Placental Abruption: Clinical Indicators, Histological Findings, and its Impact on Neonatal Health

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Abstract

Placental abruption involves premature placental separation from the uterine wall, resulting in adverse maternal and neonatal outcomes. Using data from 287 confirmed cases at two large Canadian hospitals, we examined clinical, lifestyle, imaging, and postpartum histological measures, alongside neonatal health indicators. Canonical correlation analysis revealed moderate relationships among these variables, suggesting potential markers for earlier detection and timely intervention. Specific clinical indicators and histological features were associated with preterm birth and low birth weight. The analysis highlighted the placenta's role in reflecting maternal conditions and emphasized the need for proactive prenatal care. Although limited by the lack of histological data from healthy pregnancy, these findings support targeted follow-up studies to assess diagnostic and predictive accuracy. Identifying such markers may aid clinicians in refining management strategies, potentially improving maternal and neonatal outcomes while addressing ethical considerations surrounding delivery timing. Further confirmatory research with healthy pregnancies and other complications is needed.

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First and foremost, I extend my heartfelt thanks to Professor Jemila Seid Hamid for her exceptional guidance and unwavering support throughout this thesis. Her dedication to mentorship, scientific curiosity, and rigorous methodological guidance have not only shaped this work but also nurtured my growth as an independent researcher. Her commitment to both my academic and personal development has been a profound influence, and I am truly grateful for the trust she placed in me.

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Contents

List of Tables

List of Figures

Executive Summary

1. Introduction and Context.

Placental abruption—a critical obstetric complication characterized by premature separation of the placenta from the uterine wall—remains a leading cause of maternal and neonatal morbidity and mortality. Early detection is often hindered by the nonspecific nature of symptoms (e.g., abdominal pain, vaginal bleeding) and the limited sensitivity of ultrasonography. Diagnosis is generally confirmed either clinically at delivery or postpartum via histopathological examination. Therefore, identifying reliable prenatal markers or risk factors for abruption could improve outcomes by facilitating earlier and more targeted clinical interventions.

2. Methodology.

This thesis draws on data from 287 women with confirmed placental abruption at two major Canadian hospitals. Three main categories of variables were analyzed:

- Clinical and Lifestyle Factors: Maternal age, body mass index (BMI), smoking/drug use, ultrasound abnormalities (e.g., placental hematoma, hypoechogenic areas), and coexisting conditions like hypertension.
- Placental Histological Features: Placental weight, presence of retroplacental clots, infarctions, fibrin deposition, chorioamnionitis, and other tissue-level anomalies.
- Neonatal Outcomes: Birth weight, gestational age at delivery, Apgar scores, admission to neonatal intensive care, and neonatal death.

Because of the multidimensional characteristc of these data, canonical correlation analysis (CCA) was used to examine relationships between entire sets of variables simultaneously. This approach goes beyond pairwise correlations, allowing for a more nuanced understanding of how maternal clinical profiles align with placental pathology and neonatal health. Rigorous data cleaning, multiple imputation for missing values, and consultation with clinical experts were undertaken to ensure coherent and interpretable sets of variables.

3. Key Findings.

The following are the key findings from the thesis:

(a) Descriptive Patterns. Mothers who experienced placental abruption ranged widely in age, with an average of 31 years. Smoking was observed in about 14% of cases, and hypertension in 13%. Ultrasound findings (e.g., placental hematomas, hypoechogenic areas) were noted in 18% of this abruption cohort. Placental histology frequently showed retroplacental clots (54%), fibrin deposition (13%), and placental infarctions (15%), showing the presence of both vascular and inflammatory pathways.

(b) Associations between Histology and Neonatal Outcomes. CCA revealed that lower placental weight, infarctions, and chorioamnionitis correlated negatively with neonatal outcomes. Specifically, greater placental weight was associated with higher birth weight, longer gestational age, and improved Apgar scores.

(c) Associations between Histology and Clinical Indicators. Maternal hypertension, smoking, and abnormal ultrasound findings (e.g., hematomas, hypoechogenic regions) were associated with key histopathological features. Placental infarctions and meconium staining, for instance, related to both vascular dysfunction and fetal distress. These insights highlight a potential opportunity to monitor and manage modifiable risk factors such as smoking or suboptimal blood pressure before complications like abruption become acute.

(d) Associations between Clinical Indicators and Neonatal Outcomes. A separate CCA assessing clinical variables and neonatal health showed moderate correlations. Adverse clinical profiles (e.g., placenta hematoma on ultrasound, preterm premature rupture of membranes) aligned with lower birth weight, reduced gestational age, and lower Apgar scores. Notably, maternal age in this sample was modestly associated with better outcomes.

4. Potential Impacts

By identifying clinical and ultrasound markers that consistently correlate with key histological findings and adverse neonatal outcomes, this research points to opportunities for more proactive prenatal care. If confirmed in larger prospective studies, systematic screening could enable earlier detection of pregnancies at risk. Interventions such as closer fetal monitoring, strict blood-pressure control may help reduce the likelihood or severity of abruption.

5. Conclusions and Future Directions.

While these findings are exploratory, they point to possible ways for early-warning strategies and more effective management of placental abruption. Future research will benefit from:

- Inclusion of Healthy Controls: Comparing abruption cases to uncomplicated pregnancies would establish how much certain biomarkers deviate from the norm.
- Longitudinal Studies: Prospective designs could strengthen causal inferences and evaluate if identified clinical markers can predict abruption risk accurately.
- Predictive Modeling: Combining CCA with regression, machine learning, or structural equation models could refine risk stratification and guide individualized prenatal care.

By integrating maternal clinical data, placental histology, and neonatal outcomes within a multivariate framework, this thesis enhances understanding of placental abruption's etiology and informs potential preventive strategies. A more comprehensive look at the data could help reduce the serious impact of placental abruption on mothers, newborns, and the healthcare system.

Chapter 1

Introduction and Objectives

1.1 Introduction

Placental abruption, an obstetric complication involving premature detachment of the placenta from the uterine wall, significantly threatens maternal and fetal health [1]. It is characterized by the separation of maternal blood vessels from the placenta, leading to the formation of a hematoma between the placenta and uterine wall, which can severely compromise fetal oxygenation and maternal well-being [2, 3]. Timely recognition and clinical intervention are essential due to the acute and unpredictable nature of placental abruption [4].

The incidence of placental abruption varies geographically. In the United States, incidence rates have risen from 7.4 per 1000 deliveries in 1980 to approximately 11 per 1000 by recent estimates, contrasting with declines observed in European nations like Finland, where rates dropped from 7.4 to 3.3 per 1000 deliveries from 1994 to 2009 [1]. Similarly, Canada reported a peak incidence of 12.05 per 1000 deliveries in 1996, with slight declines thereafter [5]. Notably, data from Asian and African populations remain limited, marking a gap in current epidemiological understanding.

Several demographic, medical, behavioral, and socioeconomic factors contribute to the risk of placental abruption. The strongest predictor of placental abruption is a history of previous abruption, significantly elevating recurrence risk [6]. Chronic hypertension and related conditions, such as preeclampsia, substantially increase the likelihood of abruption. Antihypertensive treatments, however, may mitigate this risk by controlling maternal blood pressure and preventing arterial damage [7]. Anatomical uterine anomalies, particularly septate uteri, also raise abruption risk [7]. Behavioral factors such as tobacco use and alcohol consumption during pregnancy are additional prominent contributors [8, 9]. Socioeconomic disparities, multiple gestations, and certain immune responses, including increased interleukin-6 (IL-6) and anti-paternal HLA antibodies, further compound the risk [7]. Severe maternal trauma significantly elevates abruption risk, while minor injuries rarely have substantial effects [9, 10].

Diagnostic accuracy remains a significant challenge due to the variability of clinical presentations. Placental abruption can present overtly or remain concealed, complicating prompt diagnosis. Ultrasonography, although highly specific, demonstrates limited sensitivity, often leading to missed diagnoses [11]. Magnetic resonance imaging (MRI), despite better accuracy in evaluating hematoma extent, is infrequently used due to cost and accessibility constraints [12, 13]. Computed tomography (CT) imaging post-trauma has demonstrated high sensitivity but lower specificity and is typically reserved for assessing maternal injuries rather than routine abruption screening [10, 14]. Fetal heart rate monitoring provides additional indirect evidence of fetal distress but lacks specificity in identifying abruption.

Placental abruption significantly impacts maternal and neonatal outcomes. Acutely, it substantially elevates the risk of cesarean delivery and severe postpartum hemorrhage, often necessitating extensive surgical interventions and critical care management [15]. Long-term maternal risks include persistent renal impairment, cardiovascular complications, and increased recurrence risk in future pregnancies [16, 17]. Neonatal outcomes are equally concerning, frequently involving low birth weight, preterm birth, intrauterine growth restriction, and respiratory distress syndrome, often necessitating neonatal intensive care [18]. Long-term neonatal complications include developmental delays and an increased risk of neurological impairments such as cerebral palsy due to hypoxic conditions experienced during birth [15].

The multifaceted nature of placental abruption highlights the complexity and necessity of accurate and timely diagnostic approaches. Improved diagnostic precision could significantly enhance clinical outcomes by facilitating earlier interventions, reducing both immediate and long-term health complications.

1.2 Rationale and Objectives

1.2.1 Rationale

One of the significant challenges in the diagnosis, monitoring, and intervention of placental abruption is the absence of reliable predictive models [19]. Currently, definitive diagnosis often occurs post-factum, typically confirmed during or after delivery [4]. Placental abruption is typically diagnosed through clinical evaluation, but post-partum histological examination of the placenta is used to confirm abruption. Histological analysis can also provide insights into the severity and causes of abruption [20]. This retrospective confirmation and analysis, while accurate, does not aid in the proactive monitoring or timely intervention, which is needed to prevent the negative maternal and child outcomes [21]. The lack of predictive models that can be used as an early warning means that placental abruptions often occur suddenly and unexpectedly, with potentially severe consequences if not acted upon in a timely manner.

Placental abruption with presumed delayed intervention could have devastating consequences [2, 16]. If placental abruption occurs, it can lead to the interruption of oxygen supply to the fetus, which can quickly result in severe outcomes for the baby [22]. In these situations, clinicians may choose to act cautiously by initiating emergency interventions, such as cesarean sections, to reduce potential risks [23]. Although such interventions may lead to preterm births, they are often considered a safer alternative to the catastrophic outcomes of unmanaged placental abruption, which poses immediate risks to both the mother and baby [23]. This situation highlights the critical need for more refined diagnostic tools that can accurately predict placental abruption, allowing for timely and appropriate management and intervention.

Previous studies, including the publication by Elsasser and colleagues [14], predominantly employed univariate statistical methods to explore associations between clinical presentations and histopathological findings from mothers with placental abruption. These studies report weak pairwise associations between clinical presentations, histological findings, and outcomes [14, 20]. However, the use of univariate methods limits the depth of analysis to isolated, pairwise correlations, thereby potentially overlooking the multidimensional interactions among various clinical and histological variables.

Placental abruption is a condition with multifaceted (often not unique) clinical presentations, and is potentially associated with various risk factors. These group of variables may be associated with each other and with maternal and child outcomes, in ways that a simple pair-wise correlation may not detect. Moreover, the associations between clinical presentations (which may be used as potential indicators of the timing and severity of placental abruption) and histopathological findings (which are known to be accurate in diagnosis of placental abruption post-partum) are likely not simple. Multivariate statistical and computational framework might allow us to reveal associations that we might not otherwise see in univariate settings.

1.2.2 Objectives

The overall objective of this thesis is to perform exploratory multivariate analysis with the aim of understanding associations between various clinical and exposure variables, imaging measurements taken during pregnancy, and health outcomes. The specific objectives are:

1. to study the clinical and histological characteristics of placental abruption, with the aim of understanding whom abruption affects, what pregnancy symptoms and complications are and the physical characteristics of the placenta obtained from women who experienced abruption.

2. to perform canonical correlation analysis (CCA) with the aim of quantifying and investigating multivariate associations between two groups of variables: One group consisting of clinical indicators, exposure variables, imaging data, and another group consisting of histological features known to be indicative of placental abruption. The main objective here is to identify sets of clinical, exposure and imaging variables that can be useful in facilitating early diagnosis and timely intervention of placental abruption.

3. to perform CCA between sets of histological measurements and sets of neonatal outcomes with the purpose of quantifying and investigating their multivariate associations. The objective here is to investigate the impact of abruption on neonatal outcomes. By integrating the results we find from this analysis with that of objectives 1 and 3, we also aim to provide supportive evidence for the pregnancy markers that we identify as potential indicators of abruption.

4. to perform CCA between sets of clinical, exposure and imaging variables and sets of neonatal outcomes. The results from this analysis will provide estimates of direct associations between these two sets of variables. The results will also be interpreted together with the results from objectives 1-3, to address the overarching objective of identifying potential markers of abruptions that can be used for early diagnosis, and ultimately allow timely intervention to prevent bad maternal and child outcomes.

1.3 Thesis Organization

An extensive literature review on placental abruption was done and the findings are presented in Chapter 1. The rationale and thesis objectives are also provided in Chapter 1. In Chapter 2, we provide descriptions of the data sets used in the thesis including the study design and data collection procedures. Detailed descriptions of the statistical methods used as well as the analysis strategies employed are also provided in Chapter 2. In Chapters 3-6, we provide the results and interpretations corresponding to the 4 specific objectives outlined above. Clinical and histological characteristics of placental abruption, focusing more on the descriptive analyses of demographic, clinical and physical placental features are provided in Chapter 3. Chapter 4 examines pair-wise and multivariate associations between histological markers of abruption and neonatal outcomes. This chapter also includes detailed interpretations of the findings and provides discussions in light of current literature. In Chapter 5, we investigate associations between histological features and clinical indicators. The results are interpreted in the context of our findings presented in Chapter 3 and 4, as well as what is available in the literature. The results of the CCA between clinical indicators and neonatal outcomes are provided in Chapter 6. Detailed interpretations and discussions are also provided in this chapter. Chapter 7 summarizes the key findings, provides discussion on their implications, and highlights the strengths and limitations of the thesis. Potential directions for future research are also outlined in Chapter 7.

Chapter 2

Materials and Methods

Canonical Correlation Analysis (CCA) will be utilized to address the overarching thesis objective. As such, we provide detailed descriptions of the CCA methodology in this chapter, where we outline the mathematical formulations, the optimization process as well as interpretations and presentations of results from CCA. In this chapter, we also provide details on the statistical analysis strategy including data preparation and organization, handling missing data, variable selection and variable grouping into the different categories. We also provide detailed descriptions of the placental abruption dataset used in the thesis, including study design and data collection.

2.1 Canonical Correlation Analysis

2.1.1 Introduction

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2.2 Canonical Correlation Analysis

2.2.1 Introduction

CCA is a powerful multivariate statistical tool used to quantify linear association (correlations) between two sets of variables (i.e. between two multivariate datasets, say $\mathbf{X}_{p\times m}$ and $\mathbf{Y}_{q\times n}$) [24]. Originating from Hotelling's work in 1936, CCA allows us to generate two sets of orthogonal linear combinations from the original datasets, $\mathbf{X}$ and $\mathbf{Y}$, where the resulting linear combinations sequentially maximize the correlation between the two sets of variables [25]. Due to its ability to reveal relationships that might not be easily seen in pair-wise analysis, CCA has been widely used in practical applications including in psychology, ecology, economics and biomedical sciences [24].

For instance, in psychology, CCA was employed to examine the interplay between personality traits and cognitive measures, such as IQ scores [26]. Similarly, in ecological research, CCA was utilized to explore the relationships between environmental variables and specific distributions, particularly in marine ecosystems, offering a clearer view of how environmental gradients shape biodiversity [27].

Healthcare applications of CCA have also been indicated to have important contributions. For example, in a study involving pulmonary hypertension, CCA was used to study associations between clinical measurements, such as systolic and diastolic pressure, with hemodynamic indices derived from computational fluid dynamics simulations [28]. In cardiac surgery, CCA was utilized to examine relationships between various risk factors and patient outcomes such as myocardial infarctions and wound complications, facilitating an understanding of how pre- and peri-operative variables influence post-operative results [29].

In the field of epidemiology, CCA has been shown to be instrumental in investigating the relationships between environmental exposures and other risk factors and clinical presentations (symptoms) of in human encephalitis [30]. In neuroscience, CCA has proven to be important in integrating large datasets, such as those linking brain imaging with genetic information [31]. Likewise, in genomics, CCA was used to investigate associations between genetic markers and physiological indicators of chronic kidney disease, offering a detailed understanding of how genetic variants contribute to complex health conditions [32].

The broad applicability of CCA across disciplines emphasizes its value as an exploratory statistical method. Its flexibility in handling diverse data types and its strength in revealing complex associations reinforce its importance in advancing scientific inquiry across a wide array of research areas.

2.2.2 Mathematical Formulations

CCA is grounded on the variance-covariance or correlation matrices, which capture the linear relationships between two sets of variables [25]. Consider two random vectors, $\mathbf{x} = (X_1, X_2, \ldots, X_p)'$ and $\mathbf{y} = (Y_1, Y_2, \ldots, Y_q)'$. Suppose also that X and Y measurements are obtained from a random sample of n and m individuals, respectively, leading to matrices $\mathbf{X}_{p\times n}$ and $\mathbf{Y}_{q\times m}$. The foundation of CCA lies in examining the combined variance-covariance (sometimes simply referred to as covariance) structure for the two sets of data, represented by the matrix Σ:

$$\Sigma = \begin{pmatrix} \Sigma_{XX} & \Sigma_{XY} \\ \Sigma_{YX} & \Sigma_{YY} \end{pmatrix},$$

where:

$$\begin{aligned} &\Sigma_{XX} \quad \text{is the } p \times p \text{ covariance matrix of } \mathbf{X}, \\ &\Sigma_{YY} \quad \text{is the } q \times q \text{ covariance matrix of } \mathbf{Y}, \\ &\Sigma_{XY} \quad \text{is the } p \times q \text{ cross-covariance matrix between } \mathbf{X} \text{ and } \mathbf{Y}, \\ &\Sigma_{YX} = \Sigma'_{XY} \text{ is the transpose of } \Sigma_{XY}. \end{aligned}$$

The diagonal blocks Σ_{XX} and Σ_{YY} represent the within variance-covariances for $\mathbf{X}$ and $\mathbf{Y}$, respectively. On the other hand, the off-diagonal blocks $\Sigma_{XY} = \Sigma'_{YX}$ describe the covariances (often referred to as cross-covariances) between the two sets of variables.

