%)
Race	Birth certificate		107,972 (<1%)
Non-Hispanic White		3,661,238 (32%)	
Non-Hispanic Black		729,663 (6%)	
Asian		1,286,066 (11%)	
Pacific Islander		59,714 (<1%)	
Hispanic		5,690,623 (49%)	
American Indian/Alaskan		51,741 (<1%)	
Other		7,769 (<1%)	
BMI	Birth certificate		8,766,133 (76%)
Underweight		115,280 (1%)	
Normal		1,402,154 (12%)	
Overweight		728,383 (6%)	
Obese		582,836 (5%)	
Education level	Birth certificate		241,330 (2%)
Some high school or less		3,448,416 (30%)	
Highschool diploma or equivalent		3,146,483 (27%)	
Some college		2,333,925 (20%)	
College graduate or more		2,424,632 (21%)	
Payer status	Birth certificate		27,753 (<1%)
Medi-Cal		5,296,259 (46%)	

Private		5,785,390 (50%)	
Self-pay, none, or medically unattended		286,899 (2%)	
Other		198,485 (2%)	
Parity	Birth certificate		8,984 (<1%)
0		4,511,516 (39%)	
1		3,643,736 (31%)	
2		1,979,760 (17%)	
3+		1450790 (13%)	

Maternal medical history

Hypertension	ICD-9-CM codes 401-405, 642.0-642.2, 642.9 (not concomitant with preeclampsia and gestational hypertension)	122,007 (1%)	80,627 (<1%)
Pre-gestational diabetes mellitus (DM)	ICD-9-CM codes 250.0x, 250.1x, 250.2x, 250.3x, 648.0 (not concomitant with gestational diabetes)	87,343 (<1%)	80,627 (<1%)
Smoking (during or 3 months before pregnancy)	Birth certificate and ICD-9-CM codes 305.1, 649.0	196,613 (2%)	63,422 (<1%)
Asthma	ICD-9-CM code 493	163,209 (1%)	80,627 (<1%)
Anemia	ICD-9-CM codes 280-285, 648.2	870,469 (8%)	80,627 (<1%)
Rheumatoid Arthritis (RA)	ICD-9-CM codes 714	4,736 (<1%)	80,627 (<1%)

Obstetrical complications

Gestational age (GA) at delivery [days]	Birth certificate	276 (268, 282)	1,029,583 (9%)
Preeclampsia and gestational HTN	ICD-9-CM codes 642.4, 642.5, 642.6, 642.7, 642.3	559,007 (5%)	80,627 (<1%)
Gestational diabetes mellitus (GDM)	ICD-9-CM code 648.8	558,944 (5%)	80,627 (<1%)
Spontaneous pre-term birth (PTB)	Gestational age <37 weeks and ICD-9-CM codes 644, 658.1 or mention of premature rupture of membranes, premature labor or tocolysis in birth certificate	602,545 (5%)	1,029,583 (9%)
Medically indicated pre-term birth (PTB)	Gestational age <37 weeks and ICD-9-CM codes 73.0, 73.1, 73.4, 74 or mention of medical induction, artificial rupture of	783,129 (7%)	1,029,583 (9%)

|			
	membranes, or cesarean delivery in birth certificate		
Unclassified pre-term birth (PTB)	Gestational age <37 weeks and not concomitant with codes used to define spontaneous and medically indicated PTB	254,293 (2%)	1,029,583 (9%)
Cesarean delivery (CS)	Birth certificate and ICD-9-CM code 74	3,176,350 (27%)	0 (0%)
Operative vaginal delivery (OVD)	Birth certificate (mention of forceps or vacuum delivery)	195,031 (2%)	7,440,071 (64%)
Postpartum hemorrhage (PPH)	ICD-9-CM code 666	286,858 (2%)	80,627 (<1%)
Chorioamnionitis	ICD-9-CM code 658.4	237,782 (2%)	80,627 (<1%)
Small for gestational age (SGA)	Birthweight <10th percentile for gestational age and sex‡	1,097,366 (9%)	621,672 (5%)
Obstetrical history			
Prior stillbirth	Birth certificate	145,930 (1%)	9,375 (<1%)
Prior miscarriage	Birth certificate	1,893,525 (16%)	8,969 (<1%)
Prenatal fetal findings			
Infant sex	Birth certificate		113 (<1%)
Male		5,929,249 (51%)	
Female		5,665,424 (49%)	
Birthweight [Kg]	Birth certificate	3.37 (3.03, 3.69)	12,290 (<1%)

‡ According to Talge NM, Mudd LM, Sikorskii A, Basso O. United States birth weight reference corrected for implausible gestational age estimates. *Pediatrics*. 2014 May 1;133(5):844-53.

Supplementary Table 3. [Performance of the five ensemble methods, Related to STAR Methods] AUPRC and AUC of the five ensemble methods to predict neonatal morbidities (for each morbidity, the highest AUPRC/AUC is shown in bold)

