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Longitudinal Twin Growth Discordance Patterns and Adverse Perinatal Outcomes

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TITLE PAGE

Longitudinal Twin Growth Discordance Patterns and Adverse Perinatal Outcomes

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CONDENSATION PAGE

Tweetable statement:

Five distinct growth discordance patterns in twin pregnancies were identified using a machine learning algorithm. Integrating inter-twin discordance in growth and cerebroplacental ratio Doppler improves the predictive accuracy for perinatal outcomes.

Short Title: Longitudinal twin growth discordance patterns and adverse perinatal outcomes

AJOG at a Glance

Why was this study conducted?

- To examine distinct growth patterns in twins and assess whether tracking these patterns throughout pregnancy, along with fetal Doppler assessment, could improve predictions of adverse perinatal outcomes.

What are the key findings?

- Five unique growth patterns between twin pairs were identified. Twins in the "high-stable" discordance group, characterized by consistently high growth differences, were associated with significantly higher risks of adverse outcomes at birth.

- A predictive model integrating inter-twin growth discordance trajectory with cerebroplacental ratio discordance demonstrated superior predictive accuracy for adverse perinatal outcomes.

What does this study add to what is already known?

- Incorporating longitudinal growth trajectories and cerebroplacental blood flow discordance may provide a more accurate approach for predicting perinatal outcomes in twin pregnancies than relying on isolated measurements of estimated fetal weight differences.

ABSTRACT

Objective

The objective of this study was to conduct a longitudinal assessment of inter-twin growth and Doppler discordance, to identify possible distinct patterns, and to investigate the predictive value of longitudinal discordance patterns for adverse perinatal outcomes in twin pregnancies

Methods

This retrospective cohort study included twin pregnancies followed and delivered at a tertiary University Hospital in London (UK), between 2010 and 2023. We included pregnancies with at least three ultrasound assessments after 18 weeks and delivery after 34 weeks' gestation. Monoamniotic twin pregnancies, pregnancies with twin-to-twin transfusion syndrome, genetic or structural abnormalities, or incomplete data were excluded. Data on chorionicity, biometry, Doppler indices, maternal characteristics, and obstetric as well as neonatal outcomes were extracted from electronic records. Doppler assessment included velocimetry of the umbilical artery, middle cerebral artery and cerebroplacental ratio. Inter-twin growth discordance was calculated for each scan.

The primary outcome was a composite of perinatal mortality and neonatal morbidity. Statistical analysis involved multilevel mixed-effects regression models and unsupervised machine learning algorithms, specifically k-means clustering, to identify distinct patterns of inter-twin discordance and their predictive value. Predictive models were compared

using the area under the receiver operating characteristics curve, calibration intercept, and slope, validated with repeated cross-validation. Analyses were performed using R, with significance set at $p<0.05$.

Results

Data from a total of 823 twin pregnancies (647 dichorionic, 176 monochorionic) were analyzed. Five distinct patterns of inter-twin growth discordance—*low-stable (n=204, 24.8%)*, *mild-decreasing (n=171, 20.8%), low-increasing (n=173, 21.0%)*, *mild-increasing (n=189, 23.0%)*, and *high-stable (n=86, 10.4%)*—were derived using an unsupervised learning algorithm that clustered twin pairs based on the progression and patterns of discordance over gestation. In the high-stable cluster, the rates of perinatal morbidity (46.5%, 40/86) and mortality (9.3%, 8/86) were significantly higher, compared to the low-stable (reference) cluster ($p<0.001$). High-stable growth pattern was also associated with a significantly higher risk of composite adverse perinatal outcomes (Odds ratio 70.19, 95% confidence interval 24.18-299.03, $p<0.001$; adjusted Odds ratio 76.44, 95% confidence interval 25.39-333.02, $p<0.001$). The model integrating discordance pattern with CPR discordance at the last ultrasound before delivery demonstrated superior predictive accuracy, evidenced by the highest area under the receiver operating characteristics curve of 0.802 (95% confidence interval 0.712 – 0.892 0.046, $p<0.001$), compared to only discordance patterns (area under the receiver operating characteristics curve 0.785, 95% confidence interval 0.697 -0.873), intertwin weight discordance at the last ultrasound prior to delivery (area under the receiver operating characteristics curve 0.677, 95% confidence interval 0.545 - 0.809), combination of single measurements of

estimated fetal weight and CPR discordance at the last ultrasound prior to delivery (area under the receiver operating characteristics curve 0.702, 95% confidence interval 0.586 -0.818) and single measurement of CPR discordance only at the last ultrasound (area under the receiver operating characteristics curve 0.633, 95% confidence interval 0.515 – 0.751).

Conclusion

We identified five distinct trajectories of inter-twin fetal growth discordance using an unsupervised machine learning algorithm. Consistent high discordance is associated with increased rates of adverse perinatal outcomes, with a dose-response relationship. Additionally, a predictive model integrating discordance trajectory and CPR discordance at the last visit demonstrated superior predictive accuracy for the prediction of composite adverse perinatal outcomes, compared to either of these measurements alone or a single value of estimated fetal weight discordance at the last ultrasound prior to delivery.

Keywords

Discordance; longitudinal, perinatal, neonatal; morbidity; mortality; adverse; outcomes; neonatal unit; artificial intelligence; machine learning; fetal growth restriction; small for gestational age; stillbirth; intrauterine demise; fetal death; singleton pregnancy; twin; multiple pregnancy

INTRODUCTION

Twin pregnancies are associated with increased perinatal morbidity and mortality.[1-3] Medically indicated preterm birth is relatively common among twin pregnancies, due to various complications like preeclampsia, twin-to-twin transfusion syndrome (TTTS) and selective fetal growth restriction (sFGR).[4] Twin pregnancies with growth discordance contribute to this excess risk of prematurity, as well as perinatal loss and neonatal morbidity.[5,6] Hence, accurate definitions of inter-twin growth discordance and follow-up strategies based on the severity of discordance are crucial in preventing perinatal morbidity and mortality in twin pregnancies.

Several cut-offs for inter-twin size discordance have been suggested.[7-9] While the ISUOG[7] and the Delphi consensus[10] recommend a 25% threshold for inter-twin discordance to define sFGR along with additional criteria, the RCOG[11], NICE[12], and ACOG-SMFM[8] guidelines suggest a criterion of 20% inter-twin estimated fetal weight discordance.

There are still unresolved questions regarding the predictors of perinatal morbidity and mortality in twin pregnancies with size discordance. It is still unclear whether the adverse outcomes are influenced by the severity of growth discordance or gestational age at onset and pattern. Hiersch et al addressed this research question by grouping their twin pregnancy cohort based on the severity, timing, and pattern of growth discordance, and reported that progressive discordance greater than 10% detected before 24 weeks of gestation had the strongest association with adverse outcomes.[13] Doppler studies, which are a vital part of twin pregnancy surveillance and frequently influence delivery decisions, were not analyzed in that study. Therefore, the objective of our study was to conduct a longitudinal assessment of inter-twin growth and Doppler discordance, to identify possible distinct patterns, and to investigate the predictive value of these discordance patterns for adverse perinatal outcomes in twin pregnancies.