These matrices collectively form the basis for deriving the canonical coefficients, canonical loadings, canonical variates, canonical scores and the correlations between them, which are the results from CCA.

The Objective in CCA is to find two sets of vectors, say $\mathbf{a}_i$ and $\mathbf{b}_i$, that define the two sets of linear combinations of (from the original $\mathbf{x}$ and $\mathbf{y}$ variables), such that the correlation between these linear combinations are sequentially maximized [24]. These linear combinations (referred to as the *canonical variates*) are expressed as:

$$\mathbf{u}_i = \mathbf{a}_i'\mathbf{x}, \qquad \mathbf{v}_i = \mathbf{b}_i'\mathbf{y},$$

where $\mathbf{u}_i$ and $\mathbf{v}_i$ represent the i^{th} pair of canonical variates. The vectors $\mathbf{a}_i$ and $\mathbf{b}_i$ are called *canonical coefficients* or *canonical weights.*

The primary goal of CCA is to maximize the correlation between the canonical variates $\mathbf{u}_i$ and $\mathbf{v}_i$. The correlation is given by:

$$\rho_i = \text{cor}(\mathbf{u}_i, \mathbf{v}_i) = \text{cor}(\mathbf{a}_i'\mathbf{x}, \mathbf{b}_i'\mathbf{y}) = \frac{\mathbf{a}_i'\Sigma_{XY}\mathbf{b}_i}{\sqrt{\mathbf{a}_i'\Sigma_{XX}\mathbf{a}_i}\sqrt{\mathbf{b}_i'\Sigma_{YY}\mathbf{b}_i}}.$$

This optimization problem is subject to the normalization constraints:

$$\mathbf{a}_i'\Sigma_{XX}\mathbf{a}_i = 1 \quad \text{and} \quad \mathbf{b}_i'\Sigma_{YY}\mathbf{b}_i = 1.$$

These constraints ensure that the canonical variates have unit variance. Through the maximization process, additional constraints are imposed such that the pairs of canonical variates are uncorrelated with each other, which is done by selecting canonical coefficients that are orthogonal to each other.

Note that the above expression (for the correlation between the canonical variates) is obtained, because we have

$$\text{cov}(\mathbf{u}_i, \mathbf{v}_i) = \text{cov}(\mathbf{a}_i'\mathbf{x}, \mathbf{b}_i'\mathbf{y}) = \mathbf{a}_i'\text{cov}(\mathbf{x}, \mathbf{y})\mathbf{b}_i = \mathbf{a}_i'\Sigma_{XY}\mathbf{b}_i,$$

$$\text{var}(\mathbf{u}_i) = \text{var}(\mathbf{a}_i'\mathbf{x}) = \mathbf{a}_i'\text{cov}(\mathbf{x})\mathbf{a}_i = \mathbf{a}_i'\Sigma_{XX}\mathbf{a}_i,$$

$$\text{var}(\mathbf{v}_i) = \text{var}(\mathbf{b}_i'\mathbf{Y}) = \mathbf{b}_i'\text{cov}(\mathbf{y})\mathbf{b}_i = \mathbf{b}_i'\Sigma_{YY}\mathbf{b}_i.$$

Sequential maximization of the correlations between the canonical variates can be converted to an eigen analysis problem, leading to solutions where the canonical correlations and canonical coefficients can be found from the eigenvalues and vectors of $\Sigma_{XX}^{-1/2}\Sigma_{XY}\Sigma_{YY}^{-1}\Sigma_{YX}\Sigma_{XX}^{-1/2}$ and $\Sigma_{YY}^{-1/2}\Sigma_{YX}\Sigma_{XX}^{-1}\Sigma_{XY}\Sigma_{YY}^{-1/2}$. It has also been shown that eigen analysis of $\Sigma_{XX}^{-1}\Sigma_{XY}\Sigma_{YY}^{-1}\Sigma_{YX}$ and $\Sigma_{YY}^{-1}\Sigma_{YX}\Sigma_{XX}^{-1}\Sigma_{XY}$ lead to the same solutions. Here, we will describe the solutions from singular value decomposition (SVD) in more detail, SVD is the easiest and most commonly used approach.

Let ρ_i represent the correlation between the i^{th} pair of canonical variates. The eigenvalues λ_i (of the above matrices) correspond to the square of the canonical correlations, i.e. $\rho_i^2 = \lambda_i$ and $\lambda_1 > \lambda_2 > ... > \lambda_r.$, where $r = min(p, q)$. The canonical correlations also correspond to the singular values obtained from the SVD.

Consider $\mathbf{\Omega} = \Sigma_{XX}^{-1/2}\Sigma_{XY}\Sigma_{YY}^{-1/2}$, where $\Sigma_{XX} = \Sigma_{XX}^{-1/2}\Sigma_{XX}^{-1/2}$ and $\Sigma_{YY} = \Sigma_{YY}^{-1/2}\Sigma_{YY}^{-1/2}$. The SVD of Ω can be written as:

$$\mathbf{\Omega} = \mathbf{PSQ}',$$

where $\mathbf{P}$ and $\mathbf{Q}$ are orthogonal matrices consisting of the left and right singular vectors as their column vectors, and $\mathbf{S}$ is a diagonal matrix with the singular values (the square of the eigenvalues) as its diagonal elements. The canonical coefficients are, therefore, given by:

$$\mathbf{A} = \Sigma_{XX}^{-1/2}\mathbf{P} \quad \text{and} \quad \mathbf{B} = \Sigma_{YY}^{-1/2}\mathbf{Q},$$

where $\mathbf{A} = (\mathbf{a}_1, \mathbf{a}_2, ..., \mathbf{a}_r)$, $\mathbf{B} = (\mathbf{b}_1, \mathbf{b}_2, ..., \mathbf{b}_r)$ and $r = min(p, q)$.

In CCA, the canonical variates $\mathbf{u}_i$ and $\mathbf{v}_i$ are determined sequentially. After determining the first pair $(\mathbf{u}_1, \mathbf{v}_1)$ that corresponds to the maximum correlation ρ_1, the second pair $(\mathbf{u}_2, \mathbf{v}_2)$ is found such that ρ_2 is the second largest correlation, subject to the additional constraint that the pair $\mathbf{u}_2$ and $\mathbf{v}_2$ are uncorrelated with $\mathbf{u}_1$ and $\mathbf{v}_1$. This process continues until we find $r = \min(p, q)$ pairs of canonical variates.

The resulting canonical variates $\mathbf{u}_1, \mathbf{u}_2, \ldots, \mathbf{u}_r$ are mutually orthogonal, as are the canonical variates $\mathbf{v}_1, \mathbf{v}_2, \ldots, \mathbf{v}_r$. This orthogonality implies that the linear relationship captured by each pair of canonical variates is unique.

In practice, the population within covariance matrices Σ_{XX} and Σ_{YY} as well as the cross-covariance Σ_{XY}, are unknown. As such, the sample within and between covariances, which are unbiased estimators of the unknown population covariances, are used. We denote the estimator of $\hat{\Sigma}$ by

$$\hat{\Sigma} = \begin{pmatrix} \hat{\Sigma}_{XX} & \hat{\Sigma}_{XY} \\ \hat{\Sigma}_{YX} & \hat{\Sigma}_{YY} \end{pmatrix}.$$

It is crucial that the estimates of the within covariance matrices are of full rank (or non-singular) for the solutions to exist. Regularization methods are available for situations where the number of predictors is large relative to the sample size, or when singularity or ill-conditioning arises because of various other reasons. Ill-conditioning or singularity, for instance, can arise when there is linear dependency or strong linear relationships between some of the variables within each of the two datasets.

2.2.3 Presentation and interpretation of CCA Results

The results of CCA are often presented in the form of the canonical correlations and the canonical loadings or canonical coefficients. The canonical coefficients represent the relative importance or contributions of each original variables to the new sets of linear combinations (the canonical variates). [33]. These coefficients, for the leading canonical variates, are often presented using pairs of bargraphs. Circular bargraphs (referred to heliograms, helio diagrams or helioplots) are also used to highlight not only the magnitude of the coefficients, but also the direction of the relationships between the original variables and the corresponding canonical variates. It is also common to select the leading variables, corresponding to the largest contributions, and present them using a diagram referred to as finger plot.

Canonical loadings or structural coefficients are also one of the most commonly used quantities used to interpret the results from CCA. The canonical loadings are the correlations between the original variables and the corresponding canonical variates.

The loadings reflect the variance the original variables share with a particular canonical variate. Variables that are highly correlated with a canonical variate are considered more important for deriving a meaningful interpretation of pairs of the leading canonical variates, that are shown to be strongly associated. [33]. Generally, variables with a loading of 0.3 or higher in absolute value are selected for their potential to provide meaningful interpretations of the associated canonical variates [34, 35]

In addition to canonical loadings and canonical correlations, canonical cross-correlations (also referred to as canonical cross-loadings) are also used in our interpretation of CCA results. Canonical cross-loadings are used to determine percentages of variations in the canonical variates explained by the original variables of the other datasets and are calculated by considering the correlations between the $\mathbf{x}$ variables with the $\mathbf{y}$ canonical variates ($\mathbf{v}$ variables) and the correlations between $\mathbf{y}$ and the $\mathbf{x}$ canonical variates ($\mathbf{u}$ variables).

Illustrative Example

To demonstrate how a canonical correlation analysis can be set up, we present the following illustrative example. Suppose we have $n = 10$ observations and eight total variables (Table 2.1): four in $\mathbf{X}$ (X_1, X_2, X_3, X_4) and four in $\mathbf{Y}$ (Y_1, Y_2, Y_3, Y_4)

Table 2.1: A illustrative example with $n = 10$ observations, four variables in $\mathbf{X}$, and four in $\mathbf{Y}$

Data Set X

ID	X_1	X_2	X_3	X_4
1	4.2	2.1	1.9	3.3
2	5.0	2.3	2.2	3.8
3	4.8	2.0	2.1	3.4
4	5.1	2.5	2.4	3.6
5	5.2	2.3	2.5	3.5
6	4.9	2.2	2.0	3.2
7	5.3	2.4	2.6	3.9
8	4.7	1.9	1.8	3.1
9	5.0	2.1	2.4	3.5
10	5.4	2.6	2.7	4.0

Data Set Y

ID	Y_1	Y_2	Y_3	Y_4
1	7.9	1.7	4.1	0.9
2	8.1	1.4	4.4	1.0
3	8.3	1.6	4.3	0.8
4	7.8	1.5	4.2	1.1
5	8.0	1.6	4.0	1.2
6	7.9	1.3	3.9	0.9
7	8.1	1.5	4.5	1.0
8	7.8	1.4	4.1	0.8
9	8.2	1.6	4.3	1.1
10	8.0	1.5	4.2	0.9

In canonical correlation analysis, we typically derive linear combinations (canonical variates) for each set of variables and then measure the correlation between these variates to determine how strongly the sets $\mathbf{X}$ and $\mathbf{Y}$ relate to each other.

Output and Interpretation The canonical correlation analysis shows a strong linear association between the variable sets $\mathbf{X}$ and $\mathbf{Y}$ with a canonical correlation of $\rho = 0.96$. (Figure 2.1)

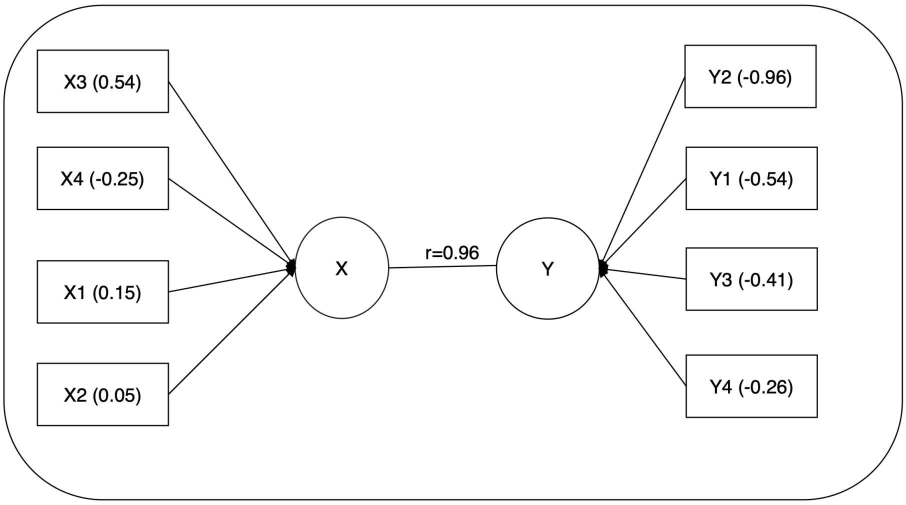

Figure 2.1: Finger plot illustrating the first canonical variates obtained from the data sets **X** and **Y**, with a canonical correlation of 0.96

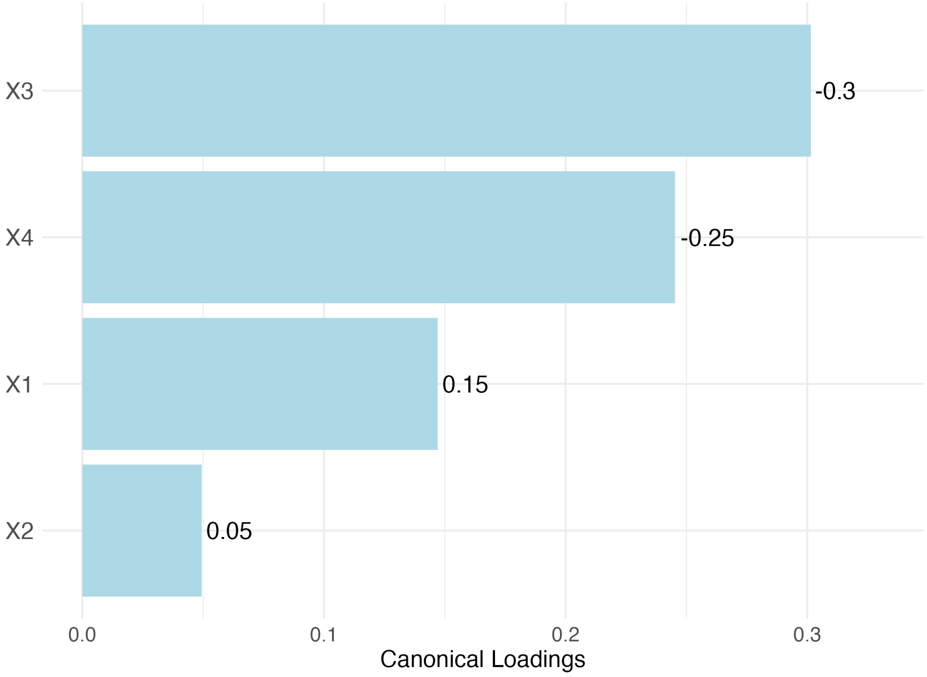

Figure 2.2: Canonical loadings for the **X** variable set in the first canonical correlation

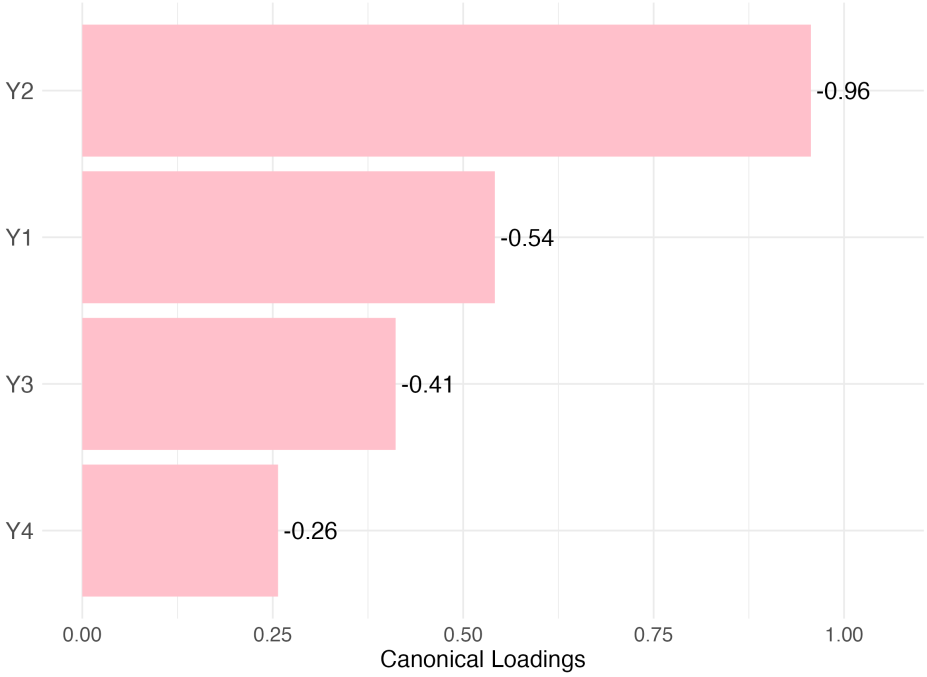

Figure 2.3: Canonical loadings for the **Y** variable set in the first canonical correlation

The canonical loadings for the **X** variates are

$$X_1 = 0.15, \quad X_2 = 0.05, \quad X_3 = 0.54, \quad X_4 = -0.25.$$

A positive loading indicates that an increase in the variable contributes to an increase in the corresponding canonical variate. In contrast, a negative loading indicates that an increase in the variable contributes to a decrease in the canonical variate. For instance, the loading for X_3 is positive (0.54), suggesting that higher values of X_3 lead to higher scores on the canonical variate for **X** (Figure 2.2). Conversely, X_4 has a negative loading (-0.25), meaning that higher values of X_4 correspond to lower scores on this variate. The canonical loadings for the **Y** variates are

$$Y_1 = -0.54, \quad Y_2 = -0.96, \quad Y_3 = -0.41, \quad Y_4 = -0.26.$$

All loadings for the **Y** variates are negative (Figure 2.3). This indicates that an increase in any of these variables is associated with a decrease in the canonical variate for **Y**. In particular, Y_2 has a large negative loading (-0.96), which implies that higher values of Y_2 strongly contribute to lowering the canonical variate for **Y**.

In summary, the analysis shows that the strong linear association ($\rho = 0.96$) is reflected in the direction and magnitude of the loadings. Variables with positive loadings contribute in the same direction as the canonical variate, while those with negative loadings contribute in the opposite direction.