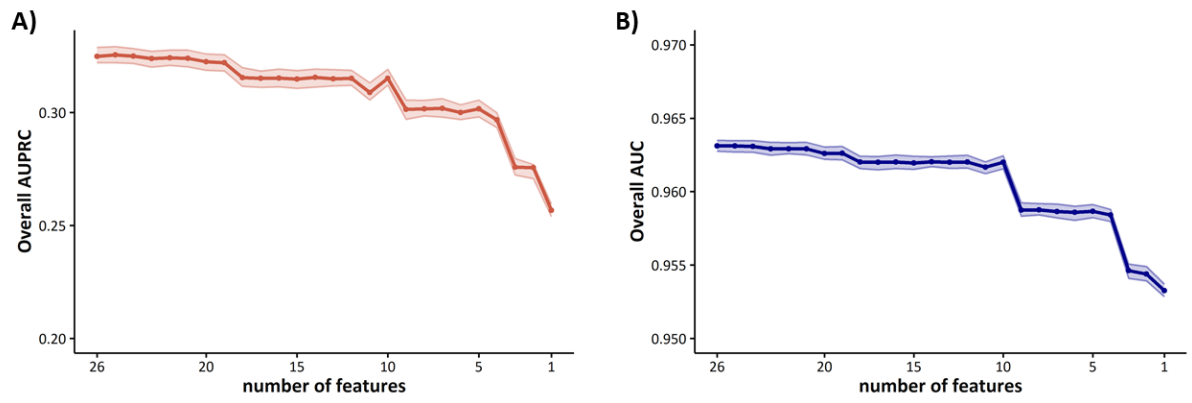|	AUPRC					AUC				
	Average	**Weighted average**	**Stacked prediction**	**Logistic regression**	**NN**	**Average**	**Weighted average**	**Stacked prediction**	**Logistic regression**	**NN**
RDS	0.383	0.412	**0.421**	0.392	0.381	0.896	0.903	**0.913**	0.894	0.901
IVH	0.154	**0.158**	0.158	0.150	0.149	0.957	0.960	**0.962**	0.958	0.953
NEC	0.048	**0.049**	0.049	0.047	0.046	0.939	0.943	**0.946**	0.944	0.933
ROP	0.248	0.261	**0.262**	0.255	0.245	0.990	0.991	**0.991**	0.989	0.985
BPD	0.197	0.204	**0.205**	0.199	0.192	0.983	0.983	**0.984**	0.983	0.976
PDA	0.170	0.179	**0.180**	0.170	0.166	0.776	0.779	**0.787**	0.780	0.777
PVL	0.009	0.009	**0.009**	0.008	0.009	0.960	**0.963**	0.951	0.962	0.956
Sepsis	0.109	0.116	**0.122**	0.116	0.117	0.797	0.806	**0.839**	0.832	0.828
Pulmonary hem.	0.028	**0.029**	0.028	0.025	0.026	0.879	**0.882**	0.880	0.876	0.873
CP	**2.8 E-04**	1.9 E-04	1.0 E-04	1.6 E-04	1.3 E-05	**0.729**	0.722	0.660	0.716	0.294
Pulmonary HTN	1.1 E-03	**1.2 E-03**	1.1 E-03	9.9 E-04	1.1 E-03	0.779	**0.788**	0.785	0.779	0.775
Jaundice	0.306	0.325	**0.333**	0.325	0.324	0.686	0.701	**0.715**	0.714	0.706
Overall	0.281	0.311	**0.326**	0.305	0.312	0.958	0.961	**0.963**	0.960	0.961

Supplementary Table 4 [Performance of the deep NN and standard approaches, Related to STAR Methods] AUPRC and AUC of the deep NN model, standard multivariable logistic regression, multi-task logistic regression and multivariate random forest to predict neonatal morbidities (for each morbidity, the highest AUPRC/AUC is shown in bold)