METHODS

Study population and data collection

This is a retrospective cohort study of twin pregnancies followed up and delivered at St. George's University Hospital, London between 2010 and 2023. We included all twin pregnancies that had at least three ultrasound biometric assessments after 18 weeks and delivered after 34 weeks' gestation. The exclusion criteria were monoamniotic twin pregnancies, monochorionic twin pregnancies complicated by TTTS, those affected by genetic or major structural abnormalities, and those with incomplete data. To focus on late-onset fetal growth restriction where management is controversial and to ensure consistent trajectory modeling, only twin pregnancies delivering beyond 34 weeks were included in this study. Cases were extracted from electronic records (ViewPoint version 5.6.8.428, ViewPoint Bildverarbeitung GMBH, Wessling, Germany) and data on chorionicity, biometric measurements (biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL) and EFW)[14], Doppler indices (Umbilical artery pulsatility index (UA PI), middle cerebral artery (MCA) PI, cerebroplacental ratio (CPR)) were extracted. All biometric and fetal Doppler assessments were performed in accordance with ISUOG guidelines and EFW was calculated using Hadlock IV formula.[7,14] Maternal characteristics (age, parity, body mass index (BMI) at booking visit , ethnicity, mode of conception, smoking status), obstetric (pregnancy outcomes, mode of delivery, gestational age (GA) at delivery) and neonatal outcomes (birthweight, neonatal intensive care unit (NNU) admission, neonatal morbidity, neonatal death) were extracted from electronic medical records.

Chorionicity was determined by evaluating the number of placental masses, the presence or absence of the lambda sign at the junction of the intertwin membrane and placenta, and the thickness of the intertwin membrane at the placental insertion site within the chorion during the 11–14 weeks gestational window.[7] GA was established during the first trimester by measuring the crown–rump length of the larger fetus in naturally conceived pregnancies.[15] For pregnancies conceived via in-vitro fertilization (IVF), GA was calculated based on the oocyte retrieval date or the embryonic age from fertilization. Inter-twin EFW discordance (as percentage) was calculated for each scan during follow-up, by the formula (larger twin's EFW-smaller twin's EFW)/larger twin's EFW) x100.

Study outcomes

The primary outcome measure was a composite adverse neonatal outcome of perinatal morbidity and/or mortality among those who delivered at or after 34 weeks of gestation. Perinatal morbidity was defined as the presence of any of the following for the neonate: need for mechanical ventilation, sepsis, interventricular/periventricular hemorrhage, respiratory distress syndrome and necrotizing enterocolitis. Perinatal mortality was defined as intrauterine fetal demise after 20 weeks' gestation or neonatal death in the first week of life.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was followed to ensure comprehensive reporting.[16] This research complied with all relevant national regulations, and institutional policies and as per the tenets of the Helsinki Declaration (as revised in 2013) for research with human subjects.

Statistical analysis

Continuous variables are presented as median and interquartile range, and categorical variables are presented as count and percentage of total. Between-group comparisons were made with the Wilcoxon signed-rank test, t-test, Kruskal-Wallis test, or Chi-squared test where appropriate. The relationship between GA at scan and progression of inter-twin weight discordance was modeled with multilevel mixed-effects regression models using random intercepts for same-pregnancy measurements and random slopes for GA at measurement. Restricted cubic splines were used for fixed GA at measurement terms to allow for nonlinear changes in discordance progression. After obtaining the best possible model fit, which was compared between candidate models using the likelihood ratio test, the random effects (intercept and slope) of pregnancy were extracted from the model. These random effects contain information about the trajectories and were subjected to an unsupervised learning algorithm, k-means clustering, to find distinct patterns of discordance progression. The optimal number of clusters was determined by examining the change in total within-square (WSS) values with a change in the number of clusters. The elbow method was used to select the inflection point where the decrease in WSS levels off as the number of clusters increases. We also conferred with content experts (clinicians) to ensure the resulting number of clusters and the trajectories they represent match with the clinical reality. After obtaining the optimum number of clusters, the discordance progression in each cluster was plotted, and were given names according to their trajectories with the help of clinicians. The main advantage of using a clustering algorithm over any other types (regression, gradient boosters etc) that rely on a ground truth is that clustering algorithms are resilient to overfitting. Clustering algorithms use only the explanatory variables and do not optimize anything based on ground truths. The association of Dopplers or Doppler discordance at the last visit, discordance at the last visit, patient and pregnancy characteristics, and discordance progression patterns were investigated with logistic regression analyses. Multivariable analysis included any variable with a $P<0.20$ in the univariable analysis. Different combinations of these parameters (last Dopplers, last discordance, last Dopplers & discordance, discordance progression trajectory, discordance trajectory, and last Dopplers) were compared against each other using 3 metrics (C-statistics [i.e., area under the receiver operating characteristics curve (AUROC)], calibration intercept and calibration slope) in repeated 3-fold cross-validation. Cross-validation was repeated for 1,000 iterations each constituting a 3-fold cross-validation for a total of 3,000 training validation sets. All analyses were conducted using R for statistical computing software and P values below 0.05 were considered statistically significant.

RESULTS

Between 2010 and 2023, 823 twin pregnancies met the eligibility criteria for inclusion in this study. The selection process and exclusions are detailed in Figure S1. The baseline characteristics of the study population, stratified by chorionicity, are presented in Table 1. There were 647 dichorionic and 176 monochorionic twin pregnancies in the cohort.

Determination of inter-twin size discordance progression clusters

Figure S2 presents a two-part analysis integral to understanding the clustering behavior within our dataset derived from a multi-level regression model. After multilevel modeling of discordance progression and extractions of random effects, patient-level values of intercept and slope were clustered with an unsupervised k-means algorithm. The optimal number of clusters was selected as 5, which was the elbow point in the graph depicting the change in WSS versus the number of clusters (Figure S2).

Description of the inter-twin size discordance patterns

The visual inspection of discordance progression in these five clusters revealed five distinct trajectories which were named based on their starting point and progression from there on. Figure 1 shows the five distinct growth trajectories, among the 823 twin pregnancies, across various GA windows, with evolution from 18 weeks to 34 weeks of gestation as follows: i) low-stable (n=204, 24.8%): This cluster demonstrates a consistently low discordance, remaining stable and below 5% throughout the gestational period. The stability in this trajectory suggests minimal variation in growth rates between the twins over time, ii) mild-decreasing (n=171, 20.8%): Initially starting at approximately 10% discordance at 18 weeks, this trajectory shows a mild decrease, approaching closer to 5% by 34 weeks' gestation. This pattern indicates a convergence in fetal growth rates as gestation progresses, iii) low-increasing (n=173, 21.0%): Starting with low discordance, this trajectory depicts a gradual increase from below 5% to approximately 12.5% by 34 weeks, suggesting a divergence in growth rates as the pregnancy advances, iv) mild-increasing (n=189, 23.0%): Beginning with mild discordance around 10%, this trajectory shows a more pronounced increase compared to the low-increasing cluster, reaching up to about 22.5% by 34 weeks. This indicates a significant divergence in growth rates, with one twin growing substantially faster than the other as gestation continues, v) high-stable (n=86, 10.4%): This trajectory maintains a relatively high level of discordance, starting and ending at around 27.5%, indicating persistent significant discordance throughout pregnancy without substantial changes in the relative growth rates of the twins.