2.3 Placental Abruption Dataset

Data used in this thesis was obtained from two major Canadian hospitals: the Ottawa Hospital (TOH) and the Children's Hospital of Eastern Ontario (CHEO), and it involves all pregnant women with a confirmed cases of placental abruption (PA) as documented in the EPICHyperspace pathology archives. Data consists of 1)demographic and exposure variables (eg. age, smoking, drug use), clinical measurements including pregnancy complications, ultrasound assessments and other comorbidity 2) histological variables obtained from detailed pathological analysis of the placentas obtained from others with confirmed cases of placental abruption 3) maternal and neonatal outcomes.

2.3.1 Study Design and Settings

Data was obtained from a retrospective cohort study. Placental abruption cases with a clinical or pathological diagnosis of placental abruption between October 1, 2013, and April 30, 2020, were identified using the Laboratory Information Service Program (EPIC-Hyperspace). Maternal demographics, neonatal outcomes, and placental gross and histopathological findings were extracted and recorded in REDCap. Clinical diagnosis of abruption was defined as either obstetric ultrasound detection of subchorionic or retroplacental hematoma or a clinical presentation involving vaginal bleeding, abdominal pain, uterine contractions, and/or uterine tenderness, as documented in TOH electronic medical records (EMRs). Pathological diagnosis was confirmed post-delivery based on CHEO EPIC reports, which included placental examination findings indicating retroplacental clots. Institutional approval was obtained prior to study initiation (CHEOREB 20/22).

2.3.2 Histological Analysis and Measurements

After delivery, placentas were trimmed, weighed and other biometric measurements taken. Potential complications such as fetal growth restriction (FGR) were also documented [36]. List of the variables from the histological analysis of placenta are provided in Table 2.2

Table 2.2: List of histological measurements and their description

Variable	**Description**
Weight	Weight of the placenta at delivery
Retroplacental Clot (RPC)	Presence of retroplacental clot
Blood Clot	Presence of a blood clot in the placenta
Fibrin Deposition	Presence of fibrin deposition
Villi Presence	Presence of villi in the placenta
Infarction	Presence of infarctions in the placenta
Chorioamnionitis	Presence of chorioamnionitis
Funisitis	Presence of funisitis
Acute Deciduitis	Presence of acute deciduitis
Meconium-Stained Membranes	Presence of meconium-stained membranes
Villous Maldevelopment (VMD)	Presence of villous maldevelopment
Chronic Villitis (CV)	Presence of chronic villitis
Circumvallate	Circumvallate
Parenchymal consolidation	Presence of Parenchymal consolidation

2.3.3 Clinical Indicators and Outcome Data

The outcome data (Table 2.3) focuses on neonatal health, these include birth weight, neonatal survival, neonatal intensive care unit (NICU) admissions, and interventions such as positive pressure ventilation and blood transfusions. Additional indicators such as cardiac status, hemoglobin levels and birth weight are also recorded. The clinical data (Table 2.4) consists of a broad range of maternal and fetal health measures collected during pregnancy. These include maternal behaviors such as smoking and drug use, imaging data from ultrasounds (eg. lesions) as well as maternal blood pressure. Uterine contractions, bleeding pain and other maternal symptoms were also recorded. Fetal heart rate patterns were also monitored to examine fetal well-being.

Table 2.3: Description of Selected Outcome Variables

Variable	**Description**
Neonatal Death	Neonatal death
NICU Admission	Neonatal Intensive Care Unit admission
Neonatal Positive Pressure Ventilation	Neonate required positive pressure ventilation
Neonatal Cardiac Status	Neonatal cardiac status
Neonatal Hemoglobin Value	Neonatal hemoglobin value
Neonatal Blood Transfusion	Neonatal blood transfusion required

Table 2.4: Description of Clinical Indicator Variables

Variable	**Description**
Age	Maternal Age
BMI	Pre-pregnancy Body Mass Index (BMI) value
Parity	Number of times the mother has given birth to a live neonate
Smoking	Mother's smoking status
Drug Use	Mother's other drug use status
Previous Abruption	History of Placenta Abruption
Hypertension	Hypertension status (chronic) of the mother
PPROM	Preterm Premature Rupture of Membranes status
SBP	Maternal systolic blood pressure (SBP)
Amniotic Fluid Volume	Amniotic fluid volume from ultrasound
Fetal Head Presence	Presence of fetal head in ultrasound
Placental Hypoechogenicity	Hypoechogenic areas in the placenta from ultrasound
Placental Hematoma	Presence of hematoma in placenta from ultrasound
Placenta Previa	Placenta previa assessment from ultrasound
Placental Lesions	Lesions in the placenta from ultrasound
Placental Lobe Assessment	Assessment of placental lobes from ultrasound
Placental Location	Location of the placenta within the uterus from ultrasound
Bleeding	Presence of maternal bleeding
Uterine Contraction	Presence of uterine contractions
Pain	Maternal pain level
Electronic Fetal Monitoring	Electronic fetal monitoring results
Fetal Movement	Fetal movement status reported by the mother
Time to Placental Delivery	Time from neonatal birth to placental delivery
Baseline Fetal Heart Rate	Baseline fetal heart rate from fetal topography
Fetal Heart Rate Variability	Variability in fetal heart rate
Fetal Heart Rate Decelerations	Decelerati on patterns in fetal heart rate
Fetal Heart Rate Accelerations	Acceleration in fetal heart rate
Neonatal Gestational Age	Gestational age of the neonate at birth
Birth Weight	Neonate birth weight
Sex	Neonate sex (Male/Female)
Delivery Type	Type of delivery
Apgar Score	Apgar score 5 minutes post-birth
Cord Blood pH7	Umbilical cord blood pH7 level
BD16	Base Deficit was 16 or higher on cord gas or neonatal gas within 1h of birth
BD10	Base deficit between 10 and 15.9 on cord gas or neonatal gas within 1h of birth

2.4 Data Preparation and Statistical Analysis

2.4.1 Data Preparation and Collection

The data was sourced from REDCap, cleaned, organized and categorized into three key sets of data: histology measurements, clinical indicators and exposure variables, and neonatal outcomes. To ensure accuracy, the categorization process (into the different sets of variables) was done in consultation with a clinician collaborator with content expertize and thorough extensive literature reviews. A data dictionary was created in collaboration with the research team including the clinician who is the primary investigator of the original study that generated the data.

To ensure consistency, several formatting steps were applied. Numerical conversions were applied to variables that were initially recorded as factors, such as Apgar scores, pH level, and gestational age. Complex variables, such as placental dimensions (length, width, height), which was recorded as one combined variable, were split into separate columns representing each of these biometric measurements. Categorical variables with sparse distributions were re-coded (collapsed into less categories) to reduce sparsity. For example, categories with very few observations were consolidated into broader, clinically meaningful groups.

2.4.2 Variable Selection

To ensure reliable analysis, variables were selected based on various criteria and clinical relevance. For categorical variables, those with a dominant value exceeding 90% of responses were flagged as low-variability and excluded, except where they were clinically important regardless of sparsity. An ad hoc variable selection process was also implemented to refine the datasets further. This included input from clinical experts to ensure the inclusion of variables relevant to the study's objectives. Additionally, variables that exhibited high correlations with one another were carefully evaluated, as they could lead to singularity, ill-conditioning and bring interpretation challenges.

2.4.3 Handling Missing Data

In epidemiological and clinical research, missing data are unavoidable, arising from patient dropouts, incomplete medical records, laboratory errors, and other logistical challenges [37]. How missing values are handled can influence the validity of study findings. Traditional ad-hoc approaches, such as complete-case analysis (list-wise deletion) or mean substitution, can introduce bias and reduce the effective sample size [38]. More robust methods that account for uncertainty and relationships among variables are preferred to ensure unbiased estimates and appropriate standard errors [39].

Missing Data Mechanisms

Rubin's framework [40] classifies missing data mechanisms into three categories:

- **Missing Completely at Random (MCAR)**: The probability of a data point being missing is unrelated to both observed and unobserved values. In this case, the subset of complete observations remains representative of the entire sample, but the reduced sample size still compromises statistical power.
- **Missing at Random (MAR)**: Missingness depends on observed data but not on the missing values themselves. For instance, older participants might be more likely to miss follow-up visits, but age is recorded. Under MAR, incorporating these observed predictors in the imputation model can lead to unbiased parameter estimates.
- **Missing Not at Random (MNAR)**: The missingness is related to the unobserved values themselves (i.e., even after accounting for observed variables). In these cases, standard methods cannot guarantee unbiased estimates without making additional assumptions or performing sensitivity analyses.

In this thesis, we assume that missingness is MAR after including relevant covariates in the imputation model (e.g., age, comorbidities, and clinical indicators). This assumption is common in many biomedical studies but should be critically evaluated to acknowledge possible biases if true MNAR processes are present [41].

Multiple Imputation by Chained Equations (MICE)

Multiple Imputation (MI) is a principled approach recommended for handling missing data under the MAR assumption [40]. Instead of replacing a missing value with a single estimate (e.g., the mean), MI creates multiple (e.g., m=5 to m=20) versions of the dataset, imputing each missing value with draws from the predictive distribution of that variable given observed data. Each completed dataset is then analyzed as if there were no missing data, and the results are combined (pooled) to reflect both within-imputation and between-imputation variability [40].

Among the various MI techniques, Multiple Imputation by Chained Equations (MICE) is especially flexible and widely used in biomedical research [42]. MICE proceeds iteratively by fitting a regression model for each incomplete variable in turn, using the other variables (observed or already imputed) as predictors. Each missing value is then replaced by a draw from its predictive distribution, preserving important relationships among variables. After several cycles, the imputed values stabilize, and one obtains a single imputed dataset. This process is repeated m times to capture the uncertainty of the missing data.

Handling Missing Data

In this study, a substantial amount of data were missing across multiple variables, rendering complete-case analysis impractical due to potential bias. We implemented multiple imputation (MI) using the `mice` package in R [43]. This approach preserves the inherent relationships among variables while reducing bias and improving efficiency in subsequent analyses [40].

We performed the imputation process separately for each of the three major blocks of data. This is because, we did not want to introduce correlations between the different sets of variables during the imputation process. Hence, our estimates for the canonical correlations are conservative.

- **Histology variables:** Placental measurements and histopathological features.
- **Clinical/Exposure variables:** Demographic factors, blood pressure, ultrasound findings, etc.
- **Outcomes:** Neonatal status, NICU admission, hemoglobin levels, etc.

Different imputation methods were applied depending on the variable type:

- **Continuous variables** (e.g., maternal age, placental weight) were imputed using *predictive mean matching* (PMM), which preserves the observed distribution by drawing imputed values from *donor* observations with similar predicted means.
- **Binary variables** (e.g., yes/no indicators for smoking or hypertension) were imputed using a *logistic regression* model.

- **Categorical variables with more than two levels** (e.g., drug type, certain histopathological features) were imputed using *polytomous regression*.

Auxiliary variables were included, where available, to strengthen the plausibility of the missing-at-random (MAR) assumption and to improve the quality of the imputations. During imputation, each variable in a block was used as a predictor for the others, and irrelevant predictors were excluded if they did not meaningfully improve the imputation model fit.

2.4.4 Statistical Analysis

In chapter 3, we performed and presented descriptive statistics to provide an overview of the maternal, clinical, and placental characteristics associated with placental abruption cases in this cohort. This chapter aims to highlight key patterns and variations in the study population. Continuous variables were summarized using mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. We also provided additional quantiles (or percentiles) for selected variables to better understand their distributions. For categorical variables, frequencies and percentages were used to summarize the data. The results were presented in Tables, narratively (in paragraphs) and graphically.

To explore the relationships between the variables, initial pairwise correlations were calculated within and between all datasets. These correlations were visualized using heatmaps to provide an intuitive view of relationships within and between the different sets of variables. Strong correlations were flagged for further examination, particularly those that have the potential cause singularity or near-singularity (ill-conditioning). Identifying these strong relationships also enhances our interpretation of the results.

CCA was performed for 3 pairs of datasets separately: between clinical measurements and histological variables, between clinical measurements and outcomes as well as between histological variables and outcomes. To evaluate the strength of correlations between pairs of canonical variates, a scree plot was generated, and our interpretations, focused on the leading canonical variates, is provided narriatively. Canonical loadings were visualized using bar graphs and the leading variables with their corresponding loadings were presented using finger plots. The canonical coefficients and cross-loadings were also used to provide additional interpretations of the CCA findings [44]. All analyses were performed using the R statistical software [45]. The `CCA` package was used to perform CCA [46]

Chapter 3

Clinical and Histological Characteristics of Placental Abruption

In this chapter, we will explore abnormalities associated with placental abruption and present findings from the analysis of retrospective data collected from women who experienced placental abruption. The results focus primarily on clinical and histological presentations, aiming to characterize placental abruptions comprehensively. We will interpret these findings in the context of existing literature (when available) on healthy pregnancies as well as pregnancies complicated by conditions other than placental abruption.

3.1 Demographic and Lifestyle Characteristics

This demographic and life-style snapshot emphasizes the diversity of maternal factors present in the study cohort (Table 3.1), many of which are established risk factors for pregnancy complications including placental complications. Understanding these characteristics is critical for interpreting the subsequent clinical and pregnancy outcomes infor the study population.

The mean maternal age in our cohort was 31.0 years (SD = 5.5), with 22% (n=59) of mothers aged 35 or older. Literature suggests that advanced maternal age ($>$ 35 years) can be associated with several pregnancy complications, including hypertensive disorders and gestational diabetes [47]. However, given that this dataset only includes women with abruption and lacks a control group, we cannot definitively conclude that advanced maternal age is overrepresented among abruption cases.

To provide context, national survey data for Canada suggest an average maternal age of around 30 years, with approximately 15–20% of mothers being 35 years or older and around 5% under 20 years [48]. While our observed proportion of mothers over 35 years (22%) is slightly above that range, it is important to note that these national estimates may not perfectly align with our specific cohort.

In terms of parity, a known risk factor for certain pregnancy complications [49], 78% (n=205) of mothers in our cohort were nulliparous (0 previous births), with only 4.9% (n=13) having more than one previous delivery. In contrast, data from the general Canadian maternal population indicate that around 40% of births are to first-time mothers [50], while roughly 25% are to women with more than one previous birth. Thus, our sample contains a greater proportion of first-time mothers and fewer multiparous women than might be expected based on broader population statistics.

Table 3.1: Summary of demographic and behavioural (life-style) variables from data involving mothers with placental abruption. Frequencies and percentages are presented unless specified otherwise.

Demographic and Behavioural Variables (N=287)	**n (%)**
Age, Mean ± SD	31.0 ± 5.5
Age Category	
20–35	206 (75)
>35	59 (22)
<20	8 (2.9)
BMI, Mean (SD)	25.3 (6.2)
BMI Category	
Underweight (<18.5)	14 (6.6)
Normal (18.5–24.9)	111 (52)
Obese (≥30)	49 (23)
Overweight (25.0–29.9)	38 (18)
Parity	
0	205 (78)
1	46 (17)
>1	13 (4.9)
Natural Conception	231 (92)
Smoking	36 (14)
Cannabis Use	12 (4.9)
Drug Use	8 (3.3)
History of Abruption	15 (6.9)

A total of 231 mothers (92%) reported natural conception, aligning with Canadian data that indicate nearly all pregnancies (about 97%) result from natural conception [48, 50]. Furthermore, 6.9% (n=15) of mothers had a history of placental abruption, which is higher than the reported 1–2% rate in the general population. Although a history of abruption is recognized as a strong risk factor for recurrence [4], again, direct comparisons should be viewed with caution given our cohort's case-based design.

Looking at maternal body mass index (BMI), the mean was 25.3 (SD = 6.2), with slightly more than half (52%) classified as having a normal BMI (18.5–24.9), 23% classified as obese (≥30), and 18% as overweight (25.0–29.9). Canadian estimates place around 55% of pregnant women in the normal range, with 20% each in the overweight and obese categories, suggesting that the BMI distribution in our sample, though broadly comparable, may reflect a marginally higher prevalence of elevated BMI. Although high BMI is associated with numerous pregnancy complications [51], the lack of a non-abruption comparison group limits our ability to ascertain whether obesity or overweight status is particularly overrepresented.

For maternal behaviors, 14% (n=36) of our cohort reported smoking during pregnancy, while 4.9% (n=12) reported cannabis use and 3.3% (n=8) reported other drug use. By comparison, national data indicate roughly 10% of mothers smoke during pregnancy, 5% use cannabis, and about 2% use other illicit drugs [48]. Each of these behaviors is linked to poorer pregnancy outcomes [52–55]. Again, because our study cohort is restricted to placental abruption cases, caution is warranted in interpreting these frequencies as higher or lower than those in the general population.

Overall, the demographic and lifestyle characteristics of this abruption cohort reveal notable parallels, as well as some differences, relative to approximate estimates for the general Canadian maternal population. However, these observations do not establish causation or definitively identify risk factors, given the absence of a comparator group and the fact that our sample consists solely of women experiencing placental abruption.

3.2 Ultrasound Findings

Ultrasound results indicated abnormalities in 18.1% of placental abruption cases (Table 3.2). Hematomas were most common (36.5%), followed by accessory lobes (25.0%), placenta previa (13.5%), and hypoechogenic areas (7.7%). These findings suggest diverse ultrasound presentations of abruption, with hematomas being a frequent observation consistent with existing literature [56]. However, without a comparison group of healthy pregnancies, the specificity of these ultrasound findings for placental abruption cannot be conclusively established.

Table 3.2: Ultrasound findings of mothers with placental abruption.

Ultrasound Findings (N = 287)	**n (%)**
No abnormalities	235 (81.9%)
Any abnormalities (at least one)	52 (18.1%)
Single abnormalities	
Hematoma	19 (36.5%)
Accessory Lobe	13 (25.0%)
Previa	7 (13.5%)
Hypoechogenicity	4 (7.7%)
Lesions	1 (1.9%)
Combined abnormalities	
Hypoechogenicity + Hematoma	4 (7.7%)
Hematoma + Previa	2 (3.8%)
Hypoechogenicity + Lesions	2 (3.8%)

The detection of hypoechogenic areas and hematomas underscores the significance of vascular disruptions within the placenta in the pathophysiology of abruption. These vascular abnormalities can compromise blood flow and reduce placental transfer capacity, both of which are essential for fetal development [57, 58]. Hematomas, in particular, are sonographic signs of placental abruption and have been associated with increased risks of preterm delivery and fetal demise [56, 59]. Later chapters (Chapters 5 and 6) will show that hypoechogenicity and hematoma are strongly associated with histological findings and hold potential for facilitating earlier detection of abruption.