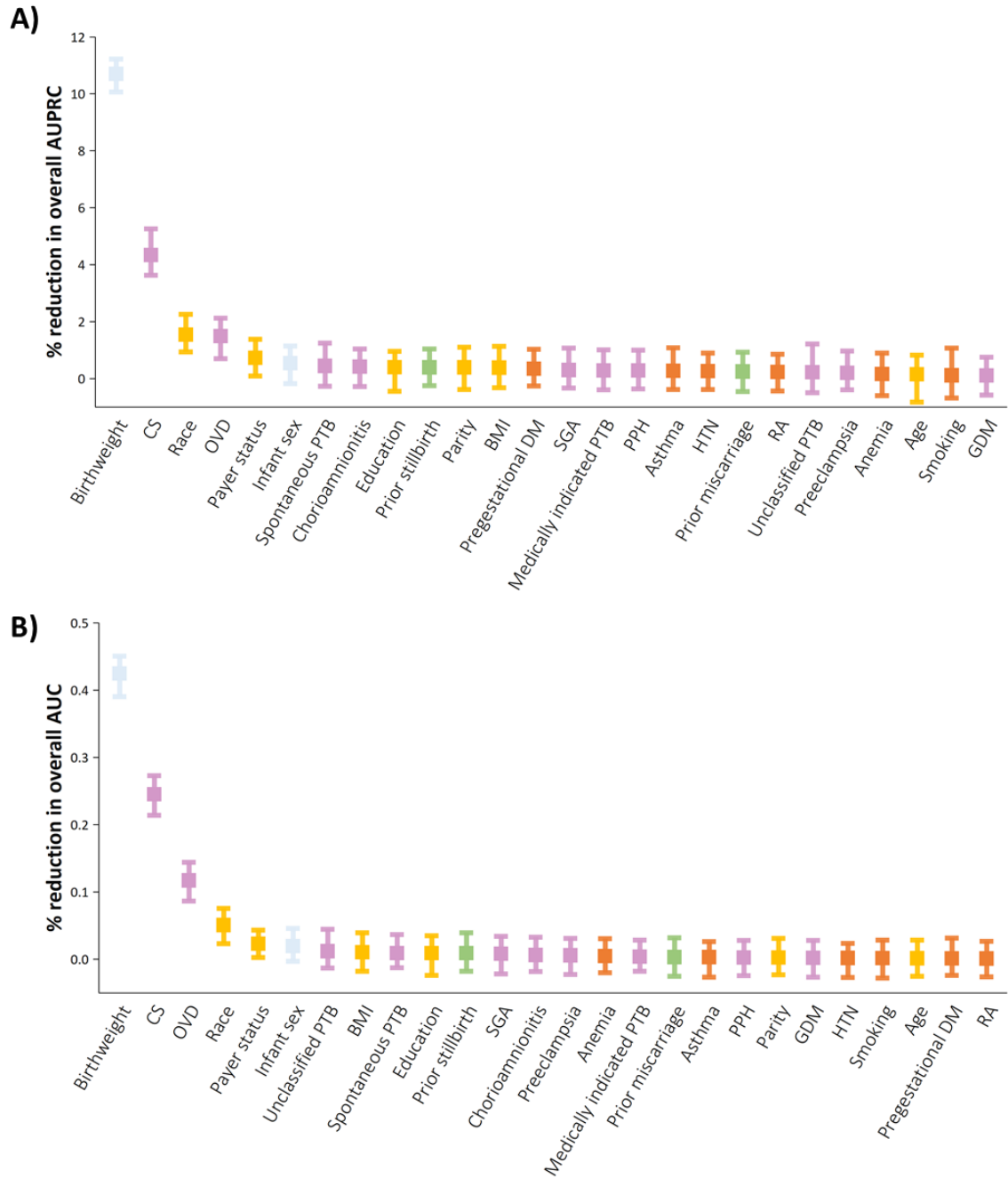|	AUPRC				AUC			
	Deep NN	**Logistic regression**	**Multi-task logistic regression**	**Multivariate random forest**	**Deep NN**	**Logistic regression**	**Multi-task logistic regression**	**Multivariate random forest**
RDS	**0.421**	0.409	0.126	0.401	**0.913**	0.908	0.801	0.885
IVH	**0.158**	0.146	0.048	0.131	**0.962**	0.959	0.899	0.925
NEC	**0.049**	0.045	0.015	0.032	**0.946**	0.938	0.866	0.864
ROP	**0.262**	0.240	0.074	0.254	**0.991**	0.989	0.947	0.978
BPD	**0.205**	0.185	0.048	0.191	**0.984**	0.975	0.939	0.959
PDA	**0.180**	0.169	0.060	0.167	**0.787**	0.777	0.695	0.751
PVL	**0.009**	0.005	0.002	0.003	**0.951**	0.877	0.891	0.701
Sepsis	**0.122**	0.094	0.027	0.081	**0.839**	0.798	0.622	0.739
Pulmonary hem.	**0.028**	0.023	0.005	0.016	**0.880**	0.854	0.808	0.769
CP	**1.0 E-04**	2.1 E-05	9.1 E-05	1.8 E-05	**0.660**	0.467	0.595	0.503