Characteristics of inter-twin size discordance progression trajectories

Table 2 presents the characteristics and outcomes of twin pregnancies grouped into five clusters stratified by the discordance trajectories. Demographic and baseline characteristics such as maternal age, maternal BMI, parity and smoking status did not differ significantly across clusters. When stratified by chorionicity, there was a higher prevalence of monochorionic twins in the low-increasing (83.8%, 145/173) and mild-increasing clusters (79.9%, 151/189) compared to the high-stable cluster (51.2%, 44/86) ($p<0.001$). The umbilical artery PI multiples of median (MoM) for the smaller twin varied significantly, particularly being higher in the high-stable cluster with a median of 1.2 (IQR 1.0-1.5) compared to 1.0 (IQR 0.9-1.1) in the low-stable cluster ($p=0.001$). The MCA PI MoM and CPR for both the larger and smaller twins showed no significant variation across clusters ($p>0.05$).

Outcomes of inter-twin size discordance progression trajectories

The outcomes of twin pregnancies across all discordance trajectory clusters are presented in Table 2. The median gestational age at delivery varied significantly among groups, with the high-stable cluster delivering at a median of 35.4 weeks (IQR 34.5–36.6), lower than the other clusters, particularly the low-stable cluster with a median delivery at 37.1 weeks (IQR 36.4–37.5; $p<0.001$ across all groups). Perinatal morbidity rates also differed significantly, reaching 46.5% (40/86) in the high-stable cluster, compared to 1.5% (3/204) in the low-stable, 4.7% (8/171) in the mild-decreasing, 12.1% (21/173) in the low-increasing, and 19.0% (36/189) in the mild-increasing clusters ($p<0.001$ across all groups) (Table 2).

Similarly, NNU admission rates were significantly higher in the high-stable group at 48.8% (42/86), compared to 6.4% (13/204) in the low-stable, 9.9% (17/171) in the mild-decreasing, 19.1% (33/173) in the low-increasing, and 24.9% (47/189) in the mild-increasing clusters (p<0.001 across all groups). For perinatal mortality, the high-stable cluster exhibited a significantly elevated rate of 9.3% (8/86), while mortality was not recorded in the low-stable or mild-decreasing clusters and was 1.1% (2/189) in the mild-increasing group (p<0.001 across all groups) (Table 2).

Prognostic performance of inter-twin size discordance progression trajectories compared to Dopplers

Table 3 demonstrates factors associated with composite adverse perinatal outcomes, which include perinatal morbidity or mortality in twin pregnancies using logistic regression analysis. Monochorionicity was significantly associated with a higher risk of adverse outcomes compared to dichorionic twin pregnancies in univariable analysis (OR 1.61, 95% CI 1.02-2.50, p=0.035), but this association was not significant in the multivariable analysis (aOR 0.82, 95% CI 0.46-1.39, p=0.468). Notably, the cluster analysis revealed significant variations: the high-stable cluster exhibited a significantly higher risk of adverse outcomes (OR 70.19, 95% CI 24.18-299.03, p<0.001; aOR 76.44, 95% CI 25.39-333.02, p<0.001). The low-increasing and mild-increasing clusters also showed significantly elevated risks in both univariable and multivariable analyses, with the low-increasing cluster and the mild-increasing cluster showing an aOR of 10.59 (95% CI 3.52-45.81, p<0.001) and aOR of 18.06 (95% CI 6.31-76.27, p<0.001) in the multivariable analysis, respectively. Regarding the ultrasound measurements, on univariable analysis, there were significantly higher odds of composite adverse perinatal outcomes with increased UA PI discordance (OR 1.03, 95% CI 1.01-1.04, p<0.001; aOR 1.00, 95% CI 0.98-1.03, p=0.841), MCA PI discordance (OR 1.03, 95% CI 1.01-1.05, p<0.001; aOR 1.01, 95% CI 0.99-1.04, p=0.264), and CPR discordance (OR 11.64, 95% CI 4.56-29.82, p<0.001; aOR 6.84, 95% CI 0.86-66.17, p=0.082), however on multivariable analysis, these associations were attenuated and were not statistically significant (p>0.05).

Next, we analyzed the performance of various predictive models utilizing the last Doppler measurements (CPR discordance), weight discordance at the last visit, combinations of these factors, and patterns derived from unsupervised learning in estimating composite adverse perinatal outcomes in twin pregnancies using cross-validation samples (Table 4, Figure 3). Notably, the model integrating discordance trajectory with CPR discordance at the last ultrasound prior to delivery demonstrated superior predictive accuracy, evidenced by the highest AUROC of 0.802 (95% CI 0.712-0.892, p<0.001), suggesting robust discriminatory power, compared to the discordance clusters alone, identified by the unsupervised machine learning algorithm (AUROC 0.785, 95% CI 0.697 – 0.873), intertwin weight discordance at the last ultrasound prior to delivery (AUROC 0.677, 95% CI 0.545 – 0.809), combination of single measurements of EFW and CPR discordance at the last ultrasound before delivery (AUROC 0.702, 95% CI 0.586 -0.818) and single measurement of CPR discordance only at the last ultrasound (AUROC 0.633, 95% CI 0.515 – 0.751). The model combining discordance trajectory and CPR discordance at the last ultrasound also showed the most favorable calibration characteristics with the lowest calibration intercept of -0.073 (SD 0.520, p=0.005) and a calibration slope close to the ideal of 1, at 0.965 (SD 0.293, p=0.003), indicating minimal bias and reliable probability estimates. Of note, discordance patterns created with an unsupervised learning algorithm outperformed any combination of inter-twin weight or CPR discordance at the last visit (Figure 3, Table 4).

COMMENT

Principal findings

In this longitudinal study, we identified five distinct trajectories of inter-twin fetal growth discordance using an unsupervised machine learning algorithm, and reported that consistent high discordance, particularly in the high-stable cluster, is associated with increased rates of adverse perinatal outcomes, including lower GA at delivery and higher rates of perinatal morbidity and mortality, with a dose-response relationship. We also report that on multivariable modeling, a predictive model integrating inter-twin discordance trajectory with CPR discordance at the last visit demonstrated superior predictive accuracy, evidenced by the highest AUROC of 0.802 (95% CI 0.712 -0.892, p<0.001) compared to either of these measurements alone or a single value of EFW discordance at the last ultrasound prior to delivery.