Accessory placental lobes, detected in (25.0%, n=13) of the abnormalities, raise the risk of infarction and tissue retention postpartum [60], thereby increasing the likelihood of postpartum hemorrhage and infection [61]. Since accessory lobes are one of the more frequent findings in our cohort, they warrant further examination for their possible link to abruption (see Chapters 5 and 6). Placenta previa, observed in (13.5%, n=7) of the abnormalities, is known to pose significant delivery risks; its presence among these abruption cases suggests the potential intersection of these two complications. Lesions, though least common at (1.9%, n=1), remain noteworthy because large vascular tumors can lead to fetal cardiac failure or polyhydramnios [62].

3.3 Symptoms and Complications

Although many of the complications summarized in Table 3.3 (e.g., bleeding, hypertension, pain) are relatively common in pregnancy, examining them in this abruption-specific cohort may help clarify how they intersect with the pathophysiology of placental separation.

Table 3.3: Symptoms, complications and other comorbidities for mothers with placental abruption. Frequency and percentage are provided

Complications (N=287)	**n (%)**
Bleeding	209 (82%)
Hypertension	33 (13%)
PPROM	61 (24%)
Systolic BP, Mean ± SD	125 ± 15
Diastolic BP, Mean ± SD	76 ± 12
Pain	111 (52%)
Hypertonic Uterine Contractions	37 (17%)

By far, the most prevalent complication observed is bleeding, which affected an overwhelming majority of the cohort (82%, n=209), aligning with the expected pathophysiology of placental separation [63]. This hemorrhage results from the rupture of maternal vessels in the decidua basalis, leading to significant maternal risks such as hypovolemia and shock [1]. Considering that bleeding is one of the most prevalent pregnancy complications in cases other than abruption, it is paramount to identify additional factors that, together with bleeding, can facilitate early detection of abruption. In subsequent confirmatory analysis, involving both abruption cases and women with healthy pregnancies, it is important to investigate the most prevalent ultrasound abnormalities combined with prevalent clinical presentations and symptoms, including bleeding. This will allow us to identify potential risk factors as well as potential clinical presentations of abruption, which in turn can allow early diagnosis and timely intervention.

Pain is also present in the majority of the cases (52%, n=111), followed by preterm premature rupture of membranes (PPROM) (24%, n=61) and hypertension (13%, n=33), including chronic hypertension and preeclampsia. Hypertension, being a vascular pathology, is indicated in literature as a potential contributor to placental separation, through endothelial dysfunction, ischemia, and compromised uteroplacental perfusion [64–66]. PPROM is shown to increase the risk of neonatal morbidity and premature detachment of the placenta [67]. Pain in pregnancy is often acute and localized, indicative of uterine irritation caused by hemorrhage and the formation of retroplacental hematomas [3, 68].

Hypertonic uterine contractions, observed in a relatively smaller percentage of our cohort (17%, n=37), arise from uterine sensitivity, can widen placental detachment and compromise fetal oxygenation [69, 70].

The summary of these complications highlights the necessity for immediate recognition and comprehensive management in cases of placental abruption. Recognizing common patterns, such as significant bleeding, hypertension, and uterine hyperactivity, in combination with the most prevalent ultrasound abnormalities, is critical for facilitating early diagnosis, and guiding timely clinical interventions aimed at improving maternal and fetal outcomes. Understanding the clinical and ultrasound presentations, and correlating them with histological findings may also help us mitigate the legal consequences of abruption.

3.4 Physical and Histological Characteristics of the Placenta

In this section, we provide an in-depth analysis of both biometric and histological characteristics of placentas collected from mothers who experienced placental abruption. Biometric measurements, such as weight, length, width, and height, provide understanding of the health of the placenta and its physical growth and structure. Meanwhile, histological examination allows us to investigate cellular and vascular changes within the placental tissue, revealing pathological conditions linked to placental dysfunction. In general, there is limited evidence related to normative values of placental physical and histological measurements [71]. For abruption cases, there is little to no evidence in this regard.

3.4.1 Biometric Measurements

The physical characteristic of the placenta often depends on gestational age. As such, we provided the summary of the measurements partitioned by gestational age. This approach will also provide comparisons with placental normative values, when available. We used gestational age categories provided by the world health organization (WHO). Our results show substantial heterogeneity in placental size and dimensions (Table 3.4). Understanding these variations is crucial, as they may have significant implications for both maternal and fetal health outcomes.

Table 3.4: Summary of placental measurements for mothers with placental abruption, stratified by gestational age groups.

Placenta Measurements	**Gestational Age Group**	**Mean (SD)**	**Median (IQR)**	**Range**	**2.5th - 97.5th Percentile**
Weight (grams)	<37 weeks	326.3 (119.5)	326.0 (172.5)	56.0 - 604.0	128.0 - 560.1
	37-41 weeks	445.3 (104.9)	433.0 (150.0)	240.0 - 746.0	283.3 - 662.5
	>41 weeks	482.9 (111.4)	474.0 (157.5)	196.0 - 756.0	318.8 - 688.8
Length (cm)	<37 weeks	17.3 (3.9)	17.0 (4.5)	7.5 - 30.0	10.9 - 26.4
	37-41 weeks	19.8 (3.4)	19.0 (4.0)	13.0 - 30.0	15.0 - 29.2
	>41 weeks	20.0 (2.2)	20.0 (2.6)	15.5 - 27.0	16.2 - 25.0
Width (cm)	<37 weeks	13.8 (2.7)	14.0 (3.5)	7.5 - 21.5	8.7 - 18.6
	37-41 weeks	15.5 (2.1)	15.5 (2.8)	9.5 - 20.5	10.9 - 20.0
	>41 weeks	15.7 (1.8)	15.6 (1.6)	11.0 - 21.5	12.1 - 18.8
Thickness (cm)	<37 weeks	2.0 (0.5)	2.0 (0.7)	0.7 - 3.3	1.4 - 3.1
	37-41 weeks	2.2 (0.5)	2.2 (0.7)	1.2 - 5.0	1.5 - 3.6
	>41 weeks	2.2 (0.5)	2.0 (0.5)	1.3 - 4.0	1.4 - 3.3

Mean placental weight increased with advancing gestational age, from 326.3g (SD=119.5) in the preterm category (<37 weeks gestation) to 445.3g (SD=104.9) at full term (37–41 weeks), and to 482.9g (SD=111.4) post-term (>41 weeks). The median weights mirrored this trend, with values of 326.0g (IQR=172.5g), 433.0g (IQR=150.0g), and 474.0g (IQR=157.5g) across the respective groups. The ranges and percentiles within each group indicated substantial variability; for instance, placenta weight ranged from 56 to 604g in the preterm group and up to 756g in the post-term group.

Mean thickness showed a slight increase with gestational age, from 2.0cm (SD=0.5) in the preterm group to 2.2cm (SD=0.5) at term and post-term. The ranges and percentiles suggested less variability in thickness compared to other dimensions. Variations in placental thickness can indicate pathological conditions. For instance, increased thickness is shown to be associated with maternal diabetes or fetal hydrops, on the other hand, decreased thickness is observed in cases of preeclampsia or fetal growth restriction [72]. In the context of placental abruption, alterations in placenta thickness may reflect underlying vascular or inflammatory processes compromising placental integrity and function.

Our findings align with existing literature emphasizing the importance of placental size and shape in fetal development and the risk of adverse outcomes [71, 73]. Understanding the factors influencing placental biometric measurements in cases of abruption may inform strategies for early detection and timely intervention, potentially improving maternal and neonatal outcomes.

3.4.2 Histological Findings

Histological examinations of placentas in this abruption-focused cohort revealed multiple features that may reflect vascular and inflammatory processes. Retroplacental clots were noted in over half of the cases (54%, n=153; Table 3.5), consistent with reports identifying these clots as a frequent finding in placental separation [68]. Inflammatory changes, including chorioamnionitis (19%, n=51) and funisitis (8.4%, n=23), were also observed, which some studies associate with adverse neonatal outcomes [74]. Further findings, such as fibrin deposition (13%, n=21) and villous abnormalities (e.g., edema, fibrosis), suggest possible vascular insufficiency and a risk of fetal hypoxia [75, 76]. Placental infarctions (15%, n=40), sometimes linked to hypertension and preeclampsia, indicate potential compromises in placental function [77].

Although these observations align with certain documented patterns in abruption, the absence of a non-abruption comparison group limits any definitive conclusions about how prevalent these pathologies may be in uncomplicated pregnancies. Further research—including comparative studies with healthy controls—would provide a clearer context for these findings and help clarify how vascular insufficiency and inflammation interact in the setting of placental abruption [78].

Table 3.5: Histological characteristics of placentas obtained from mothers with abruption.

Histology Characteristics (N=287)	**n (%)**
Retroplacental Clot	153 (54%)
Membranes Retromembranous Hematoma	95 (34%)
Compressed Villi	61 (22%)
Chorioamnionitis	51 (19%)
Infarctions	40 (15%)
Parenchymal Consolidation	23 (8.5%)
Funisitis	23 (8.4%)
Fibrin Deposition	21 (13%)
Meconium Stained Membranes	14 (5.2%)
Circumvallate/Circummarginate	14 (5.1%)

We used an UpSet plot (Figure 3.1), to investigate the presence of multiple histological markers of abruption.

This visualization highlights common patterns and overlaps in histological findings. The results show that the most frequent histological combinations involve retroplacental clots, retromembranous hematoma (80%, n=32), indicating patterns of vascular disruption and abnormal tissue development. Less frequent combinations include inflammatory markers, such as chorioamnionitis and funisitis, coupled with fibrin deposition or infarctions. This distribution suggests various independent findings

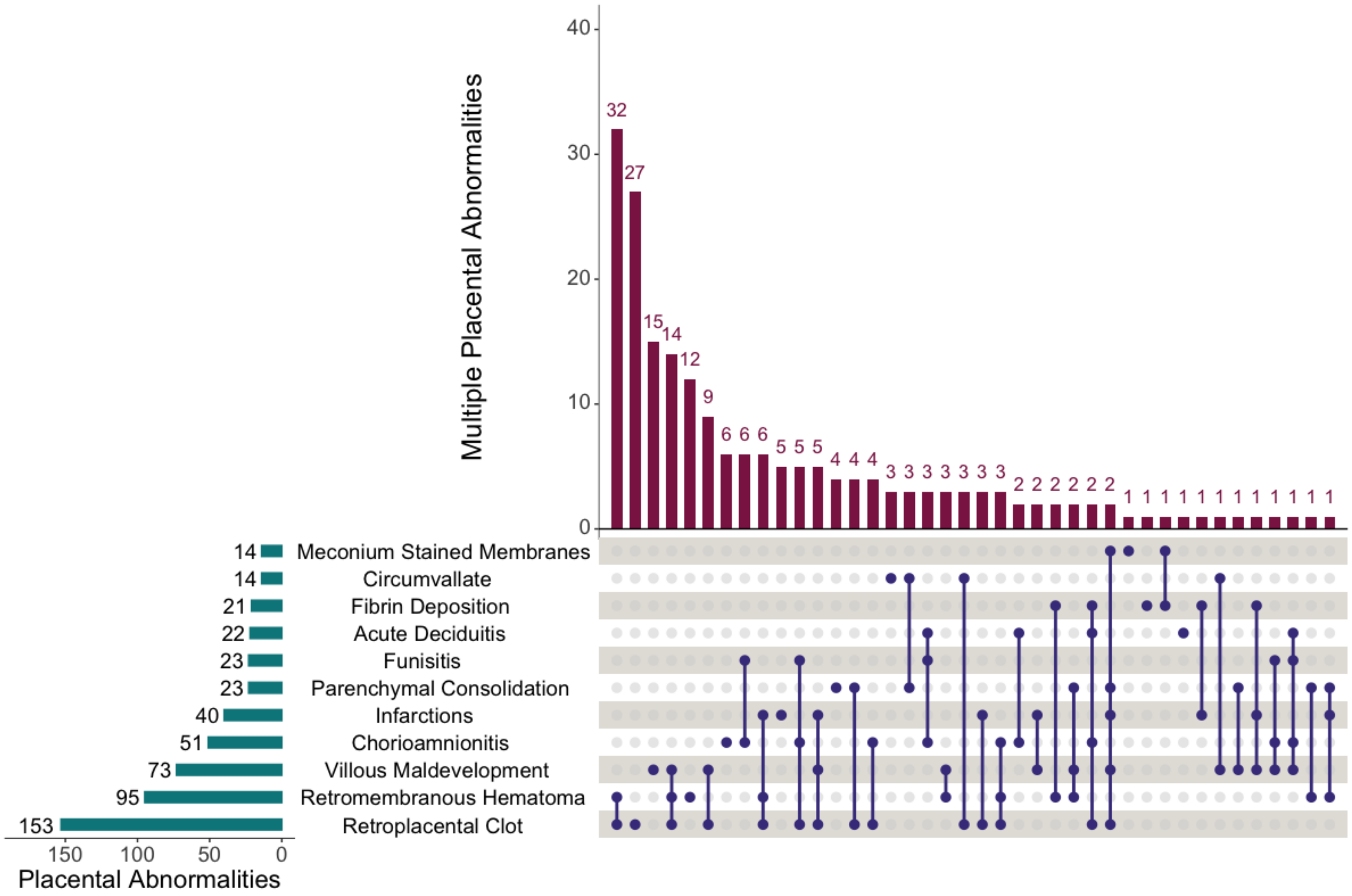

Figure 3.1: UpSet plot illustrating the presence of multiple histological abnormalities in the placenta of women with abruption. The vertical bar chart represents the frequency of unique combinations of these abnormalities. Intersection dots in the bottom indicate the specific combination of abnormalities present.

yet some overlapping pathophysiological processes, where vascular and inflammatory abnormalities often co-occur, reinforcing the multifactorial nature of placental abruption in these cases.

3.5 Summary and Discussions

This chapter describes clinical and histological features among 287 women diagnosed with placental abruption. Within this sample, recognized risk markers—such as advanced maternal age, elevated BMI, smoking, and previous abruption—were observed in some participants, whereas many women were younger and relatively healthy. Ultrasound findings were often inconclusive, underscoring the ongoing challenge of prenatally identifying abruption.

Histological examination revealed vascular and inflammatory changes (retroplacental clots, fibrin deposition, infarctions, and inflammatory infiltrates) consistent with placental abruption. Because our study did not include a comparison group without abruption, these findings simply reflect characteristics of the sample rather than demonstrating definitive causes or risk factors. Further research comparing placentas from uncomplicated pregnancies would provide valuable context for interpreting these results and assessing their broader significance. Establishing reference ranges for placental biometrics and examining how maternal health conditions influence placental histopathology may also help refine future diagnostic and management strategies for placental abruption.

Chapter 4

Association Between Histological Features and Neonatal Outcomes in Placental Abruption

Placental abruption is predominantly diagnosed on clinical grounds, relying on maternal symptoms such as abdominal pain, vaginal bleeding, uterine tenderness, and signs of fetal compromise. Despite its clinical importance, there are no universally accepted diagnostic criteria, and the evaluation often depends on clinical judgment and the exclusion of alternative pathologies [3, 79]. While histopathological examination of the placenta has been proposed as a confirmatory tool, current evidence linking placental histology to both the clinical diagnosis of abruption and subsequent fetal outcomes remains limited and inconclusive [14,19]. In this chapter, we aim to fill this evidence gap by investigating histological markers in more detail and study their association with fetal outcomes. We explore both pairwise and multivariate associations, with the aim of identifying sets of outcome variables that are associated with histological markers. We used Pearson's correlation in our pairwise associations and Canonical Correlation Analysis (CCA) in our multivariate exploratory analysis. The findings from this chapter and that of Chapter 5 will be used in Chapter 6, to facilitate our understanding of clinical presentations that may have a potential to be used in early diagnosis of abruption and ultimately lead to timely interventions.

4.1 Pairwise Correlation

We first explore pairwise relationship between the two sets of variables: histology markers and neonatal outcomes. The first set include 9 variables and the second 10 variables, listed in Table A.1 (Appendix).

Data cleaning and preparation was first done, where variables with high within group correlations were removed to avoid singularity and near-singularity problems in the CCA. Consultations with the clinical expert was done to make sure that important variables are not removed in the process and that all relevant variables are included in the analysis. Individuals and variables with high percentage of missing data were also removed, the remaining of the missing data was imputed. The pairwise within and cross-correlations for histological variables and neonatal outcome are depicted through a heatmap (Figure 4.1), and details on within dataset correlations are provided in Appendix (Figures A.2 to

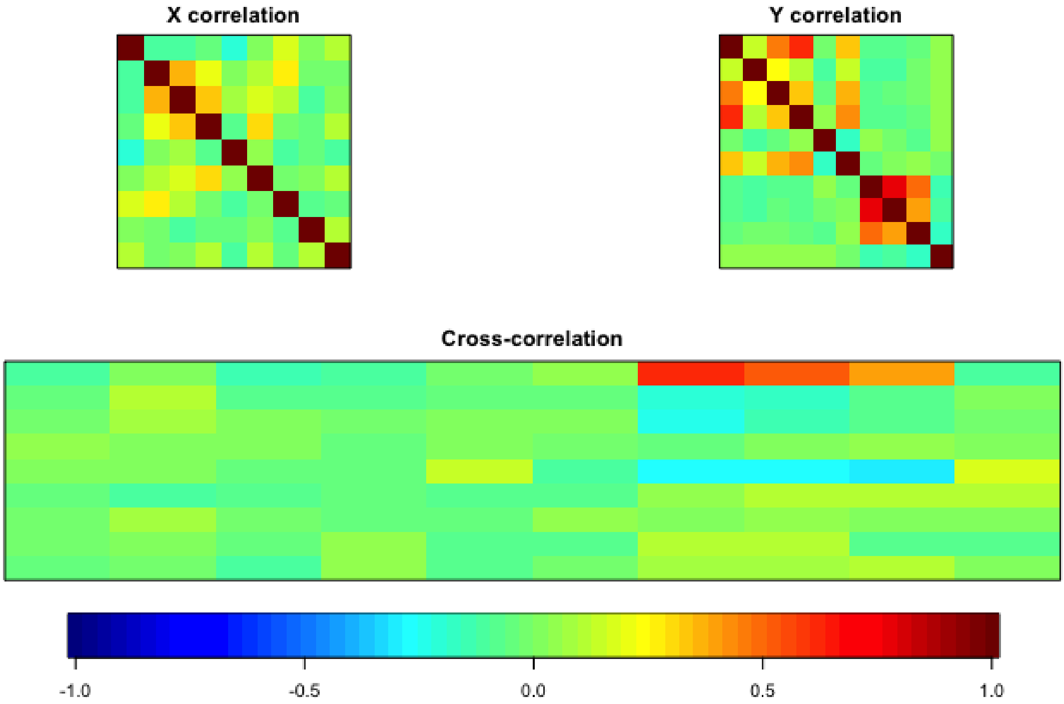

Figure 4.1: Within and cross-correlations between histological markers and neonatal outcomes, where x variables represent histological markers and y variables represent neonatal outcomes

A.3). This multi-faceted approach provides a detailed examination of within and between relationships, and later allows us provide appropriate interpretation of the CCA results.