Pulmonary HTN	**1.1 E-03**	8.6 E-04	4.9 E-04	1.8 E-04	**0.785**	0.719	0.611	0.525
Jaundice	**0.333**	0.318	0.160	0.306	**0.715**	0.704	0.523	0.668
Overall	**0.326**	0.310	0.130	0.266	**0.963**	0.961	0.935	0.878
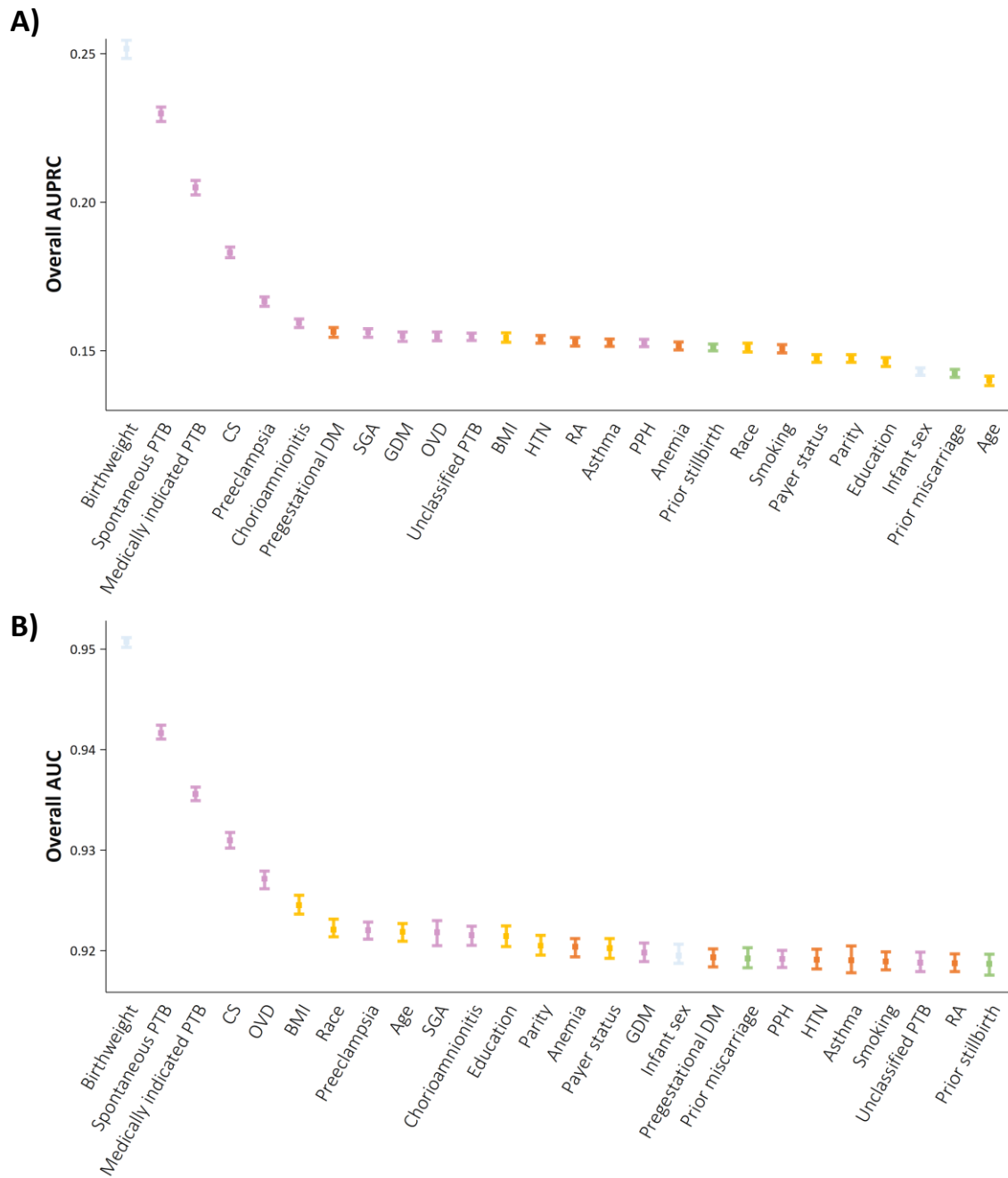
Supplementary Figure 1. [Univariable AUPRC and AUC for each feature, Related to STAR Methods] Overall test AUPRC (A) and AUC (B), with 95% confidence intervals, to predict the twelve neonatal morbidities of univariable logistic regression models considering one clinical variable at the time.
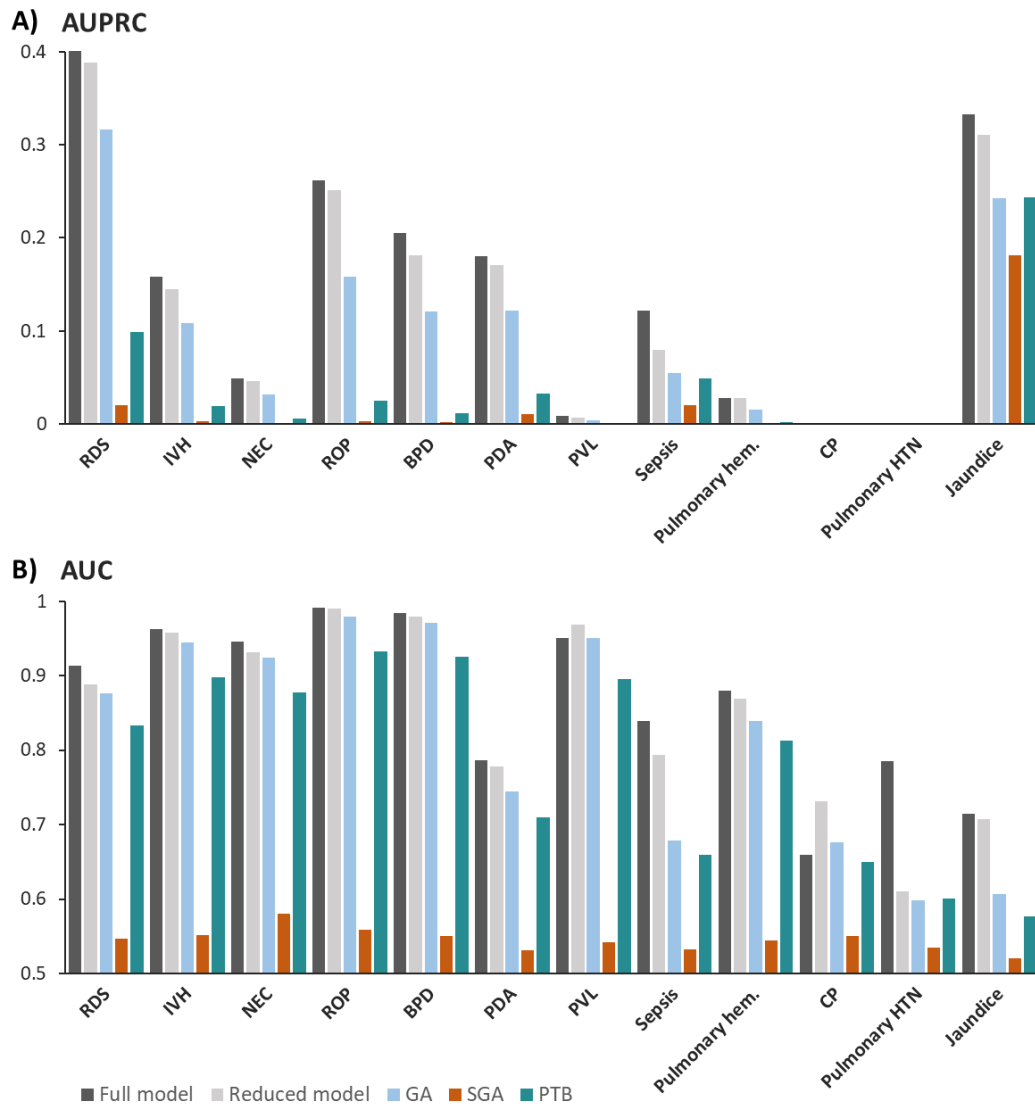
Supplementary Figure 2. [AUPRC and AUC by number of features, Related to STAR Methods] Overall test AUPRC (A) and AUC (B), with 95% confidence intervals, to predict the twelve neonatal morbidities of the model by number of clinical variables (features) included in the model.