Results in the context of what is known

Discordance in twin pregnancies has been variably defined,[7-12] with different EFW/birthweight cut-off values in the existing literature that have been associated with adverse perinatal outcomes, irrespective of chorionicity.[17,18] Nonetheless, most of the studies are based on birthweight discordance[19] and therefore, are not valuable to be able to predict adverse perinatal outcomes antenatally and define prognosis. Moreover, the inter-twin growth discordance can evolve anytime with gestation, therefore a single measurement of size discordance may not be predictive of adverse outcomes.[20] Therefore, we have utilized an unsupervised machine learning algorithm to identify five distinct growth patterns from this dataset without using any predefined thresholds. In our cohort, the high-stable cluster, characterized by consistent high discordance from the early second trimester until birth, was associated with increased rates of perinatal mortality and morbidity. Our findings are consistent with the limited available literature on longitudinal growth discordance in twin pregnancies where distinct growth trajectories and their association with perinatal outcomes have been studied. Using data from 1059 twin pregnancies, Hiersch et al classified growth patterns into four categories: no significant discordance pattern, early progressive discordance, early discordance with plateau and late discordance.[13] They reported that in their cohort, early progressive discordance (cases where discordance of > 10% was first noted before 24 weeks' gestation and the discordance subsequently increased gradually by a rate of > 0.5% per week) was associated with 3.4-fold and nearly 6-fold increased risks of preterm birth <34 weeks and preeclampsia, respectively. It is pertinent to acknowledge that the early progressive discordance group comprised of merely 2% (23/1059) of their study population. More recently, Zhu et al reported similar findings as by Hiersch et al and reported a distinct pattern of progressive discordance starting early in gestation in women who subsequently developed preeclampsia.[21] Notably, the perinatal outcomes investigated in our study differ from those examined by Hiersch et al and Zhu et al which potentially limits the direct comparison of the results. Despite employing different definitions and methodology, a comparative analysis suggests a notable alignment between the 'early progressive cohort' identified by Hiersch et al. and our 'high stable' cohort, both of which exhibited elevated rates of adverse outcomes. This parallel suggests a potential association with early-onset placental dysfunction which was also reported by Zhu et al.[21]

It is known that the accuracy of sonographic prediction of birthweight and birthweight discordance is poor in twin compared to singleton pregnancies, attributable to both fetal positions and numbers.[22,23] Accordingly, Khalil et al have reported that the overall predictions within ± 10% and ± 15% of the actual birth weight were 49.7% and 68.5% only in twin pregnancies, respectively.[24] In this context, the addition of routinely collected Doppler ultrasound parameters may lead to an improvement in predictive accuracy. Khalil et al have earlier reported that the combination of EFW discordance and CPR discordance at the last scan had the best predictive performance (AUROC 0.96; 95% CI 0.92-1.00) for perinatal mortality in twin pregnancies.[25] Additionally, the UA PI MoM, CPR MoM, EFW discordance, and CPR discordance were all independent predictors of the risk of perinatal loss, even after adjusting for potential confounders (P=0.022, P=0.002, P <0.001, and P=0.010, respectively) in their cohort.[25] This is similar to our findings where we report that a predictive model integrating inter-twin discordance trajectory combined with CPR discordance at the last visit measurements demonstrated superior predictive accuracy for adverse perinatal outcomes, in comparison to standalone size discordance. The difference in predictive accuracy between our current study (with an AUROC of 0.8) and prior work from our group (AUROC 0.96) likely reflects methodological improvements and a larger, more contemporary sample. The previously reported value of 0.96 likely indicates overfitting and a potentially biased performance estimate, often observed in smaller samples. In contrast, our use of cross-validation in a larger, more recent cohort provides a more reliable and generalizable assessment of predictive performance."

Monochorionic twins comprised a high proportion in the low-stable cluster compared to other clusters. This is not surprising as our study included those twin pregnancies that delivered beyond 34 weeks' gestation and most of the monochorionic twin pregnancies, especially those affected by growth discordance, are likely to have delivered before 34 weeks' gestation as recommended by the existing guidelines.[8]

Clinical and research implications

Our results indicate that longitudinal assessment of fetal growth in twin pregnancies might be of prognostic importance and can be used to dynamically monitor these pregnancies rather than relying on single-point measurements, for surveillance and delivery planning. The clinical burden associated with late preterm birth is frequently underestimated and twins born at late preterm gestation have poorer outcomes compared to those born at term.[26,27] While clinicians may often consider elective delivery in cases marked by EFW discordance alone, integrating Doppler ultrasound findings provides a more refined approach to the timing of delivery, potentially optimizing neonatal outcomes by allowing additional fetal maturation when feasible. While biochemical parameters such as angiogenic markers have demonstrated utility in predicting and prognosticating conditions such as preeclampsia, which impacts twin pregnancies collectively, the assessment of ultrasound parameters holds significant value in predicting adverse outcomes specifically in scenarios where one fetus may be experiencing growth discordance.[28-30]

Further research should focus on understanding the pathophysiological basis of these distinct growth trajectories, and validation of our findings in larger datasets and different settings. Putative mechanisms for growth discordance in monochorionic and dichorionic twins are attributable to different causes, therefore, it would also be prudent to stratify by chorionicity.

Strengths

The main strength of our study includes the use of unsupervised machine learning algorithms to generate discordance patterns, derived from raw parameters, rather than using one of the pre-defined thresholds of discordance reported in existing literature to be associated with adverse perinatal outcomes. Secondly, we have incorporated information from routinely collected and readily available Doppler ultrasound examinations, alongside patterns of growth discordance, for the prediction of adverse perinatal outcomes. This approach is novel and addresses a knowledge gap in existing literature.

Limitations

The main limitations include the small sample size, the retrospective nature of the cohort and, the change of practice in the management of twin pregnancies over the last decade especially following the implementation of NICE guidelines.[31] Machine learning algorithms are dependent on the characteristics of the dataset used for generating them,[32] hence, there is a possibility of bias as this cohort of twin pregnancies who delivered at a tertiary level maternal-fetal medicine unit may not be reflective of the general population, which may impact the generalizability of our results. Due to the relatively small numbers of monochorionic twins in our dataset, we are unable to stratify our results by chorionicity, which is also reflected in some of the wide confidence intervals in our estimates.

Conclusion

We identified five distinct trajectories of inter-twin growth discordance using an unsupervised machine learning algorithm, and reported that consistent high discordance, particularly in the High Stable cluster, is associated with increased rates of adverse perinatal outcomes, with a dose-response relationship. Moreover, a predictive model integrating inter-twin discordance trajectory and CPR discordance at the last visit demonstrated superior predictive accuracy for the prediction of composite adverse perinatal outcomes, compared to either of these measurements alone or a single value of EFW discordance at the last ultrasound before delivery. Future research should focus on validating our findings in prospective cohorts.