Figure 4.1 shows that the within correlations for the histology markers are weak to moderate (ranging from -0.21 to 0.34), with infarction and fibrin deposition showing the strongest association. Within the outcome dataset, birth weight shows a strong correlation with gestational age ($r=0.77$). Additionally, birthweight and Apgar scores are moderately correlated ($r=0.49$). Another moderate correlation is observed between neonatal death and neonatal cardiac depression ($r=0.45$). The remaining of the within correlations for both datasets are weak (Figures A.1 and A.2, Appendix).

The pairwise cross-correlations between the histology variables and neonatal outcome measures indicate that placental weight has a moderate positive correlation with birth weight ($r=0.59$), gestational age ($r=0.53$), and the 5-minute Apgar score ($r = 0.38$). Considering the hypothesis that abruption leads to relatively lower placental weight (compared to normal pregnancy), our results indirectly show negative association between placental abruption and neonatal health outcomes. These results are consistent with the biological significance of placental weight in supporting fetal growth and development, and hence neonatal health. The remaining cross-correlations between histology markers and neonatal outcomes are weak, with coefficients generally ranging from -0.29 to 0.28 (Figure A.3, Appendix).

4.2 Canonical Correlation Analysis (CCA)

The results from CCA reveal a relatively strong multivariate association between histological variables and neonatal outcomes, as measured by the correlation between the leading canonical variates (r=0.69) (Figure 4.2). The variables contributing the highest to this strong correlation between the two sets of variables are placental weight, presence of chorioamnionitis and presence of fibrin deposition on the histological side and birth weight, gestational age and apgar score on the neonatal outcome side.

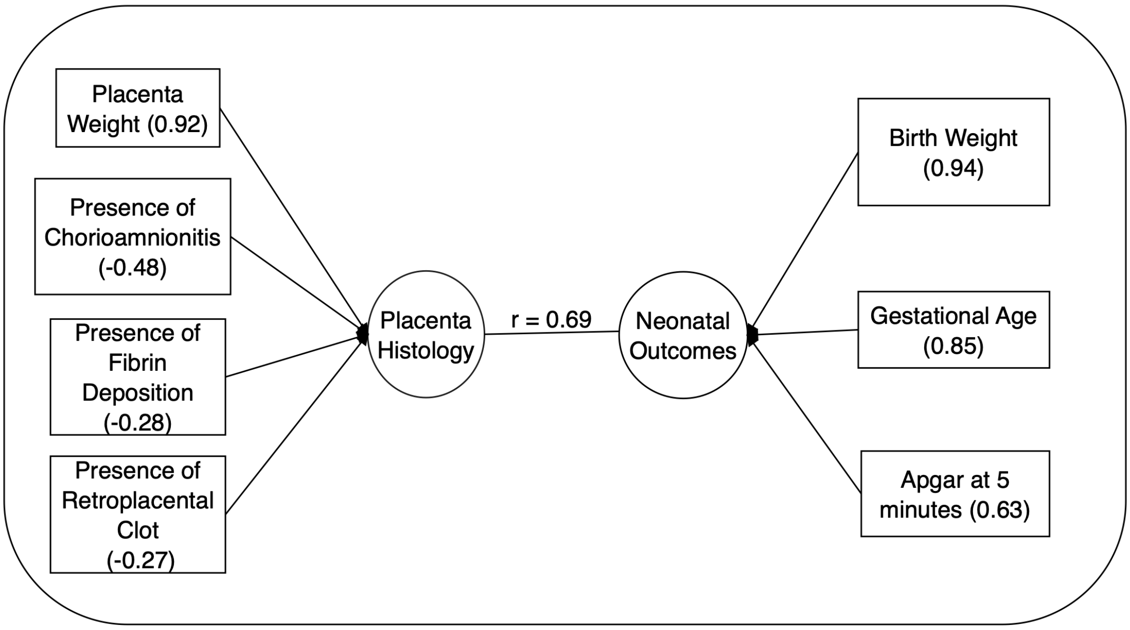

Figure 4.2: Finger plot illustrating the first canonical variates obtained from placental histology and neonatal outcomes, with a canonical correlation of 0.69. The values shown in parentheses are the canonical loadings, indicating how strongly each variable correlates with its canonical variate—higher (absolute) loadings reflect greater contribution to the overall correlation

This correlation between the leading canonical variates suggests a strong relationship between the two sets of variables. This correlation is not greater than the pairwise correlation between placental weight and birthweight. Nevertheless, the multivariate analysis through CCA reveals additional variables contributing to the leading canonical variates, these variables are indicated in the literature as potential markers of placental abruption. We will investigate this in more detail below.

Among the histology variables, placental weight appears to contribute the most to the leading canonical variate, with a high positive loading of 0.92 (Figure 4.3), reflecting its strong association canonical variate.

Its cross-loading of 0.63 also indicates that nearly 39.6% (calculated as the square of the cross-loading) of the variability in neonatal outcomes is linked to placental

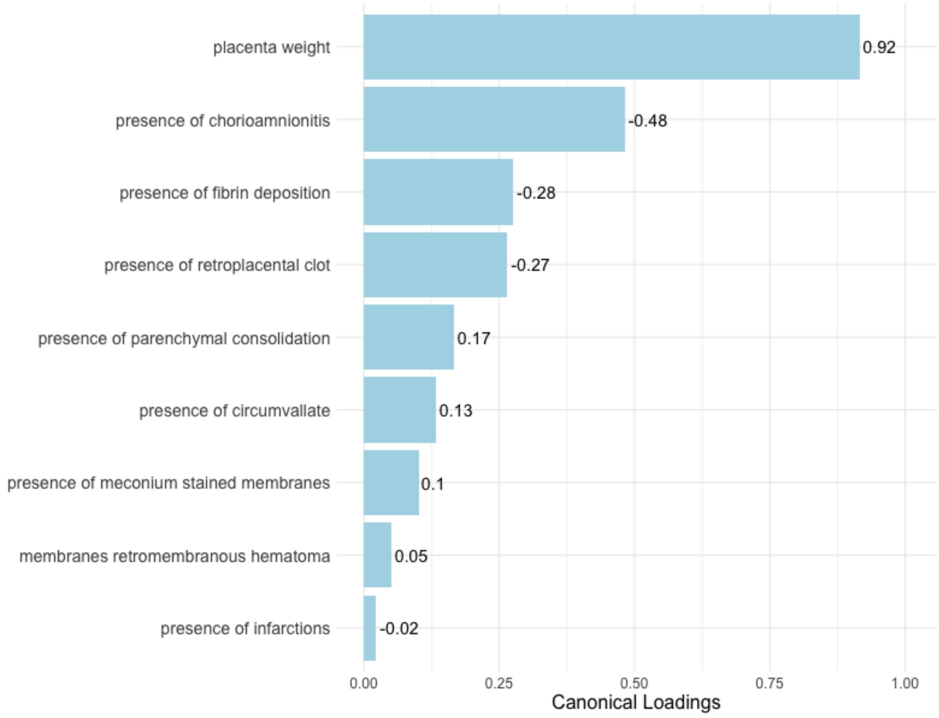

Figure 4.3: Canonical loadings (correlations between the original variables and the canonical variates) for histology variables

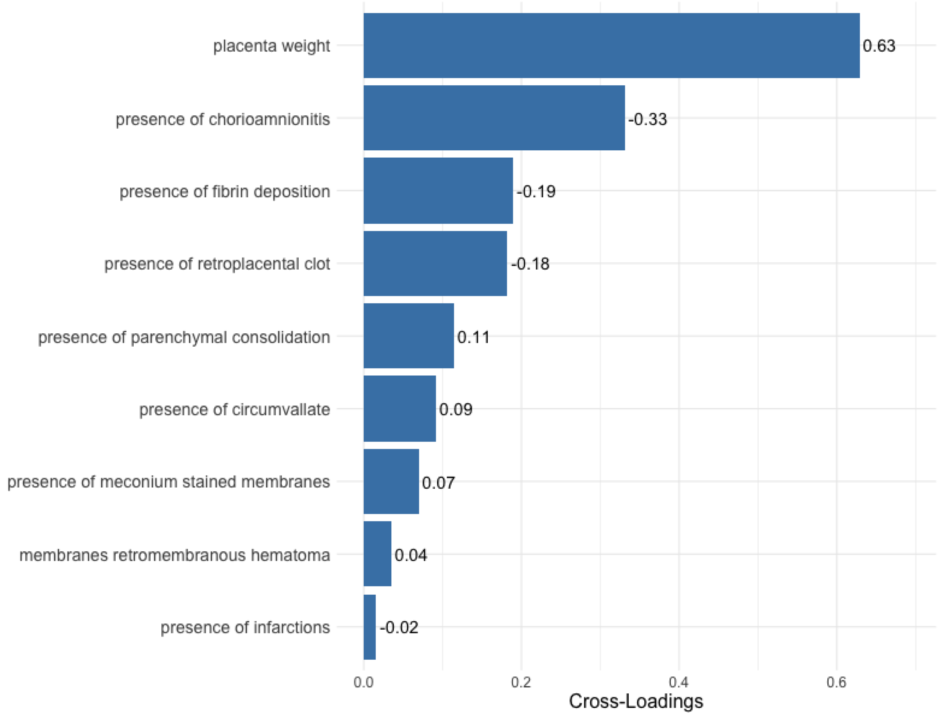

Figure 4.4: Canonical cross-loadings of histology markers corresponding to the first canonical variate obtained from CCA of histology markers and neonatal outcomes.

weight. Additionally, its canonical weight of 0.84 shows its role in the multivariate association, suggesting that well-developed placentas are closely tied to better neonatal

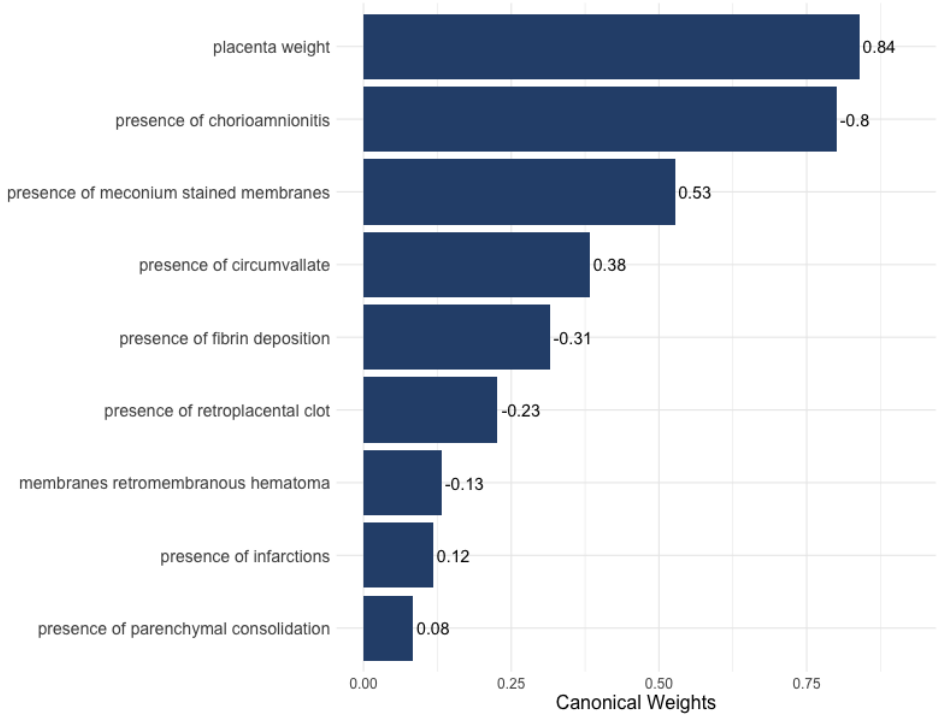

Figure 4.5: Canonical weights of histology variables corresponding to the first canonical variate obtained from CCA of histology markers and outcomes.

health outcomes, likely through their support of essential fetal growth processes. The canonical cross-loadings and canonical weights (coefficients) for the histology variables are provided in Figure 4.4 and Figure 4.5.

On the other hand, a negative canonical loading of 0.48 was observed for chorioamnionitis along with a pronounced canonical weight of 0.80, emphasizing its strong negative association with placental weight as well as neonatal outcomes. The cross-loading of 0.33 confirms its negative associations with the leading neonatal outcomes (birth weight, gestational age and apgar at 5 minutes) and reveals that approximately 10.9% of the variability in neonatal outcomes is explained by presence of chorioamnionitis. This highlights the clinical significance of intra-amniotic infections, which are also linked to placental abruption, in compromising neonatal health and reinforces the need for timely interventions to mitigate their effects.

Other histological variables contributing the most to the leading canonical variate include presence of fibrin deposition and presence of retroplacental clot, both indicated to be potential markers of placental abruption.

For neonatal outcome measures, birth weight stands out as a key variable, with a canonical loading of 0.94 (Figure 4.6), reflecting its dominant role in the first canonical variate

A cross-loading of 0.64 (Figure 4.7) also shows that about 41.2% of the variation in histological characteristics of the placenta is explained by birth weight, this particularly highlights the relationship between placental weight and birthweight since they are both the dominating variables in the respective canonical variates.

The canonical weight of 0.67 for birth weight further illustrates its critical contribution to the overall multivariate relationship (Figure 4.8).

Gestational age also demonstrates a notable association, with a canonical loading of

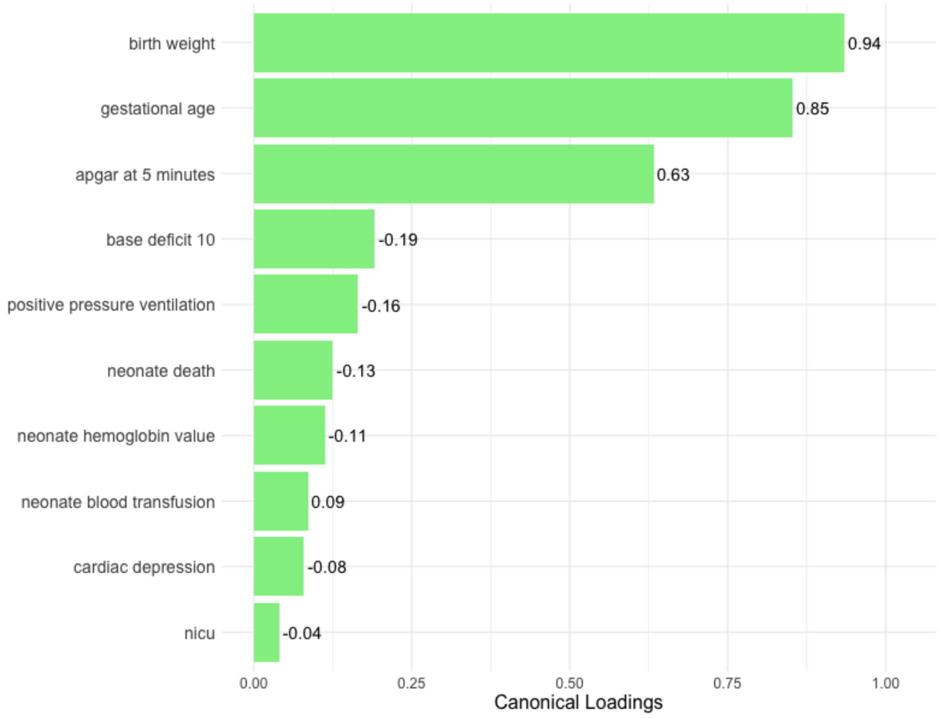

Figure 4.6: Canonical loadings for neonatal outcomes

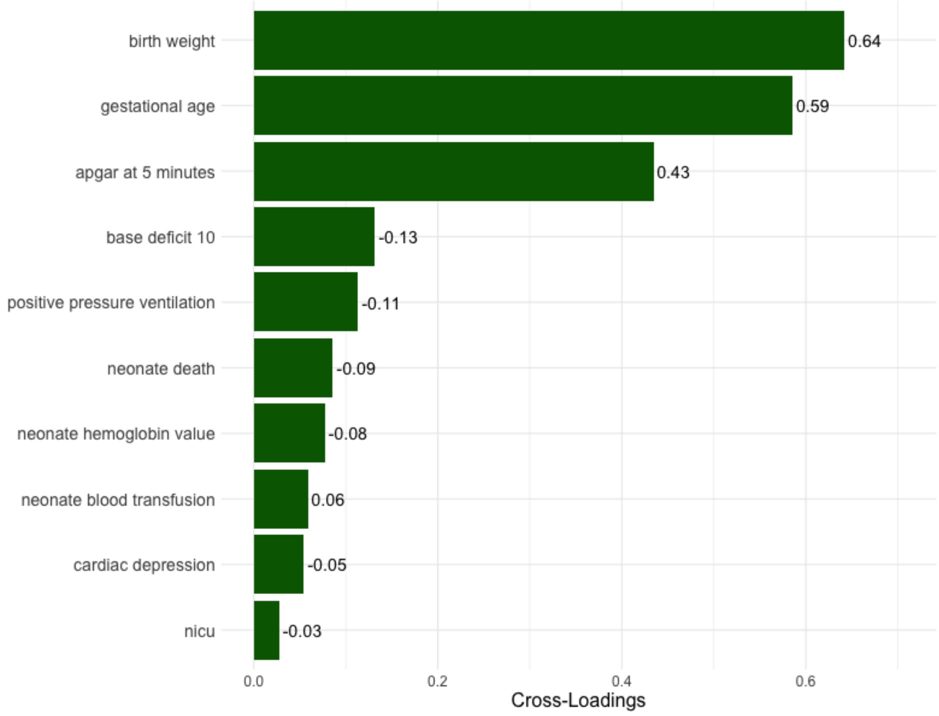

Figure 4.7: Canonical cross-loadings of neonatal outcomes corresponding to the first canonical variate obtained from CCA of neonatal outcomes and histology markers.