Supplementary Figure 3. [Feature permutation experiment, Related to STAR Methods] Percentage reduction (with 95% confidence interval) in the overall test AUPRC (A) and AUC (B) to predict the twelve neonatal morbidities of the model when randomly permuting each clinical variable (one at the time) compared to the original model.

A) AUPRC

B) AUC

Legend: ■ Full model ■ Reduced model ■ GA ■ SGA ■ PTB

Supplementary Figure 4. [Performance of the full model, the reduced model, GA, SGA and PTB, Related to STAR Methods] Test AUPRC (A) and AUC (B) for each neonatal morbidity of the full model, the reduced model, GA, SGA and PTB
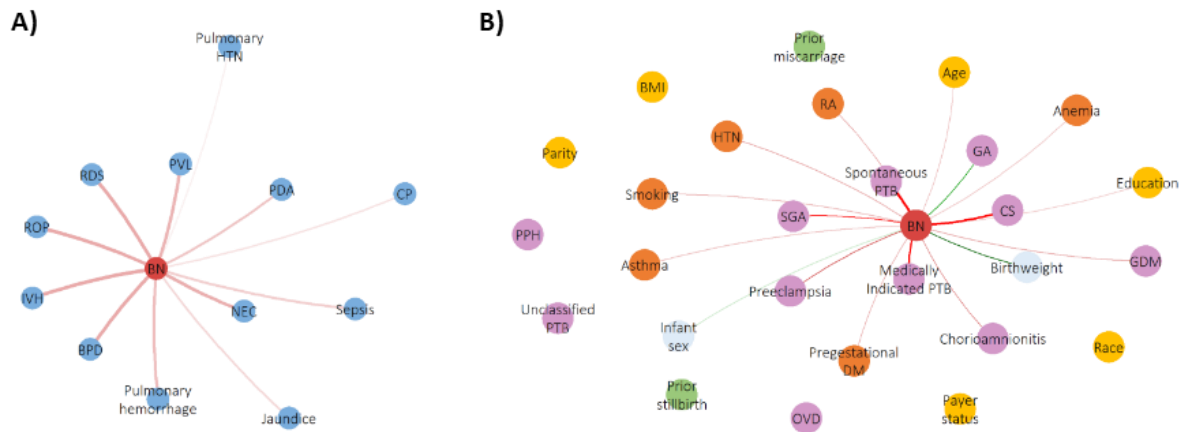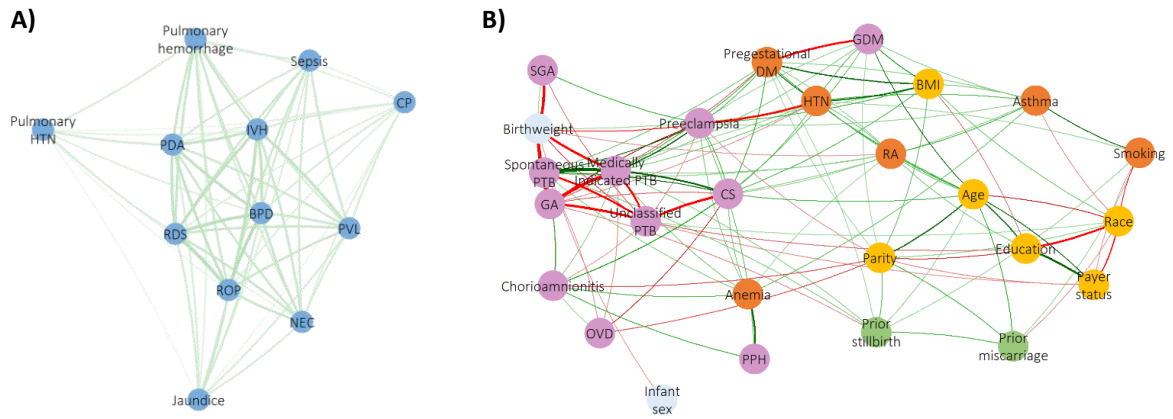
Supplementary Figure 5. [Correlation of the one-dimensional score with neonatal morbidities and clinical variables, Related to STAR Methods] Correlation network between neonatal morbidities (A) and clinical