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Table 1. Characteristics of the study cohort stratified by chorionicity

Variables	**Dichorionic twin pregnancies (n= 647)**	**Monochorionic twin pregnancies (n =176)**	**P value**
Maternal age in years, median (IQR)	34.0 (30.0-38.0)	32.0 (29.0-36.0)	<0.001
Maternal body mass index, median (IQR)	24.5 (21.6-27.9)	24.5 (21.9-28.0)	0.836
Multiparous, n (%)	292 (45.1)	67 (38.1)	0.112
Smoker, n (%)	30 (4.6)	10 (5.7)	0.708
Mode of birth, n (%)			<0.001
Elective Cesarean birth	276 (42.7)	127 (72.2)	
Emergency Cesarean birth	141 (21.8)	25 (14.2)	
Vaginal birth	230 (35.5)	24 (13.6)	
Gestational age at birth in weeks, median (IQR)	37.0 (35.9-37.4)	36.3 (35.2-36.7)	<0.001
Inter-twin estimated fetal weight discordance, % median (IQR)			
18-22 weeks	5.3 (2.1-10.2)	8.0 (3.3-15.9)	<0.001
23-26 weeks	15.4 (5.9-61.0)	10.6 (5.3-25.2)	<0.001
27-30 weeks	7.8 (3.9-13.0)	9.3 (4.1-18.5)	0.011
31-34 weeks	3.8 (0.6-11.6)	8.1 (2.3-17.8)	<0.001
Fetal Doppler assessment before delivery, median (IQR)			
Smaller twin umbilical artery (UA) pulsatility index (PI)	1.0 (0.9-1.2)	1.1 (0.9-1.4)	<0.001
Larger twin UA PI	0.9 (0.8-1.1)	1.0 (0.8-1.1)	0.521
Smaller twin middle cerebral artery (MCA) PI	1.6 (1.4-1.8)	1.6 (1.4-1.8)	0.283
Larger twin MCA PI	1.7 (1.5-1.9)	1.7 (1.5-1.9)	0.264
Smaller twin cerebroplacental ratio (CPR)	1.6 (1.3-1.9)	1.5 (0.9-1.8)	<0.001
Larger twin CPR	1.9 (1.6-2.2)	1.8 (1.5-2.2)	0.245
Inter-twin UA PI discordance, %,	15.4 (7.6-28.7)	18.4 (9.1-33.9)	0.025
Inter-twin MCA PI discordance, %	12.7 (6.5-22.8)	13.6 (6.9-23.0)	0.665
Inter-twin CPR discordance	0.2 (0.1-0.4)	0.3 (0.1-0.5)	0.082
Neonatal morbidity, n (%)	76 (11.7)	32 (18.2)	0.034
Neonatal mortality, n (%)	7 (1.1)	3 (1.7)	0.779
Admission to neonatal unit, n (%)	113 (17.5)	39 (22.2)	0.189
Composite adverse perinatal outcome, n (%)	83 (12.8)	35 (19.9)	0.017

IQR: interquartile range,

Table 2. Characteristics of longitudinal inter-twin discordance trajectory clusters

Variables	***Low-stable (n=204)***	***Mild-decreasing (n=171)***	***Low-increasing (n=173)***	***Mild-increasing (n=189)***	***High-stable (n=86)***	***P value***
Maternal age in years, median (IQR)	33.0 (29.0-36.0)	33.0 (30.0-36.0)	34.0 (31.0-38.0)	34.0 (30.0-37.0)	34.0 (29.0-37.8)	0.112
Maternal body mass index, median (IQR)	24.3 (21.8-27.1)	24.8 (21.9-28.3)	24.9 (21.8-28.8)	24.4 (21.6-27.7)	24.1 (21.5-27.9)	0.525
Multiparous, n (%)	86 (42.2)	66 (38.6)	79 (45.7)	88 (46.6)	40 (46.5)	0.528
Smoker, n (%)	7 (3.4)	9 (5.3)	9 (5.2)	9 (4.8)	6 (7.0)	0.765
Chorionicity, n (%)						<0.001
Dichorionic	166 (81.4)	141 (82.5)	145 (83.8)	151 (79.9)	44 (51.2)	
Monochorionic	38 (18.6)	30 (17.5)	28 (16.2)	38 (20.1)	42 (48.8)	
Fetal Doppler assessment before delivery, median (IQR)						
Smaller twin umbilical artery (UA) pulsatility index (PI)	1.0 (0.9-1.1)	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.2 (1.0-1.5)	0.001
Larger twin UA PI	0.9 (0.8-1.1)	1.0 (0.8-1.1)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.9 (0.8-1.1)	0.602
Smaller twin middle cerebral artery (MCA) PI	1.6 (1.4-1.8)	1.6 (1.4-1.8)	1.6 (1.4-1.8)	1.6 (1.4-1.8)	1.6 (1.4-1.8)	0.604
Larger twin MCA PI	1.7 (1.5-1.9)	1.7 (1.5-1.9)	1.7 (1.5-1.9)	1.8 (1.6-1.9)	1.7 (1.5-1.9)	0.461
Smaller twin cerebroplacental ratio (CPR)	1.8 (1.5-2.2)	1.9 (1.5-2.2)	1.8 (1.5-2.1)	2.0 (1.6-2.3)	1.9 (1.6-2.2)	0.132
Larger twin CPR	1.6 (1.2-1.9)	1.7 (1.2-2.0)	1.6 (1.3-1.9)	1.5 (1.2-1.9)	1.3 (0.9-1.8)	0.042
Inter-twin EFW discordance at 18-22 weeks, %, median (IQR)	4.0 (1.8-6.4)	8.5 (5.4-11.9)	1.6 (0.6-3.1)	8.5 (5.1-12.0)	23.9 (17.7-32.5)	<0.001
Discordance changes, %, median (IQR)						
18-22 to 23-26 weeks	3.8 (-1.4 to 52.0)	4.0 (-2.6 to 47.8)	7.0 (2.3 to 52.4)	10.9 (1.7 to 51.8)	3.1 (-4.4 to 9.7)	<0.001
23-26 to 27-30 week	-2.7 (-51.3 to 2.0)	-6.6 (-50.3 to -0.6)	-1.0 (-48.4 to 3.8)	-5.6 (-45.6 to 2.7)	0.4 (-8.5 to 5.3)	<0.001
27-30 to 31-34 weeks	-1.5 (-5.5 to 1.7)	-2.1 (-5.7 to 0.7)	1.0 (-5.0 to 6.1)	-0.6 (-7.2 to 4.8)	-0.8 (-7.5 to 3.4)	0.001
31-34 to 34+ weeks	0.5 (-1.2 to 3.4)	-0.1 (-3.4 to 1.5)	0.9 (-1.7 to 6.0)	0.6 (-3.9 to 5.8)	0.2 (-7.4 to 3.8)	0.007
Discordance at last visit, %, median (IQR)	1.8 (0.9 to 6.5)	1.8 (0.9 to 4.4)	9.0 (1.6 to 15.2)	10.7 (1.6 to 18.4)	18.2 (1.1 to 28.6)	<0.001
Inter-twin UA PI discordance	13.2 (6.4-28.7)	16.5 (7.3-28.9)	12.8 (7.5-22.6)	18.0 (8.0-30.6)	21.7 (10.9-39.8)	0.002
Inter-twin MCA PI discordance	12.5 (6.5-23.7)	12.5 (6.4-22.8)	13.4 (6.8-21.3)	12.5 (6.5-23.6)	15.2 (9.4-21.7)	0.692
Inter-twin CPR discordance	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.005
Gestational age at birth in weeks, median (IQR)	37.1 (36.4-37.5)	37.0 (36.1-37.4)	36.9 (36.0-37.3)	36.4 (35.0-37.3)	35.4 (34.5-36.6)	<0.001
Smaller twin birthweight in grams, median (IQR)	2418.0 (2160.0-2700.0)	2360.0 (2070.0-2651.0)	2250.0 (1940.0-2568.0)	2075.0 (1810.0-2404.0)	1812.5 (1531.8-2054.5)	<0.001
larger twin birthweight in grams, median (IQR)	2672.5 (2417.5-2992.5)	2540.0 (2320.0-2910.5)	2606.0 (2336.0-3000.0)	2558.0 (2300.0-2840.0)	2440.0 (2203.8-2795.0)	0.012
Inter-twin birthweight discordance,%, median (IQR)	6.8 (3.6-11.4)	6.1 (3.3-12.4)	12.3 (5.9-22.3)	15.4 (8.9-24.1)	27.4 (19.0-36.1)	<0.001
Smaller twin birthweight centile, median (IQR)	10.7 (3.5-24.7)	9.1 (3.0-23.4)	6.1 (1.1-21.4)	3.0 (1.0-13.4)	0.8 (0.3-5.6)	<0.001

