Phenotype Development and Validation for a Maternal Early Warning System

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Background.

The maternal mortality rate in the United States has increased from 9.9 per 100,000 births in 1999 to 26.4 per 100,000 births in 2015 [1] making it one of the highest maternal mortality rates among industrialized nations. Severe maternal morbidity (SMM) is a significant indicator of maternal mortality risk and is defined by 18 indications of peripartum complications. SMM has also significantly increased over the last 2 decades, from 49.5 per 10,000 births in 1993 to 144.0 per 10,000 births in 2014 [2]. Delay in diagnosis has been identified as a factor leading to SMM and maternal mortality, prompting calls for the creation of early warning systems to quickly identify patients in need of escalation of care [3]. However, several systemic and technical challenges have inhibited the creation and adoption of such predictive systems in the United States. Existing efforts in prediction of obstetric complications vary widely in the prediction task, complication definitions, and data used [2]. In this work, we model distinct, clinically actionable phenotypes for eight of the most common and dangerous complications for maternal morbidity, showing strong predictive capacity for each in real time. This work presents clinically actionable phenotypes for eight SMM outcomes: hemorrhage, sepsis, acute heart failure (AHF), acute renal failure (ARF), adult respiratory distress syndrome (ARDS), eclampsia, air and thrombotic embolism, and disseminated intravascular coagulation (DIC).

Phenotype	Definition
Acute Heart Failure / Pulmonary Edema	**Patient has any of the following criteria:** 1. Chest x-ray ordered within 4 hours of receiving IV furosemide 2. Maternal echo ordered within 4 hours of receiving IV furosemide 3. Pro BNP ordered within 4 hours of receiving IV furosemide
Acute Renal Failure	**Patient has any of the following criteria:** 1. Creatinine > 1.1 mg/dL 2. Potassium > 5.5 mmol/L
Adult Respiratory Distress Syndrome	**Patient has any of the following criteria:** 1. High flow nasal cannula ordered 2. Supplemental oxygen ordered
Air & Thrombotic Embolism	**Patient has any of the following criteria:** 1. A V/Q scan was ordered 2. Lower extremity dopplers ordered within 2 hours of receiving IV unfractionated heparin 3. CT-angiogram ordered within 2 hours of receiving IV unfractionated heparin
Disseminated Intravascular Coagulation	**Patient has any of the following criteria:** 1. A fibrinogen < 200 mg/dL within 24 hours of a platelet count < 100 2. An INR > 1.5 within 24 hours of a platelet count < 100
Eclampsia	**Patient has any of the following criteria:** 1. Two instances of SBP > 160 mmHg and/or DBP > 110 mmHg within 60 minutes 2. A CT head/neck ordered within 4 hours of SBP > 160 mmHg or DBP > 110 mmHg 3. An MRI head ordered within 4 hours of SBP > 160 mmHg or DBP > 110 mmHg
Hemorrhage	**Patient has any of the following criteria:** 1. Fall in hemoglobin of > 4 g/dL since admission 2. A ROTEM lab was ordered 3. A fibrinogen lab was ordered 4. Fresh frozen plasma was ordered 5. Cryoprecipitate was ordered 6. RBC transfusion was ordered
Sepsis	Temperature ³ 38 ° C *or* < 36° C *or* a positive blood culture ordered *plus* 2 of the following within 2 hours: 1. SBP < 100 mmHg 2. HR ³ 120 3. RR ³ 24 4. O_2 Saturation £ 92% 5. WBC ³ 17

Methods.

A trans-disciplinary team lead by clinicians developed a set of phenotype criteria for each SMM outcome, shown in the figure to the left, and a team of data scientists created models for time-series prediction of eight SMM phenotypes. These phenotypes were evaluated on a retrospective cohort of 19,419 perinatal obstetric encounters, whose characteristics are shown in Table 1. Patient data was formatted hourly, with predictions representing the patient's likelihood of meeting the phenotype within the following 4 hours. Input data included 142 features, including comorbidities, vitals, demographic information, and labs. Preliminary gradient-boosted models were used to show actionability, and exhibited strong predictive capacity summarized in Table 2. A comparison was made with the Maternal Early Warning Criteria (MEWC), and model prediction significantly outperformed MEWC early onset prediction. These results indicate that these phenotypes represent significantly predictive and actionable criteria for the development of algorithmic maternal early warning systems.

Results.

Table 1: Model Performance Comparison with MEWC Baseline

	Hemorrhage	Sepsis	AHF	ARDS	Embolism	Eclampsia	DIC	ARF
Model AUROC	0.765	0.9156	0.851	0.851	0.811	0.894	0.923	0.811
MEWC AUROC	0.522	0.608	0.614	0.557	0.572	0.547	0.564	0.562
Model Average Precision	0.0277	0.0403	0.3641	0.0643	0.0021	0.0544	0.0203	0.0439
MEWC Average Precision	0.0059	0.0051	0.0007	0.0037	0.0003	0.0039	0.00027	0.0015

Conclusion.

This set of criteria represent clinically actionable phenotypes that can be algorithmically predicted and are represent a promising basis of future maternal early warning systems to improve patient care.

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