variables (B) with the outputs of the single-unit bottleneck layer; edges are drawn between pairs of morbidities/clinical variables and bottleneck layer unit that are correlated with an absolute value of the correlation coefficient exceeding 0.1, green (red) edges indicate positive (negative) correlations, the width of the edges is proportional to the Pearson's correlation coefficient.
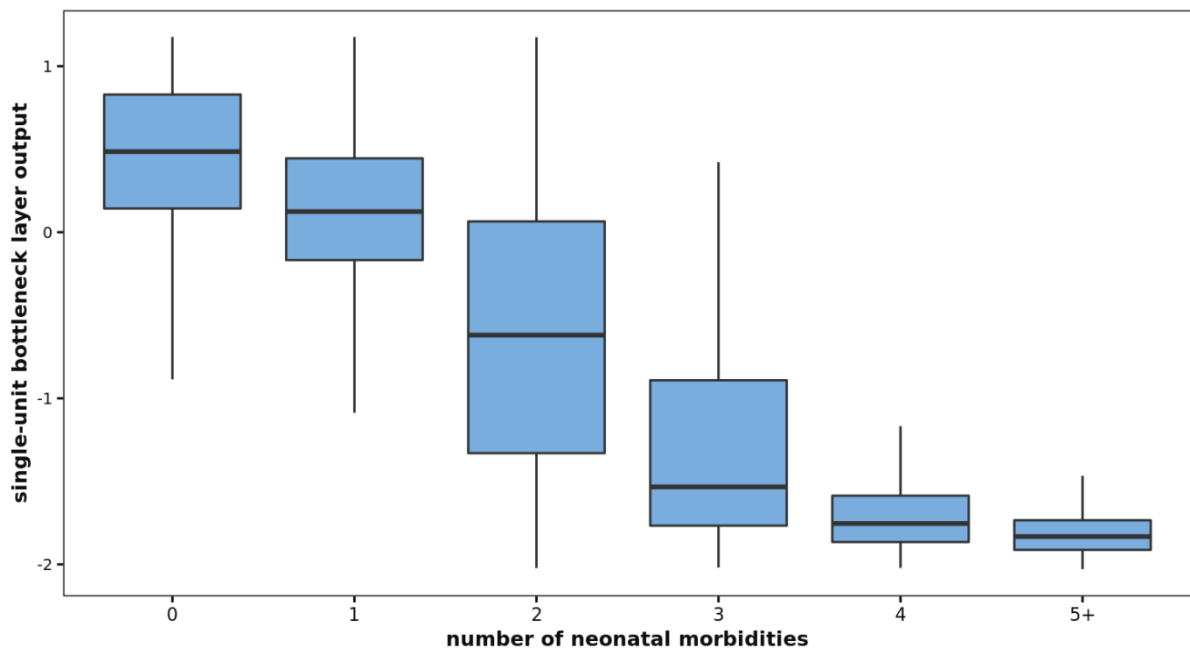
Supplementary Figure 6. [The one-dimensional score by the number of neonatal morbidities, Related to STAR Methods] Output of the single-unit bottleneck layer (y-axis) by number of neonatal morbidities observed in a livebirth
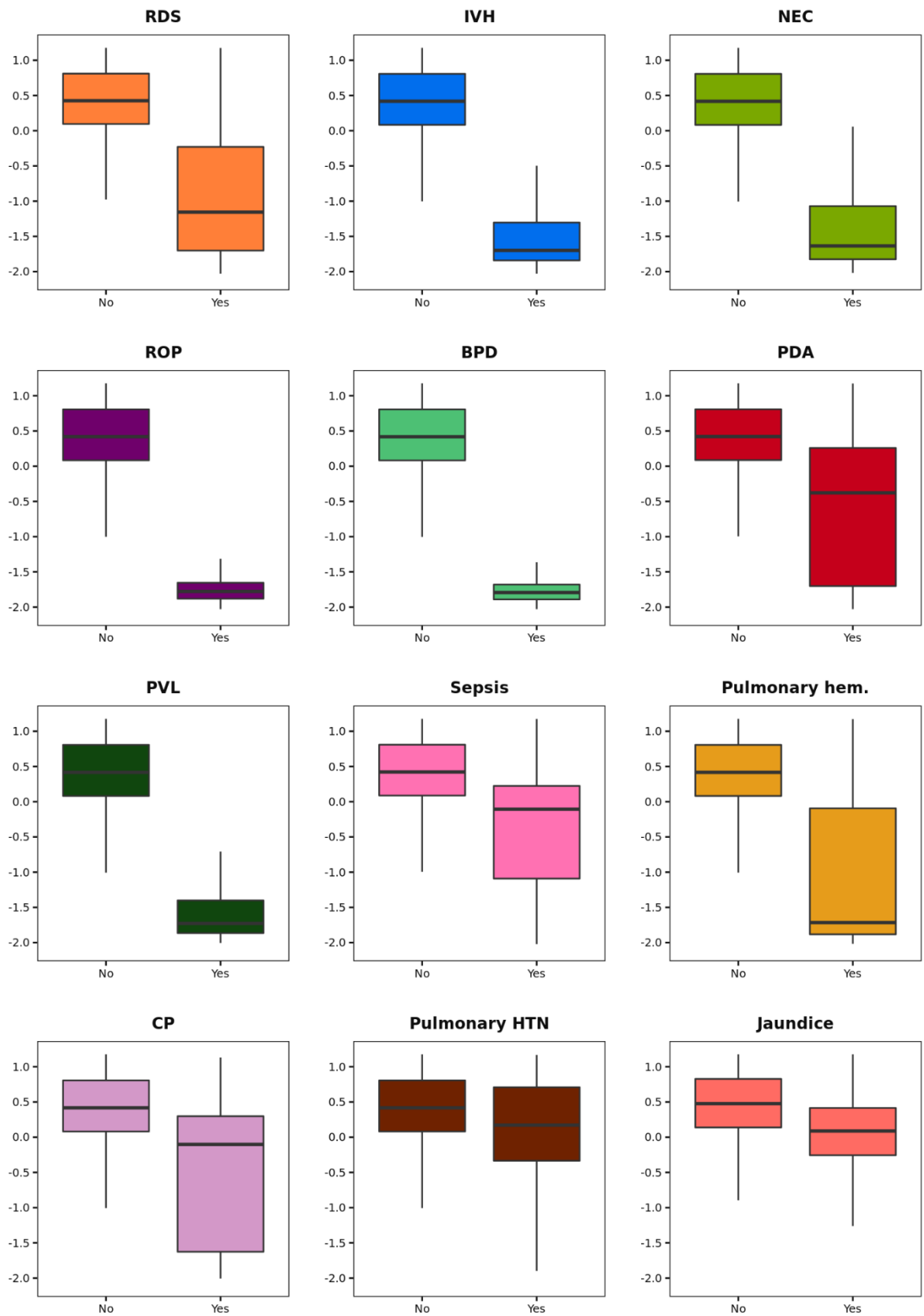
Supplementary Figure 7. [The one-dimensional score vs each neonatal morbidity, Related to STAR Methods]
Output of the single-unit bottleneck layer (y-axis) in livebirths with and without each of the twelve neonatal morbidities