Larger twin birthweight centile, median (IQR)	27.0 (12.2-49.5)	23.3 (8.4-48.3)	32.0 (16.1-62.8)	29.1 (15.7-53.8)	35.6 (18.3-61.7)	0.007
Small for gestational age (SGA) of the larger twin, n (%)	45 (22.1)	50 (29.2)	33 (19.1)	22 (11.6)	6 (7.0)	<0.001
SGA of the smaller twin, n (%)	96 (47.1)	88 (51.5)	100 (57.8)	130 (68.8)	75 (87.2)	<0.001
Neonatal morbidity, n (%)	3 (1.5)	8 (4.7)	21 (12.1)	36 (19.0)	40 (46.5)	<0.001
Neonatal mortality, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	8 (9.3)	<0.001
Neonatal unit admission, n (%)	13 (6.4)	17 (9.9)	33 (19.1)	47 (24.9)	42 (48.8)	<0.001

IQR: interquartile range

730 **Table 3.** Factors associated with composite adverse perinatal outcomes

Variables	***Levels***[#]	***No***	***Yes***	***Odds ratio (95% Confidence interval)***	***Adjusted odds ratio (95% Confidence interval)***
Maternal age in years	Mean (SD)	33.4 (5.3)	33.2 (5.9)	0.99 (0.96-1.03, p=0.736)	-
Parity	Multiparous	305 (85.0)	54 (15.0)	-	-
	Primiparous	404 (87.1)	60 (12.9)	0.84 (0.56-1.25, p=0.385)	-
Chorionicity	DC	566 (87.5)	81 (12.5)	-	-
	MC	143 (81.2)	33 (18.8)	1.61 (1.02-2.50, p=0.035)	0.82 (0.46-1.39, p=0.468)
Maternal body mass index	Mean (SD)	25.5 (5.5)	25.8 (5.3)	1.01 (0.97-1.04, p=0.710)	-
smoker	No	678 (86.6)	105 (13.4)	-	-
	Yes	31 (77.5)	9 (22.5)	1.87 (0.82-3.90, p=0.110)	1.75 (0.67-4.21, p=0.230)
Inter-twin discordance pattern	Low, stable	201 (98.5)	3 (1.5)	-	-
	Mild, decreasing	163 (95.3)	8 (4.7)	3.29 (0.93-15.20, p=0.082)	3.45 (0.97-16.03, p=0.073)
	Low, increasing	152 (87.9)	21 (12.1)	9.26 (3.12-39.70, p<0.001)	10.59 (3.52-45.81, p<0.001)
	Mild, increasing	151 (79.9)	38 (20.1)	16.86 (5.96-70.71, p<0.001)	18.06 (6.31-76.27, p<0.001)
	High, stable	42 (48.8)	44 (51.2)	70.19 (24.18-299.03, p<0.001)	76.44 (25.39-333.02, p<0.001)
Inter-twin umbilical artery pulsatility index discordance	Mean (SD)	19.2 (15.7)	26.6 (18.3)	1.03 (1.01-1.04, p<0.001)	1.00 (0.98-1.03, p=0.841)
Inter-twin middle cerebral artery pulsatility index discordance	Mean (SD)	15.2 (11.4)	19.7 (13.3)	1.03 (1.01-1.05, p<0.001)	1.01 (0.99-1.04, p=0.264)
Inter-twin cerebroplacental discordance	Mean (SD)	0.2 (0.2)	0.4 (0.2)	11.64 (4.56-29.82, p<0.001)	6.84 (0.86-66.17, p=0.082)

Data is presented as mean and SD for continuous variables and 'N(%)' for categorical (Yes/No).

Table 4. Performance of the various models for predicting composite adverse perinatal outcome in cross-validation samples (numeric)

Variables	***Last fetal Dopplers****	***Last inter-twin discordance†***	***Last inter-twin discordance† + last fetal Dopplers****	***Discordance trajectory‡***	***Discordance trajectory + Last fetal Dopplers****	***P value***
C statistics (95% confidence interval)	0.633 (0.515-0.751)	0.677 (0.545 - 0.809)	0.702 (0.586 - 0.818)	0.785 (0.697-0.873)	0.802 (0.712-0.892)	<0.001
Calibration intercept	0.003 (1.102)	0.048 (0.963)	-0.053 (0.812)	-0.051 (0.548)	-0.073 (0.520)	0.005
Calibration slope	1.015 (0.587)	1.029 (0.469)	0.976 (0.402)	0.983 (0.314)	0.965 (0.293)	0.003

*Cerebroplacental ratio discordance at the last visit
†Discordance at the last visit
‡Discordance patterns from the unsupervised learning model

FIGURE LEGENDS

Figure 1: Inter-twin growth discordance trajectories in clusters identified by the unsupervised learning algorithm