0.853 (Figure 4.6) and a cross-loading of 0.59, indicating that 34.3% of the variability in histological characteristics of the placenta is attributed to gestational age. These findings suggest that improved placental histological features are linked to extended gestation,

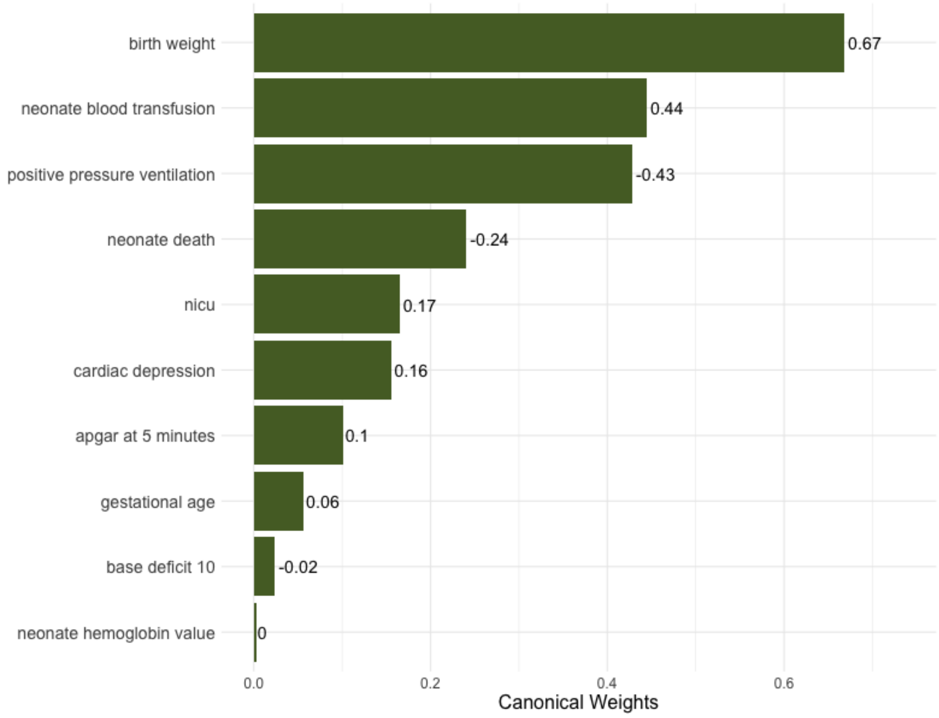

Figure 4.8: Canonical weights of neonatal outcomes corresponding to the first canonical variate obtained from CCA of neonatal outcomes and histology markers.

lowering the likelihood of complications from preterm birth. It is important to highlight that gestational age has a very low canonical weight (coefficient estimate = 0.056)(Figure 4.8), which may lead to the wrong conclusion in terms of its contributions in the overall strong association we found between histological markers and neonatal outcomes. This low coefficient in fact is because gestational age is strongly associated with other neonatal outcomes, a correlation of 0.77 with birth weight and correlation of 0.49 with apgar in 5 minutes. While we did screen variables to reduce multicollinearity, we retained gestational age in consultation with clinicians, who emphasized its critical importance in neonatal care.

The apgar score at 5 minutes, with a loading of 0.63 (Figure 4.6) and a cross-loading of 0.43, highlights the influence of placental health on the newborn's immediate vitality. This connection suggests that healthier placental conditions may support greater neonatal resilience at birth, potentially lowering the need for urgent medical interventions.

In contrast, positive pressure ventilation displays a negative canonical weight of 0.43 and a cross-loading of 0.11 (Figure 4.7 and Figure 4.8), linking the need for respiratory support in neonates to unfavorable placental histology, such as the presence of chorioamnionitis. This finding underscores a likely pathway through which placental infection or inflammation contributes to neonatal respiratory challenges, emphasizing the importance of addressing placental health to reduce such complications.

Integrating these measurements, our findings suggest that placental weight and the presence of chorioamnionitis may be associated with key neonatal outcomes, including birth weight and gestational age. The relatively strong positive weights and loadings of these variables highlight their potential relevance.

However, because this study is observational and lacks experimental controls, these

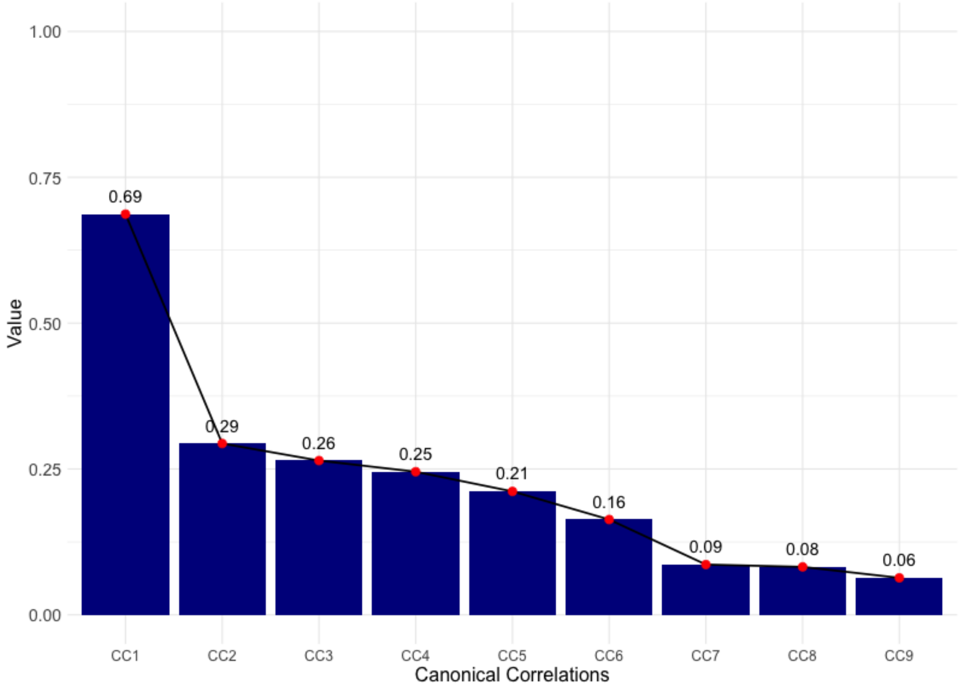

Figure 4.9: Scree plot showing decreasing canonical correlations between histological variables and outcome variables, with CC1 having the highest value (0.69)

relationships should be interpreted with caution. Further research, ideally in more controlled settings, is necessary to better understand the role of placental health in influencing neonatal outcomes.

4.3 Summary and Discussions

The strong correlation between the first canonical variates suggests an association between placental histological characteristics and neonatal health. In our observational data, placental abruption aligned with decreased placental weight, increased chorioamnionitis, fibrin deposition, and retroplacental clots. These findings indicate that such features may serve as potential indicators of placental health. However, given the observational nature of this study, further research is needed to determine whether these histological factors reliably predict adverse neonatal outcomes.

The placental weight's strong positive association with favorable neonatal outcomes again aligns with existing literature that correlates adequate placental growth with optimal fetal nutrition and oxygenation [75, 80]. Overall, small canonical coefficients, loadings and cross-loadings are observed for other biometric characteristics of the placenta (i.e. thickness, width and length). However, it is important to highlight that these measurements are highly correlated with placental weight, and hence their contribution might have been already accounted for by placental weight. We would also like to highlight that we only presented the results corresponding to the first canonical variates. Indeed, we observed moderate, but still substantial, correlations between subsequent canonical variates (Figure 4.9)

Further investigation of the second canonical variates reveals moderate but meaningful associations that provide complementary insights to the primary findings (Figure A.4 and A5, Appendix). Variables such as fibrin deposition and maternal hypertension appear as significant contributors, with strong loadings of 0.53 and -0.51, respectively. These findings suggest that fibrin deposition may act as a marker of placental abnormalities, while maternal hypertension reflects systemic maternal conditions influencing placental health

Chorioamnionitis, exhibiting a moderate negative association with neonatal outcomes, is a recognized risk factor for preterm birth and neonatal morbidity. This intrauterine infection leads to inflammation of the fetal membranes, which can initiate preterm labor and adversely affect fetal development [74]. The inflammatory processes associated with chorioamnionitis may result in fetal inflammatory response syndrome, contributing to complications such as sepsis and cerebral palsy in neonates [81]. The negative loading reflects the substantial impact that intrauterine infections can have on neonatal health, reinforcing the need for early detection and management. Although the precise etiology and risk factors for placental abruption remain incompletely understood, chorioamnionitis has been identified in the literature as a potential contributor to this condition. The inflammation and vascular compromise caused by intrauterine infection may predispose the placenta to premature separation, indirectly linking chorioamnionitis to poor neonatal outcomes [82]. This association suggests that the moderate-to-strong negative relationship between placental abruption and neonatal health outcomes observed in this study may, in part, be mediated through the presence of chorioamnionitis.

The presence of retroplacental clots and fibrin deposition, although contributing less to the variance, demonstrated noteworthy negative associations with neonatal outcomes. Retroplacental clots are both histological indicatives of placental abruption, which can result in fetal hypoxia and preterm delivery [83]. Fibrin deposition may reflect placental insufficiency. Other important histological variables reported in the literature to be associated with placental abruption, and which also appeared in our results as potentially linked to neonatal outcomes, include maternal vascular malperfusion lesions, excessive villous edema, increased syncytial knots, and chronic villitis (particularly when considered in the context of the second canonical variate) [36]. These findings further underscore the complexity of placental pathology and its multifaceted impact on neonatal health.

Regarding amniotic fluid, while it was not directly included as a primary variable our analyses, it is worth noting that amniotic fluid volume often correlates with placental weight and fetal well-being. Given that placental weight appeared as a strong contributor in our results, some of its observed associations with neonatal outcomes may indirectly reflect the role of amniotic fluid. Adequate amniotic fluid volume is crucial for fetal lung development, nutrient exchange, and overall fetal health [84], suggesting that variations in placental weight could partially encapsulate the influence of amniotic fluid on neonatal outcomes.

In terms of neonatal outcomes, the leading contributor to the first canonical variate with a strong positive association is birth weight, which is consistent with well-established scientific evidence showing that placental health in general, including adequate placental function, normal maternal spiral artery remodeling, and efficient maternal-fetal nutrient and oxygen exchange, are vital for fetal growth [85, 86]. The strong loading suggests that interventions aimed at improving placental health could have a direct positive effect on birth weight and, consequently, neonatal survival and well-being. A substantial body of scientific evidence indicates that premature separation of the placenta from the uterine wall markedly compromises placental integrity and functionality, with potential downstream effects on fetal well-being [1–3]. Consequently, identifying the underlying risk factors and pathophysiological mechanisms associated with placental abruption, as well as enhancing the accuracy and timeliness of its diagnosis, is critical for improving pregnancy outcomes.

Increased gestational age also showed a strong positive relationship with favorable placental histology. Extended gestation allows for continued fetal growth and organ maturation, reducing the risks associated with prematurity, such as respiratory distress syndrome and neurodevelopmental impairments [87].

The Apgar score at 5 minutes, reflecting the newborn's physiological status immediately after birth, was positively associated with favorable placental histology. This suggests that optimal placental function supports better neonatal adaptation to extrauterine life, possibly due to adequate fetal oxygenation and nutrient supply during labor and delivery. This also indirectly highlights the negative consequence of abruption on the birth process and the health of the newborn.

Chapter 5

Associations Between Histological Markers of Placental Abruption and Clinical Indicators

Research into the histopathology of the placenta emphasizes its potential as a diagnostic tool for pregnancy abnormalities, including placental abruption. Some studies have suggested that histopathological findings, such as vascular abnormalities or signs of inflammation, may serve as predictive markers for placental abruption, but discrepancies between histological and clinical diagnoses raise concerns about their standalone utility [14, 19, 68]. Although histology-based diagnosis enhances our understanding of placental abruption and its potential consequences, it does not permit timely intervention before pregnancy ends [22]. Moreover, there is minimal evidence establishing direct links between placental histological features and maternal health or pregnancy conditions associated with abruption [88].

To help address these gaps in the literature, we use canonical correlation analysis (CCA) to examine possible associations between histological markers of placental pathology and clinical indicators, including pregnancy-related complications, ultrasound findings, and other comorbidities (e.g., chronic and pregnancy-related hypertension). A full list of these variables is provided in Table A.1 in the Appendix. By employing this multivariate approach, our aim is to identify potential clinical indicators of placental abruption for future confirmatory analyses. While our results may provide insight into risk factors and the etiology of abruption, further research will be necessary before definitive preventative strategies can be established. Finally, we will interpret these findings in conjunction with those presented in Chapter 4, offering a broader perspective on how placental histology, clinical indicators of abruption, and neonatal outcomes interrelate.

5.1 Pairwise Relationships

We began by examining the pairwise relationships between histological markers and clinical variables. The histological dataset consisted of 9 variables, and the clinical dataset consisted of 25 variables, these are listed in Table A.1 , in the Appendix. Variables exhibiting strong within-group correlations were excluded to prevent singularity or near-singularity problems in the CCA. However, separate analysis was also performed since one of the objectives is identifying clinical indicators that are potentially associated with known histological markers of abruption. Consultations with a clinical expert ensured that important variables were retained, and that no clinically relevant factors were overlooked. Individuals and variables with substantial missing data ($> 50\%$) were removed from the analysis and remaining missing data were addressed through appropriate imputation techniques as outlined in Chapter 2.

The pairwise correlations are presented in a heatmap (Figure 5.1). The values of these correlations are also provided (Figure A.2 and Figure A.6, Appendix)

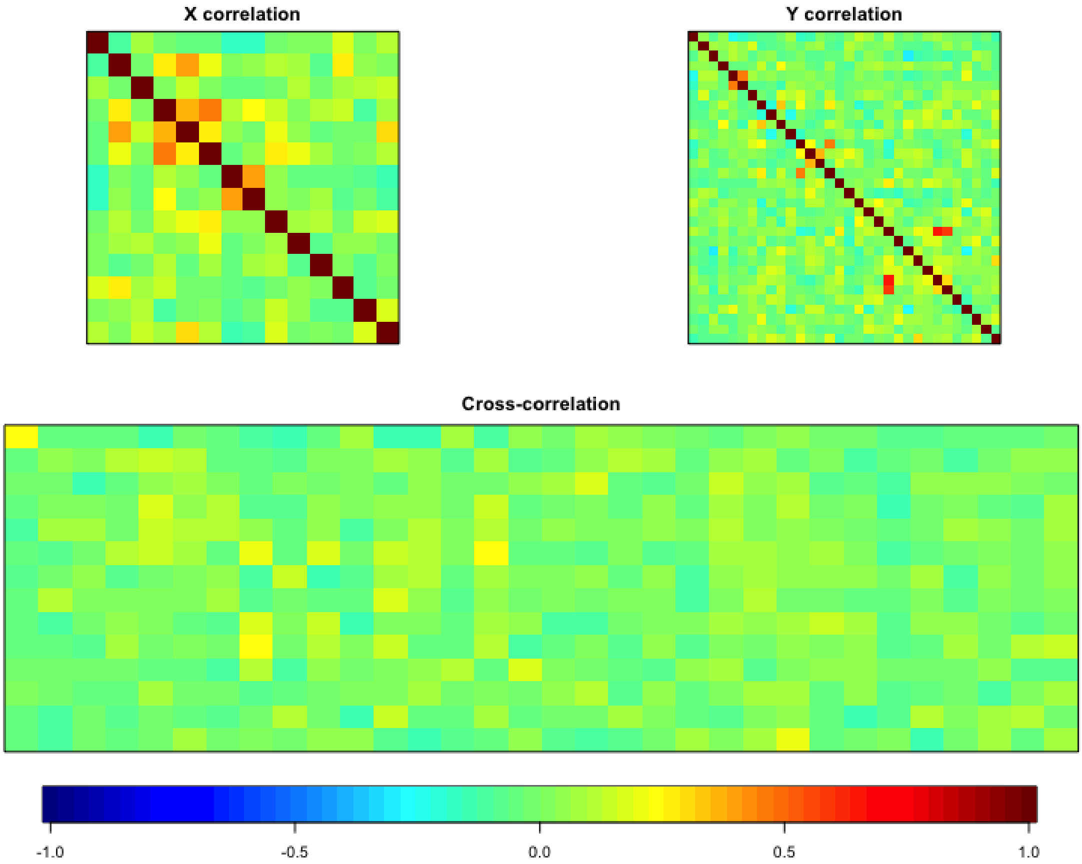

Figure 5.1: Within and cross-correlations between histological markers and clinical indicators, where x variables represent histological markers and y variables represent clinical indicators

Figure 5.1 shows that within the clinical indicators, correlations are generally low to moderate, ranging from -0.34 to 0.45, with the strongest association observed between smoking status and drug use. As indicated in Chapter 4, correlations within the histological data is also low to moderate, ranging from -0.21 to 0.34.

This low degree of inter-correlation confirms the data's suitability for CCA by minimizing concerns of singularity or near-sigularity. When examining cross-correlations (Figure A.7, Appendix), the association between maternal hypertension and villous maldevelopment (r=0.24) stands out, indicating a potential link between maternal vascular health and specific placental structural anomalies. Nonetheless, these pairwise correlations remain weak, underscoring the need for a more integrative approach such as CCA to uncover subtle, yet potentially important, patterns of association.

5.2 Canonical Correlation Analysis (CCA)

The Canonical Correlation Analysis (CCA) revealed a moderate yet significant multivariate association between placental histological features and maternal clinical indicators, reflected in the correlation between the leading canonical variates (r=0.49) (Figure 5.2). This relationship highlights how specific clinical conditions co-occur with distinct histological patterns, offering a comprehensive perspective that surpasses the insights provided by pairwise correlations.