Supplementary Figure 8. [Correlation networks of neonatal morbidities and clinical variables, Related to STAR Methods] Correlation networks between morbidities (A) and clinical variables (B). Edges are drawn between pairs of morbidities/clinical variables that are correlated with the absolute value of the correlation coefficient exceeding 0.1; green (red) edges indicate positive (negative) correlations; the width of the edges is proportional to the Pearson's correlation coefficient.

Supplementary Table 5. [AUPRC of the full model, reduced model and GA, SGA, and PTB, Related to Figure 2] AUPRC in the test dataset of the full and reduced models and models based on GA, SGA and PTB

|	AUPRC (± SE)					
	Full model	**Reduced model**	**Gestational age**	**SGA**	**PTB**	**Random classifier**
RDS	0.421 (±1.8E-04)	0.389 (±1.8E-04)	0.316 (±1.7E-04)	0.020 (±5.1E-05)	0.099 (±1.1E-04)	0.015
IVH	0.158 (±1.3E-04)	0.144 (±1.3E-04)	0.108 (±1.1E-04)	0.003 (±2.0E-05)	0.019 (±5.0E-05)	0.002
NEC	0.049 (±7.8E-05)	0.046 (±7.6E-05)	0.032 (±6.3E-05)	0.001 (±1.2E-05)	0.006 (±2.8E-05)	0.001
ROP	0.262 (±1.6E-04)	0.252 (±1.6E-04)	0.158 (±1.3E-04)	0.003 (±2.1E-05)	0.025 (±5.7E-05)	0.002
BPD	0.205 (±1.5E-04)	0.181 (±1.4E-04)	0.121 (±1.2E-04)	0.002 (±1.5E-05)	0.012 (±3.9E-05)	0.001
PDA	0.180 (±1.4E-04)	0.171 (±1.4E-04)	0.122 (±1.2E-04)	0.011 (±3.8E-05)	0.033 (±6.5E-05)	0.008
PVL	0.009 (±3.5E-05)	0.007 (±3.0E-05)	0.004 (±2.3E-05)	0.000 (±4.9E-06)	0.001 (±1.3E-05)	7.4E-05
Sepsis	0.122 (±1.2E-04)	0.079 (±9.8E-05)	0.055 (±8.2E-05)	0.020 (±5.1E-05)	0.049 (±7.8E-05)	0.009
Pulmonary hem.	0.028 (±6.0E-05)	0.028 (±6.0E-05)	0.015 (±4.4E-05)	0.000 (±7.3E-06)	0.002 (±1.6E-05)	0.0003
CP	1.0E-04 (±3.6E-06)	2.9E-04 (±6.2E-06)	2.2E-04 (±5.3E-06)	2.3E-05 (±1.8E-06)	4.4E-05 (±2.4E-06)	1.9E-05
Pulmonary HTN	0.0011 (±1.2E-05)	0.0006 (±9.0E-06)	0.0006 (±8.8E-06)	0.0002 (±4.5E-06)	0.0002 (±5.2E-06)	2.1E-04
Jaundice	0.333 (±1.7E-04)	0.310 (±1.7E-04)	0.243 (±1.6E-04)	0.181 (±1.4E-04)	0.244 (±1.6E-04)	0.135

Note: SE: standard error; random classifier: prediction model that predicts neonatal morbidities completely at random

Supplementary Table 6 [AUC of the full model, reduced model and GA, SGA, and PTB, Related to STAR Methods] AUC in the test dataset of the full and reduced models and models based on GA, SGA and PTB

	AUC (± SE)				
	Full model	**Reduced model**	**Gestational age**	**SGA**	**PTB**
RDS	0.913 (±5.5E-04)	0.889 (±6.3E-04)	0.876 (±7.3E-04)	0.547 (±6.0E-04)	0.833 (±6.5E-04)
IVH	0.962 (±1.0E-03)	0.958 (±1.1E-03)	0.945 (±1.4E-03)	0.552 (±1.7E-03)	0.898 (±1.3E-03)
NEC	0.946 (±2.0E-03)	0.931 (±2.4E-03)	0.924 (±2.5E-03)	0.580 (±3.0E-03)	0.877 (±2.4E-03)
ROP	0.991 (±4.3E-04)	0.990 (±4.3E-04)	0.979 (±7.6E-04)	0.559 (±1.7E-03)	0.933 (±7.0E-04)
BPD	0.984 (±8.0E-04)	0.979 (±9.6E-04)	0.971 (±1.2E-03)	0.551 (±2.1E-03)	0.925 (±1.1E-03)
PDA	0.787 (±1.1E-03)	0.778 (±1.1E-03)	0.745 (±1.3E-03)	0.531 (±7.5E-04)	0.710 (±1.0E-03)
PVL	0.951 (±6.4E-03)	0.968 (±3.8E-03)	0.950 (±6.2E-03)	0.542 (±8.5E-03)	0.896 (±6.6E-03)
Sepsis	0.839 (±7.5E-04)	0.794 (±8.3E-04)	0.679 (±1.2E-03)	0.532 (±7.2E-04)	0.659 (±9.5E-04)
Pulmonary hem.	0.880 (±4.8E-03)	0.869 (±5.0E-03)	0.839 (±6.3E-03)	0.545 (±4.3E-03)	0.813 (±4.8E-03)
CP	0.660 (±2.8E-02)	0.731 (±2.6E-02)	0.676 (±2.8E-02)	0.551 (±1.7E-02)	0.650 (±2.1E-02)
Pulmonary HTN	0.785 (±5.4E-03)	0.611 (±8.1E-03)	0.598 (±9.2E-03)	0.535 (±4.9E-03)	0.601 (±6.3E-03)
Jaundice	0.715 (±2.8E-04)	0.708 (±2.8E-04)	0.607 (±3.3E-04)	0.520 (±1.8E-04)	0.577 (±2.3E-04)