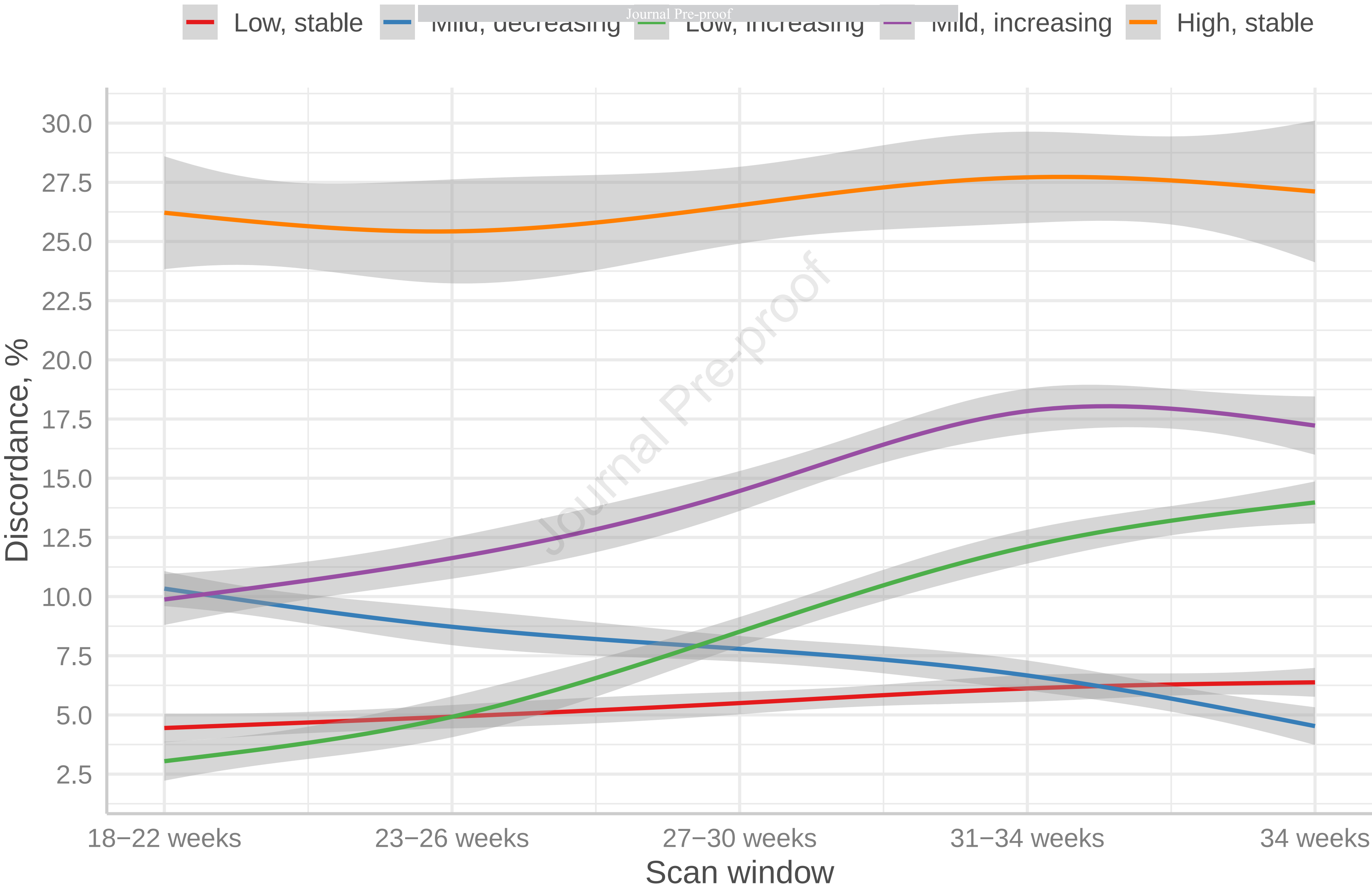
Figure 2. Incidence of perinatal morbidity, mortality and neonatal care unit admission rate in identified inter-twin growth discordance trajectories

Figure 3. Performance of the various models for predicting perinatal morbidity or mortality in cross-validation samples. Vertical black lines indicate the best value for that metric

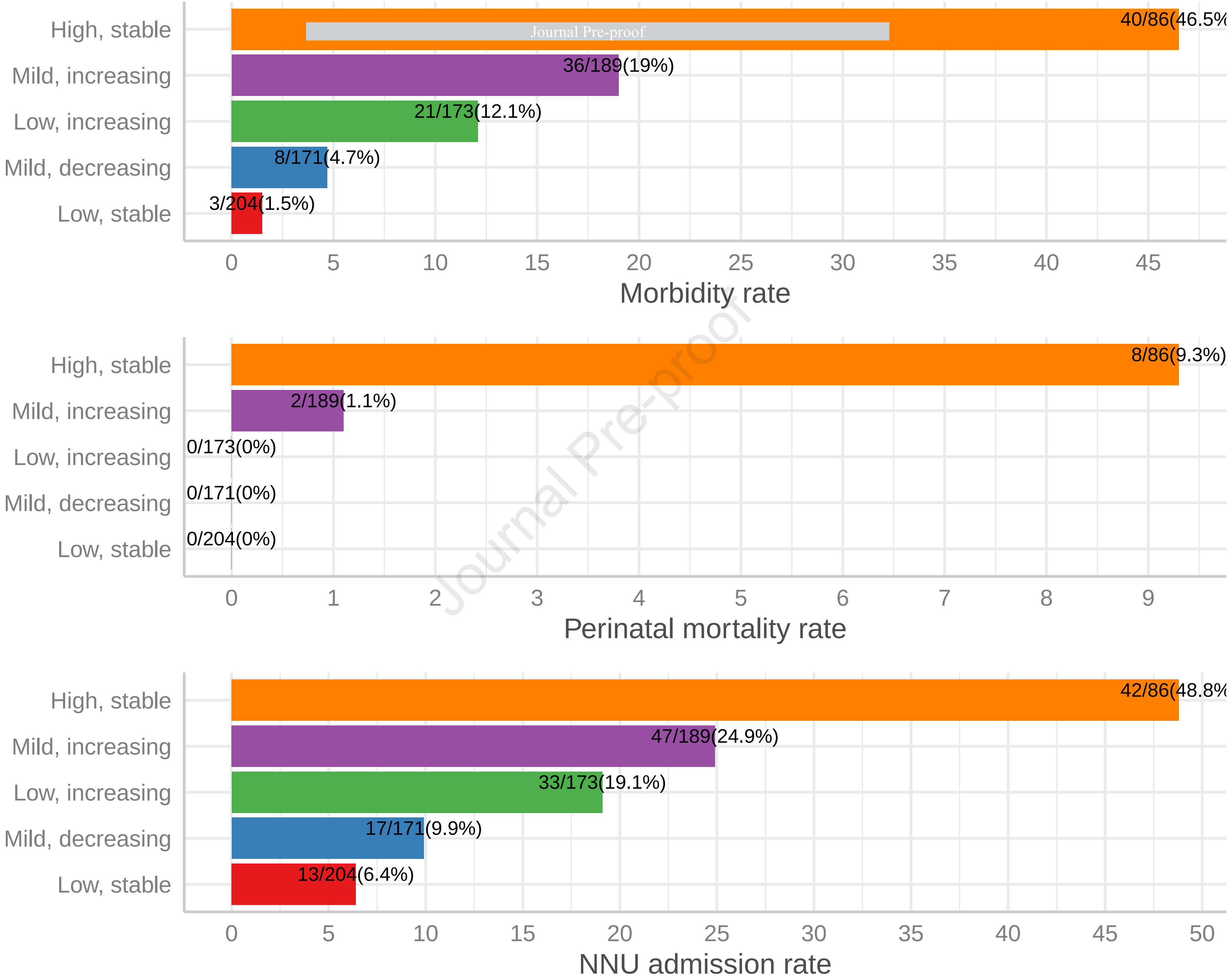
Figure S1: Study Flowchart Showing Participant Selection and Exclusion Criteria