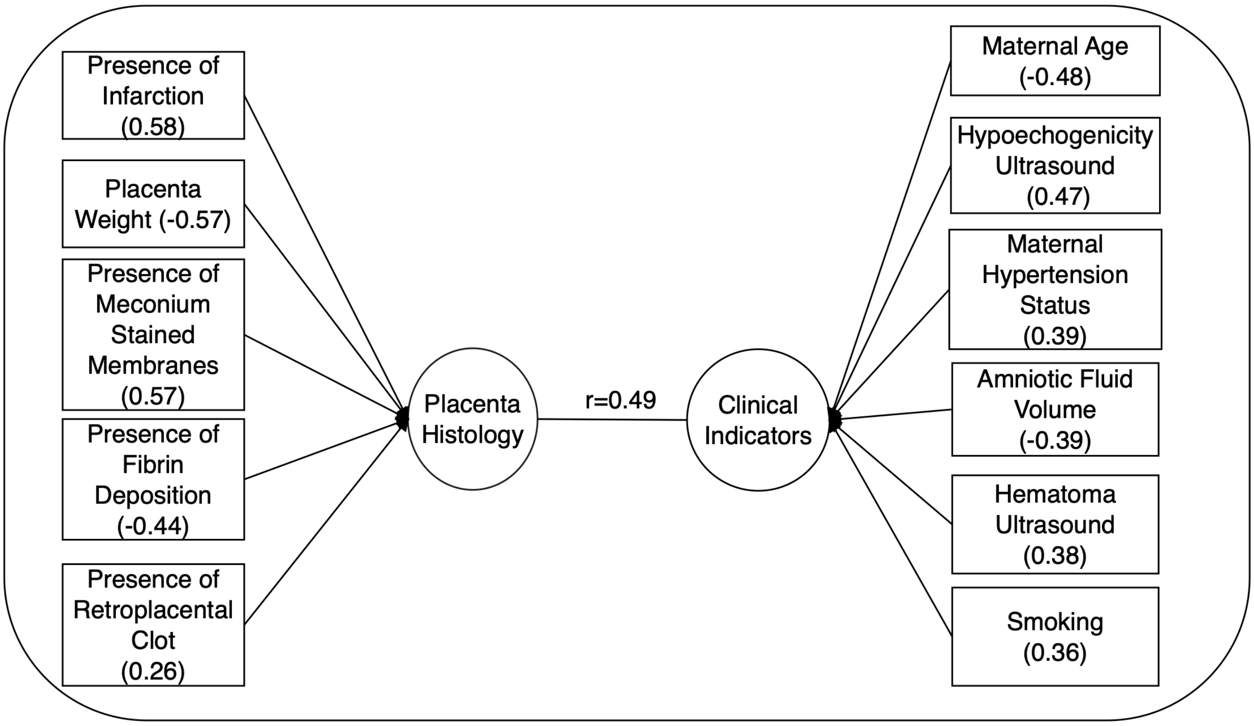

Figure 5.2: Finger plot representing the canonical correlation between the first canonical variates obtained from placental histology and maternal clinical indicators. The variables contributing the highest (with respect to the canonical loadings) are also presented

Among the histology variables, presence of infarctions (canonical loading: 0.58) emerges as a key histological marker, indicating a strong positive relationship with the leading canonical variate (Figure 5.2). This positive loading suggests that maternal conditions associated with compromised utero-placental perfusion may drive infarction formation in the placenta. The cross-loading of infarctions (0.29) (Figure 5.4) confirms that nearly 8.2% of the variation contained in the clinical variables can be attributed to the presence of infarctions.

In terms of canonical weights (Figure 5.5), infarctions have a weight of 1.15, highlighting their substantial contribution to the multivariate relationship and confirming that these lesions are strongly linked to unfavorable pregnancy environments.

Placental weight, with a negative loading of –0.57 (Figure 5.3), stands out as another critical variable. This negative loading suggests that reduced placental weight aligns with maternal conditions that may impede normal placental growth. Its cross-loading (–0.28) indicates that about 7.8% of the variability in clinical variables is explained by placental weight. Although placental weight's absolute cross-loading is comparable to that of infarctions (Figure 5.4), its negative sign differentiates its directional influence. The corresponding canonical weight (–0.56)(Figure 5.5) suggests that while placental weight is influential, its effect runs counter to variables indicating more unfavorable maternal conditions.

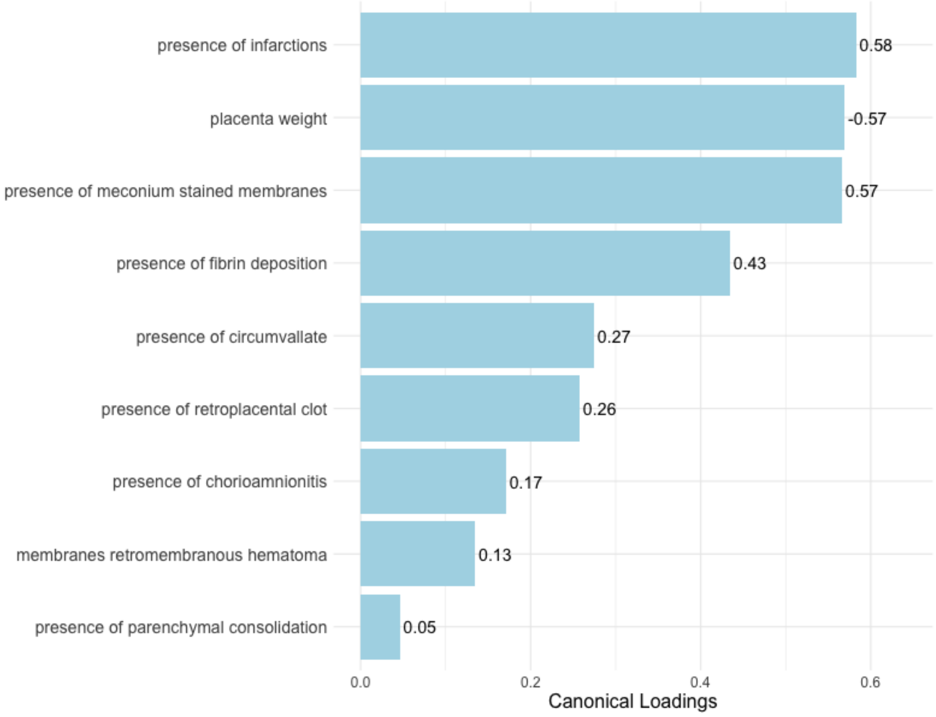

Figure 5.3: Canonical loadings for the first canonical variate corresponding to the histological markers.

Presence of meconium-stained membranes, with a loading of 0.57 (Figure 5.3), is also significantly associated with the leading canonical variate. This positive association suggests that maternal factors fostering fetal stress or hypoxia (e.g., reduced oxygenation or poor nutrient transfer) are reflected in the presence of meconium staining. The cross-loading of meconium-stained membranes (0.28) (Figure 5.4) shows that approximately 7.8% of the variation in clinical variables is attributed to this feature, while its high canonical weight of 1.9 (Figure 5.5) also suggests that meconium-stained membranes have a particularly strong influence in defining the histology-clinical relationship. Retroplacental clot has a weight of –0.09, which is relatively small, yet its recognized association with placental abruption justifies its clinical relevance despite not surpassing the 0.3 loading threshold.

Presence of chorioamnionitis (loading=0.17), presence of membranes with retro membranous hematoma (loading=0.14), and presence of parenchymal consolidation (loading=0.05) show modest positive associations with the leading canonical variates (Figure 5.3). Although their influence is less striking, their presence in the canonical variate suggests that even subtle histological alterations can be part of a larger pattern connecting the placenta's microscopic state with the maternal clinical environment.

Turning to the clinical side, maternal age (loading=–0.48) stands out, indicating that older maternal age profiles may correlate with histological patterns of compromised placental function (Figure 5.6). Its cross-loading (–0.24)(Figure 5.7)

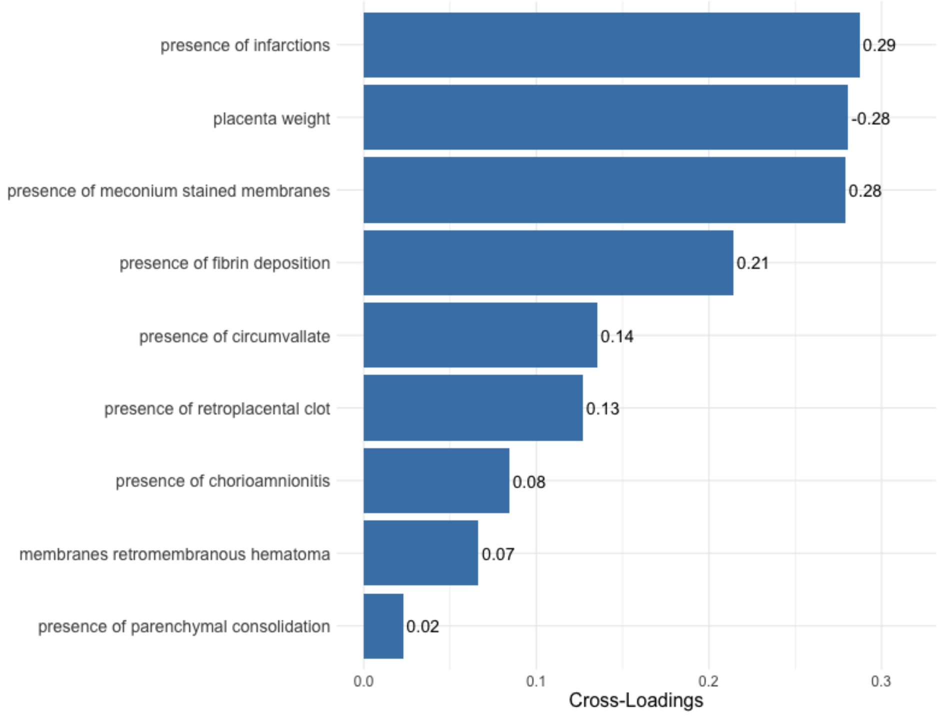

Figure 5.4: Canonical cross-loadings for histology markers representing the cross-correlation between histology markers and the first canonical variates corresponding to clinical indicators

shows about 5.7% of the variation in the histological data is explained by maternal age, while its weight of –0.28 reflects its moderate but directional influence on the first canonical variate. Placenta hypoechogenicity as seen on ultrasound (loading=0.47, cross-loading=0.23) emerges as a strong non-invasive clinical indicator of placental features, explaining approximately 5.4% of the variation in the histological data and sporting a weight of 0.85, underscoring its value as a potential marker for facilitating early diagnosis of placental abruption.

Our finding for maternal hypertension (loading=0.39) aligns with its known pathophysiological pathways, as hypertension can compromise blood flow and lead to infarctions and reduced placental mass. Its cross-loading (0.19) accounts for about 3.8% of the variation in the histological data, and its substantial canonical weight (0.84) (Figure 5.8)

indicates that controlling blood pressure (both chronic and pregnancy related hypertension) could be pivotal in preventing histopathological changes that are indicative of placental abruption. Amniotic fluid volume (loading = –0.39, cross-loading = –0.19, weight = –0.55) presents a slightly more nuanced scenario. The consistently negative loadings and weight suggest that lower fluid volumes may co-occur with adverse placental changes. However, this relationship must be interpreted with caution, as underlying intercorrelations among variables can complicate the interpretation of

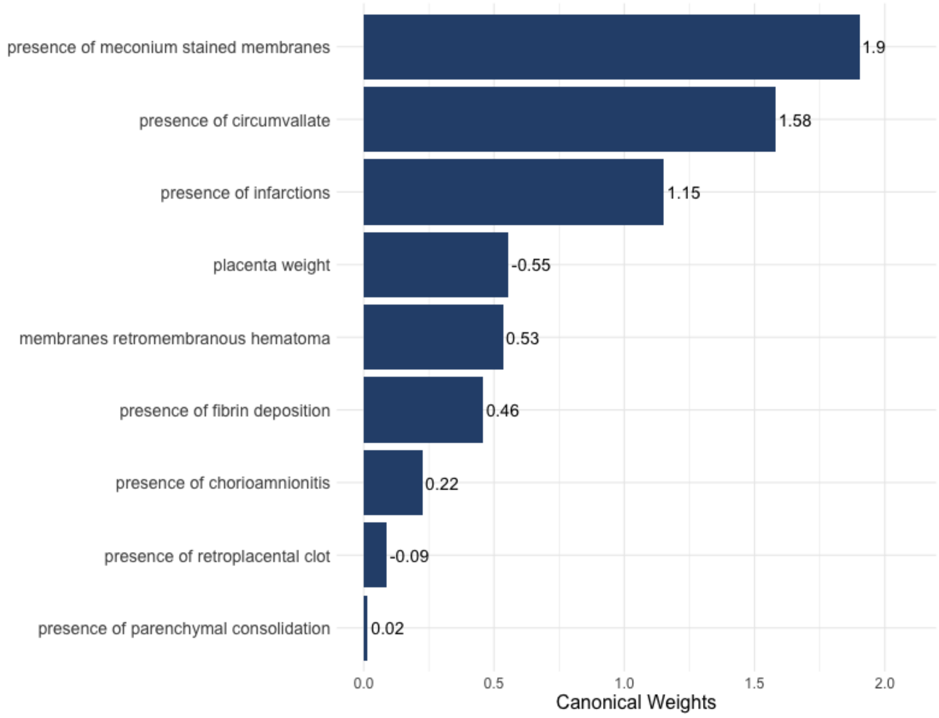

Figure 5.5: Canonical weights for histological markers for the first canonical variate in the analysis of histological markers and clinical indicators.

canonical weights and loadings when considered together.

Placenta hematoma detected by ultrasound (loading=0.36, cross-loading= 0.19, weight=1.04) also holds diagnostic significance. Its high weight signals that imaging findings of hematoma strongly shape the association between histology and clinical indicators, highlighting its potential use for early warning signs for placental abruption. Smoking (loading= 0.24, cross-loading=0.18, weight=0.99), a known modifiable risk factor associated with pregnancy complications, also emerges as a critical clinical variable potentially associated with placental abruption. Although its loading is lower than those of maternal age and other ultrasound findings, the relatively high weight and cross-loading indicate that smoking substantially influences placental morphology, likely through vascular and hypoxic mechanisms.

As seen in Figure 5.6, other clinical indicators, though less dominant, also contribute to the broader picture. For instance, fetal movement (loading=0.20), fetal baseline BPM (loading=0.20), and vaginal bleeding (loading=–0.21) also contribute notably, each variable possibly representing different facets of maternal and fetal conditions that translate into placental changes.

We would like to emphasize that our presentation focuses exclusively on the results of the first canonical variates. Notably, moderate yet significant correlations were also observed for subsequent canonical variates (Figure 5.9).

A deeper exploration of the second canonical variates reveals that variables like fibrin deposition and retromembranous hematoma, which had lower loadings in the first canonical variate, exhibit higher loadings, highlighting their significance (Figure A.8, Appendix). Maternal hypertension status also reappears with even higher loadings, further emphasizing its clinical relevance in this canonical dimension (Figure A.9, Appendix).

Figure 5.6: Canonical loadings for clinical indicators in the first canonical correlation.

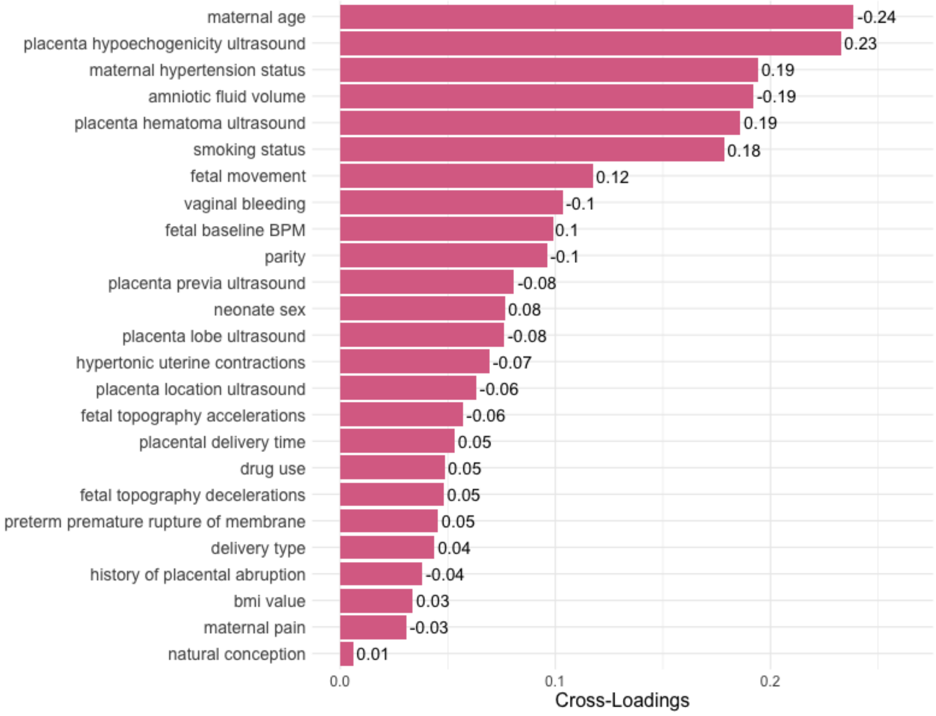

Figure 5.7: Canonical cross-loadings of clinical indicators corresponding to the first canonical variates obtained from CCA of clinical indicators and histology markers.

In summary, the canonical loadings, cross-loadings, and weights collectively underscore a multifaceted interplay between maternal clinical conditions and placental

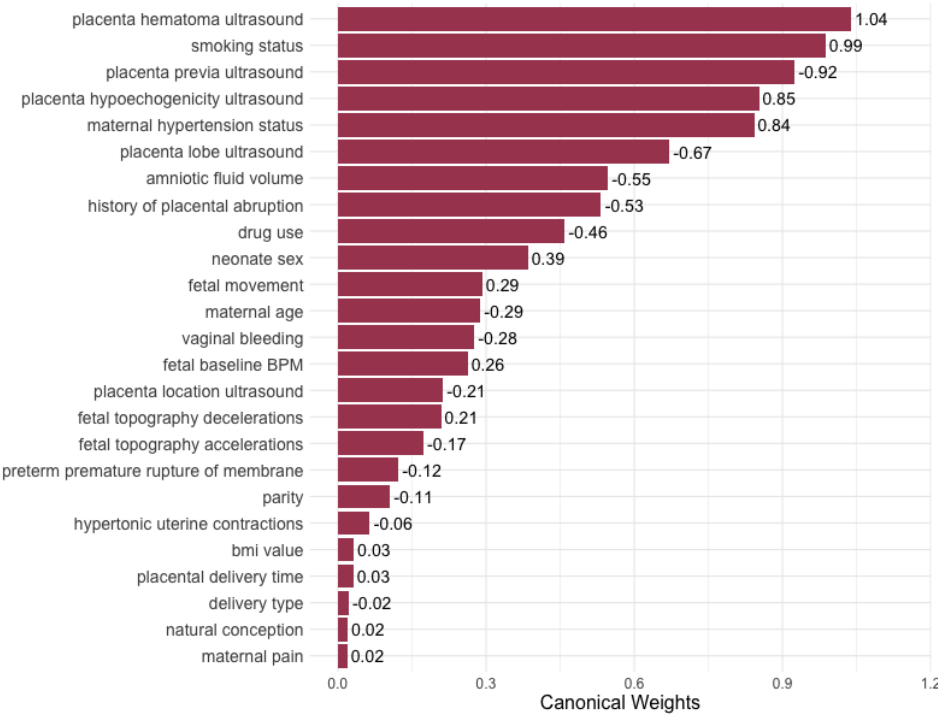

Figure 5.8: Canonical weights of clinical indicators corresponding to the first canonical variate obtained from CCA of clinical indicators and histology markers.