Note: SE: standard error; AUC of a random classifier is 0.5
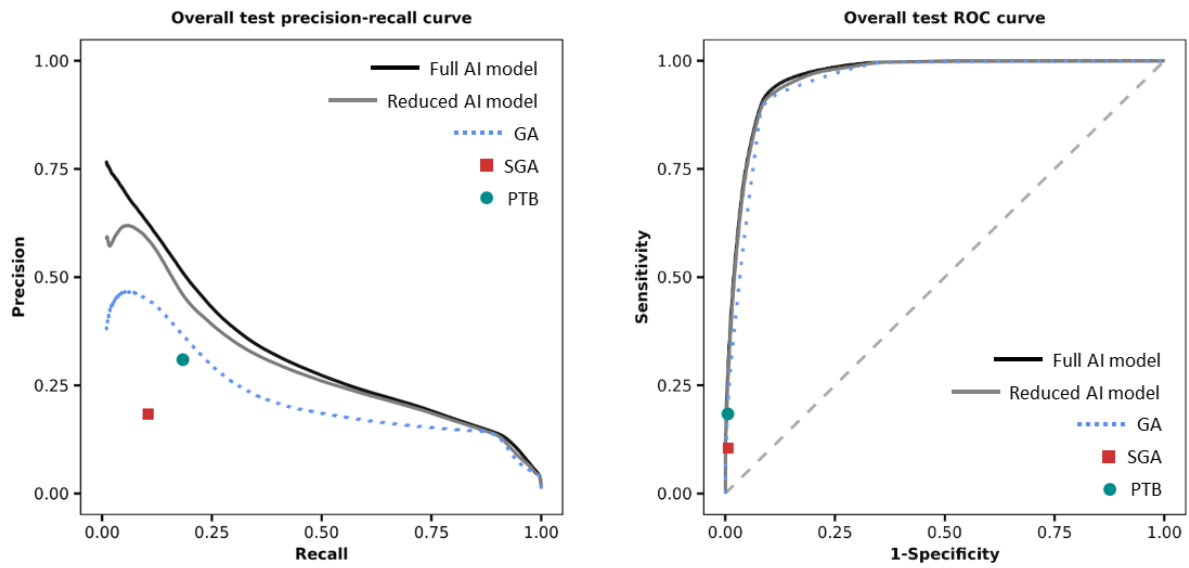
Supplementary Figure 9. [Overall performance, Related to Figure 1] Overall precision-recall curve (left) and receiver operating characteristic curve (right) in the test dataset. Overall curves were obtained by stacking the vectors of risk predictions returned by each model and the vectors of observed morbidities to form two vectors combining risk predictions and observed morbidities, respectively, across the twelve neonatal morbidities.
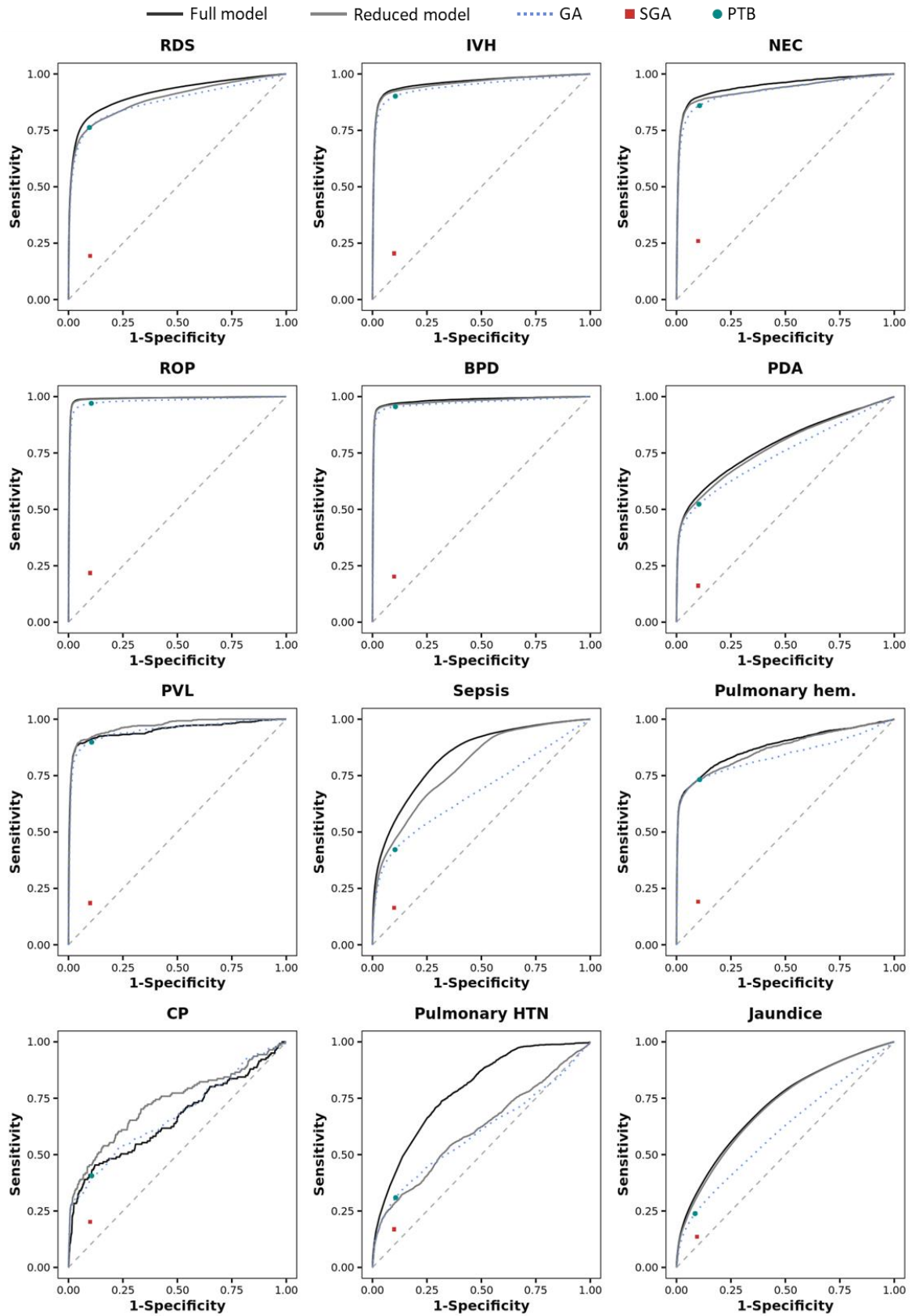
Supplementary Figure 10. [ROC for each neonatal morbidity, Related to Figure 1] Receiver operating characteristic (ROC) curves for the full model, the reduced model and the logistic regression models considering gestational age, SGA and PTB.