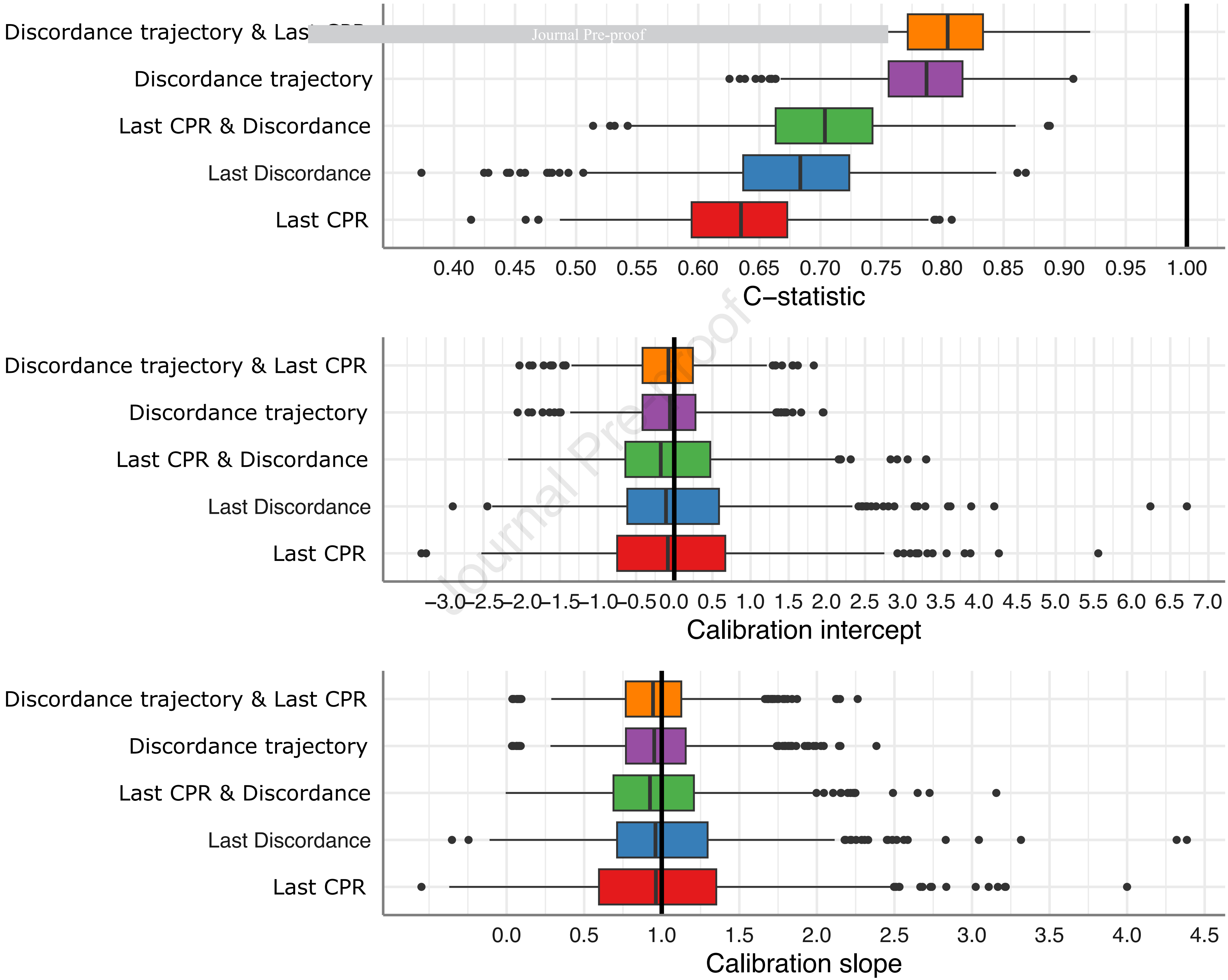
Figure S2. The optimal number of clusters and identified clusters learned from the random intercept and slope of multi-level regression model.

Panel A displays an "elbow plot," which is employed to determine the optimal number of clusters based on the total within the sum of squares (WSS). The WSS sharply declines as the number of clusters increases from 1 to 5, suggesting that additional clusters beyond five yield diminishing improvements in the compactness of the clustering. Panel B illustrates a scatterplot of the clusters formed based on the random intercepts and slopes obtained from the multi-level regression model. Each point in the plot represents a case, categorized by color to correspond to one of the five clusters identified.



Low, stable
Mild, decreasing
Low, increasing
Mild, increasing
High, stable
30.0
27.5
25.0
22.5
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
Discordance, %
18−22 weeks
23−26 weeks
27−30 weeks
31−34 weeks
34 weeks
Scan window


High, stable
Mild, increasing
Low, increasing
Mild, decreasing
Low, stable
40/86(46.5%
36/189(19%)
21/173(12.1%)
8/171(4.7%)
3/204(1.5%)
0
5
10
15
20
25
30
35
40
45
Morbidity rate
High, stable
Mild, increasing
Low, increasing
Mild, decreasing
Low, stable
8/86(9.3%)
2/189(1.1%)
0/173(0%)
0/171(0%)
0/204(0%)
0
1
2
3
4
5
6
7
8
9
Perinatal mortality rate
High, stable
Mild, increasing
Low, increasing
Mild, decreasing
Low, stable
42/86(48.8%
47/189(24.9%)
33/173(19.1%)
17/171(9.9%)
13/204(6.4%)
0
5
10
15
20
25
30
35
40
45
50
NNU admission rate



Discordance trajectory & Last CPR
Discordance trajectory
Last CPR & Discordance
Last Discordance
Last CPR
0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85 0.90 0.95 1.00
C–statistic
Discordance trajectory & Last CPR
Discordance trajectory
Last CPR & Discordance
Last Discordance
Last CPR
–3.0 –2.5 –2.0 –1.5 –1.0 –0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0
Calibration intercept
Discordance trajectory & Last CPR
Discordance trajectory
Last CPR & Discordance
Last Discordance
Last CPR
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5
Calibration slope