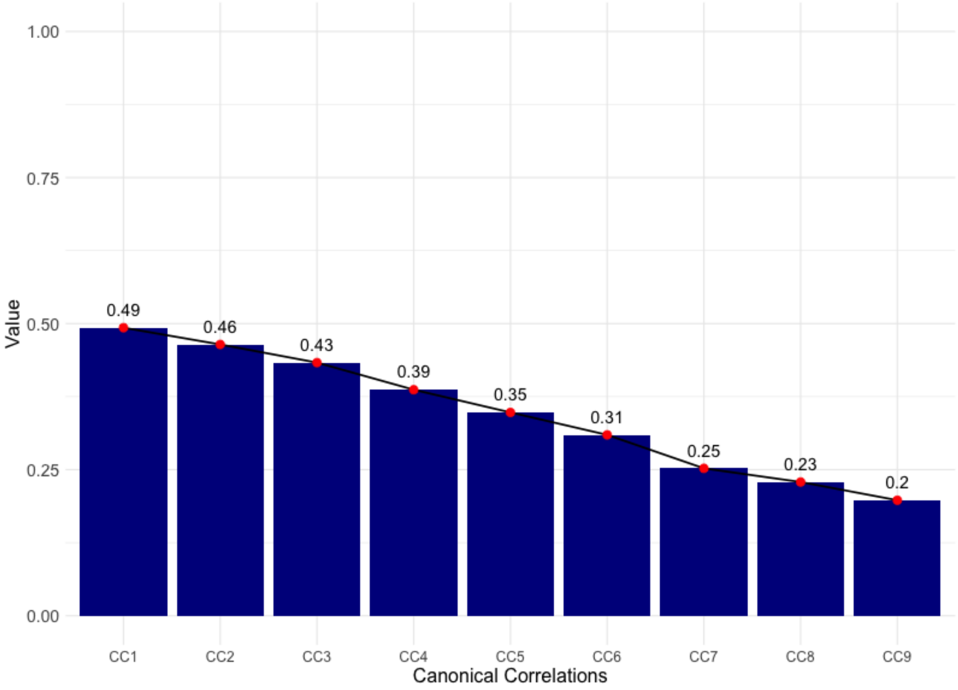

Figure 5.9: Scree plot showing decreasing canonical correlations between histological variables and clinical indicators, with CC1 having the highest canonical correlation value of 0.49

histology. Variables like infarctions, meconium-stained membranes, and placental weight are strongly aligned with particular maternal profiles. On the other hand ultrasound findings, such as placenta hypoechogenicity and hematoma, maternal age and hypertension as well as lifestyle factors like smoking offer accessible markers that may guide early diagnosis, timely intervention and preventive strategies.

5.3 Summary and Discussions

The moderate correlation between the first canonical variates suggests a meaningful relationship between specific histological characteristics of the placenta and maternal health indicators, ultrasound findings and other pregnancy complications. This finding highlights the placenta's vital role in reflecting maternal health conditions, as it both responds to and influences the intrauterine environment. Key histological features, such as the presence of infarctions and meconium-stained membranes, as well as variations in placental weight, reinforce the concept that maternal vascular health, metabolic balance, and lifestyle behaviors exert significant influence on placental structure and function. The literature supports these observations; for example, compromised maternal vascular remodeling is known to contribute to inadequate uteroplacental perfusion, ultimately manifesting in placental lesions such as infarctions [89,90]. Similarly, meconium staining, which may result from fetal distress, can be indirectly shaped by maternal factors that impact the placental environment [91]

Placental weight is hinted as a robust proxy for overall placental function, with lower placental weight commonly associated with deficient fetal nutrient and oxygen supply, often reflecting underlying maternal conditions such as hypertension or smoking. Although other placental biometric characteristics (e.g., thickness, width, and length) did not show up as primary contributors in our canonical variates, their effects may be inlcluded under placental weight. Certain histological markers, including fibrin deposition and retroplacental clots remain clinically relevant. Fibrin deposition can indicate endothelial damage and microthrombi formation, processes frequently associated with maternal hypertension or inflammation [65,92]. Retroplacental clots are a hallmark of placental abruption. Their presence signifies a pivotal event in placental pathology, reflecting the point at which cumulative maternal factors compromise placental integrity and function [2].

On the clinical side, indicators of maternal vascular dysfunction (e.g., hypertension), behavioral factors (such as smoking and drug use), and ultrasound-detected anomalies (eg. hypoechogenicity and hematoma) converge with distinct histopathological signatures. This convergence aligns with a growing body of evidence that maternal conditions shape and are reflected by placental morphology [93,94]. Detecting placental issues early through imaging, combined with close monitoring of maternal risk factors, can help reduce the risk of complications. Our results suggest that this may also the case for placental abruption, hence the variables the CCA revealed should be subjected to further confirmatory analysis to validate the findings. The results of such confirmatory analysis will help quantify the diagnostic power of such clinical and imaging variables and hence provide a means for timely intervention. Early risk management strategies, such as better blood pressure management and smoking and drug cessation programs, may also improve placental health and pregnancy outcomes, and may prevent placental abruption.

Chapter 6

Association between Clinical Indicators and Outcomes

Building on the results presented in Chapters 4 and 5, this chapter uses an exploratory multivariate approach to examine how clinical indicators (including pregnancy complications and ultrasound findings) in mothers who experienced placental abruption relate to neonatal outcomes. In Chapter 4, we observed that specific placental histological markers—reduced placental weight, chorioamnionitis, fibrin deposition, retroplacental clot, and infarction—were associated with birth weight, gestational age, and Apgar scores. These markers frequently appear in placentas from mothers with abruption, suggesting a possible link between abruption and compromised neonatal health. We also found that lower placental weight was associated with these key markers of abruption, indicating diminished placental development in affected pregnancies.

In Chapter 5, we examined maternal factors such as hypertension, smoking, and drug use, demonstrating that these clinical profiles coincide with distinct placental features. This finding implies that the maternal environment, reflected in part by her clinical characteristics, may influence placental development and, indirectly, neonatal outcomes. Additionally, Chapter 5 showed that certain placental anomalies are related to ultrasound findings, suggesting overlap between histological and imaging-based indicators of placental health.

Taken together, results from Chapters 4 and 5 suggest that maternal conditions affect placental development, as reflected in both histology and ultrasound assessments, and that these changes are in turn associated with neonatal outcomes. The present chapter extends this work by investigating direct relationships between maternal clinical indicators, ultrasound findings, and neonatal health measures. The clinical variables include those routinely monitored or easily measured during pregnancy (see Table A.1, Appendix). By evaluating whether these maternal indicators align with previously identified placental markers and neonatal outcomes, we aim to determine if they could function as early predictors or proxies for abruption risk. If maternal factors related to abruption-specific histological markers also show direct correlations with birth outcomes, then widely available clinical assessments may help identify pregnancies at increased risk.

Guided by these findings, our hypothesis is that maternal clinical indicators, considered individually and collectively, will exhibit notable associations with key neonatal measures. Specifically, we anticipate that maternal clinical profiles marked by vascular challenges or adverse lifestyle factors will be linked with lower birth weight, shorter gestational age, and lower Apgar scores, aligning with the placental changes and fetal vulnerabilities described in previous chapters.

6.1 Pairwise Association

The first stage of analysis involved pairwise correlation assessments to establish baseline understanding relationships within and between the two sets of variables (clinical indicators and neonatal outcomes). As in previous chapters, this initial exploration revealed that while certain clinical indicators displayed modest correlations with neonatal outcomes, no single variable emerged as a dominant predictor of good or bad neonatal outcome (Figure A.21, Appendix). As indicated in Chapter 5, the within correlation for neonatal outcomes show that there are some strong correlations between some of the variables (birth weight and gestational age). On the other hand, weak to moderate correlations (ranging from -0.30 to 0.45) between the clinical variables were observed.

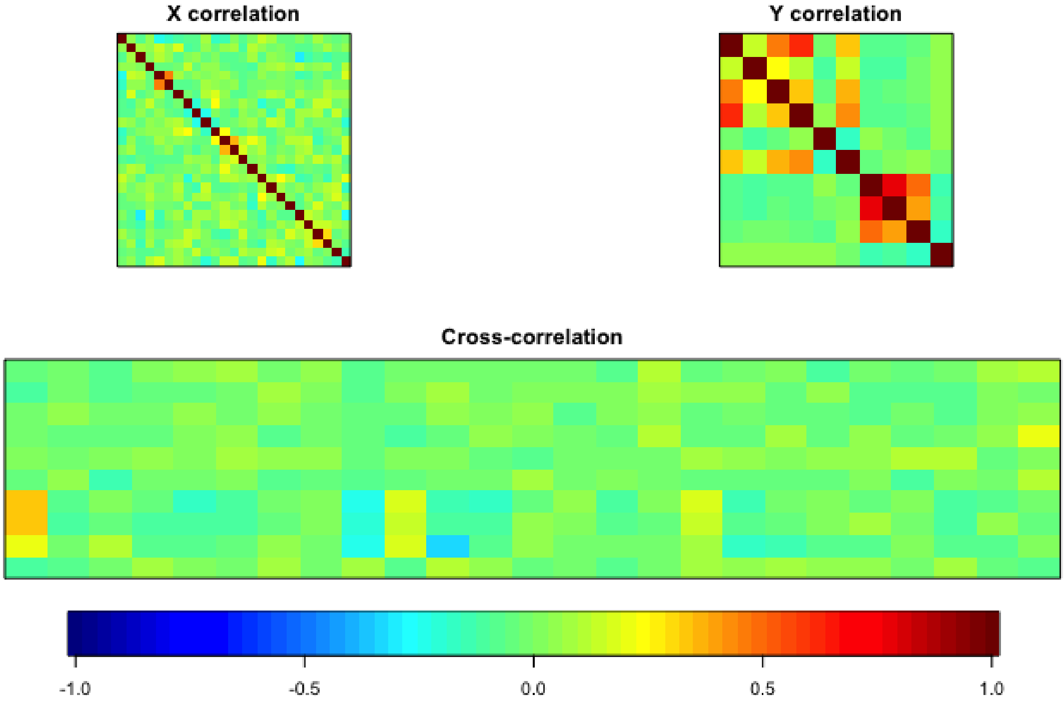

Figure 6.1: Within and cross-correlations between clinical factors and neonatal outcomes.

CCA was then employed to capture the covariance structures between multiple clinical indicators and outcome variables simultaneously. This approach aligns with the methodological rationale in Chapters 4 and 5, where CCA allowed for uncovering nuanced relationships that pairwise analyses alone could not fully characterize

6.2 Canonical Correlation Analysis (CCA)

The CCA results indicate a notable multivariate relationship between the set of clinical indicators and neonatal outcomes (Figure 6.2), as evidenced by a moderate canonical correlation between the leading canonical variates (= 0.59).

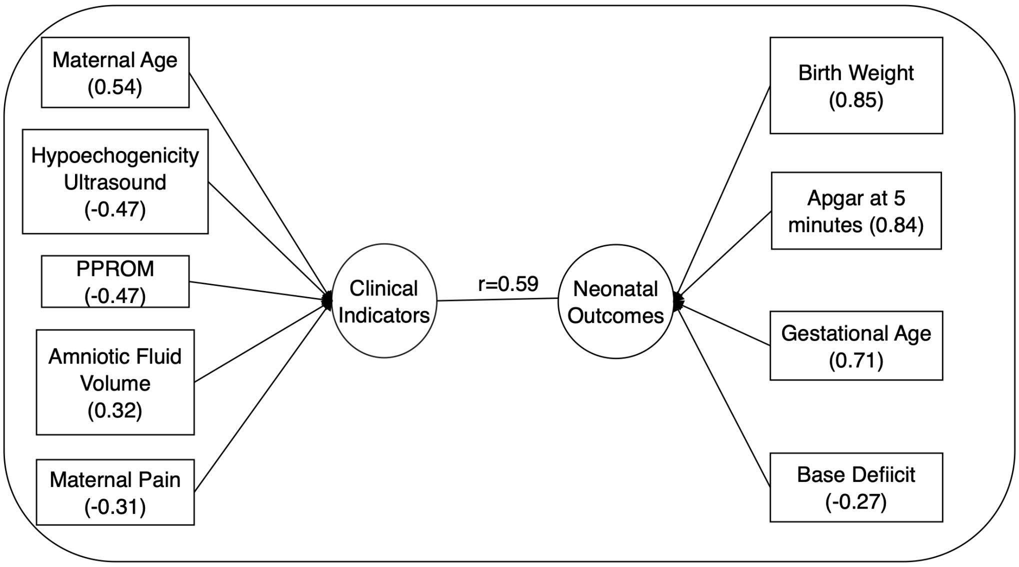

Figure 6.2: Finger plot representing the canonical correlation between the first canonical variates obtained from maternal clinical indicators and neonatal outcomes. The variables contributing the highest (with respect to the canonical loadings) are also presented.

Among the clinical variables, maternal age shows a positive canonical loading of 0.55. Its cross-loading of 0.32 (Figure 6.4) indicates that approximately 10.2% of the variance in neonatal outcomes is associated with maternal age. A positive canonical weight of 0.41 (Figure 6.5) further suggests that older maternal age in our sample may be linked to more favorable neonatal outcomes. This observation differs from studies in general obstetric populations [2, 6], where advanced maternal age is often correlated with increased risks for adverse neonatal outcomes.

A possible explanation is that older mothers in this abruption-specific cohort might have mitigating factors—such as higher parity, more attentive prenatal care, or fewer high-risk behaviors—that offset age-related risks. Additionally, our sample does not fully represent extreme age groups, which may diminish the negative effects reported elsewhere.

Nevertheless, the positive association observed here warrants further investigation, for instance by categorizing maternal age or examining interactions with parity and lifestyle factors, to better clarify the underlying mechanisms that may be driving this result.

In contrast, two clinical factors display negative relationships with the neonatal outcome variate: placenta hypoechogenicity (canonical loading = 0.47, cross-loading = 0.28) and preterm premature rupture of membranes (PPROM) (canonical loading = 0.47, cross-loading = 0.28). Each explains roughly 7–8% of the variability in neonatal outcomes. These findings are consistent with the notion that abnormal placental imaging and early membrane rupture may be associated with less favorable neonatal measures. As discussed in Chapter 4, both variables are also linked to histological indicators of placental

Figure 6.3: Canonical loadings for maternal clinical indicators in the first canonical correlation.

abruption, suggesting that they may be relevant in evaluating the risk of abruption.

Other clinical indicators, such as amniotic fluid volume (loading = 0.32, cross-loading = 0.19) and maternal pain (loading = 0.31, cross-loading = 0.18), each account for about 3–4% of the variability in neonatal outcomes (Figure 6.3 and Figure 6.4). Although their individual contributions are modest, these results suggest that maintaining an adequate amniotic fluid level could be beneficial, while reported maternal pain may signal underlying complications. Placenta hematoma seen on ultrasound and smoking also show negative loadings, indicating that placental abnormalities and lifestyle factors may have an incremental role in neonatal health. Since these two variables are notably associated with histological markers of abruption, further study could clarify their potential as predictors of abruption.

On the neonatal side (Figure 6.6), birth weight and Apgar score at 5 minutes have canonical loadings and weights of 0.85 and 0.84, respectively, making them the dominant variables in the neonatal outcome set. Birth weight's cross-loading of 0.50 indicates that it explains about 25% of the variance in the clinical variable set, while Apgar score's cross-loading of 0.49 accounts for roughly 24%. Together, these measures capture almost half of the variance in the leading canonical variate for the clinical variables. This finding is consistent with the results presented in Chapter 5. Gestational age also contributes substantially (loading = 0.71, cross-loading = 0.41), explaining about 17% of the variance in the clinical indicators.

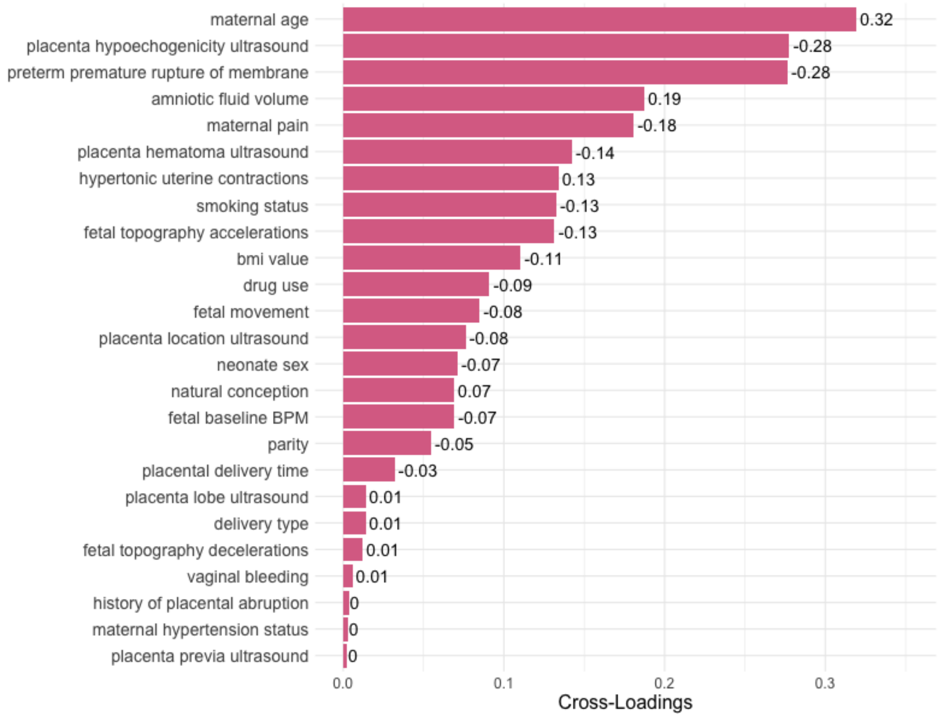

Figure 6.4: Canonical cross-loadings of clinical indicators corresponding to the first canonical variate obtained from CCA of clinical indicators and neonatal outcomes

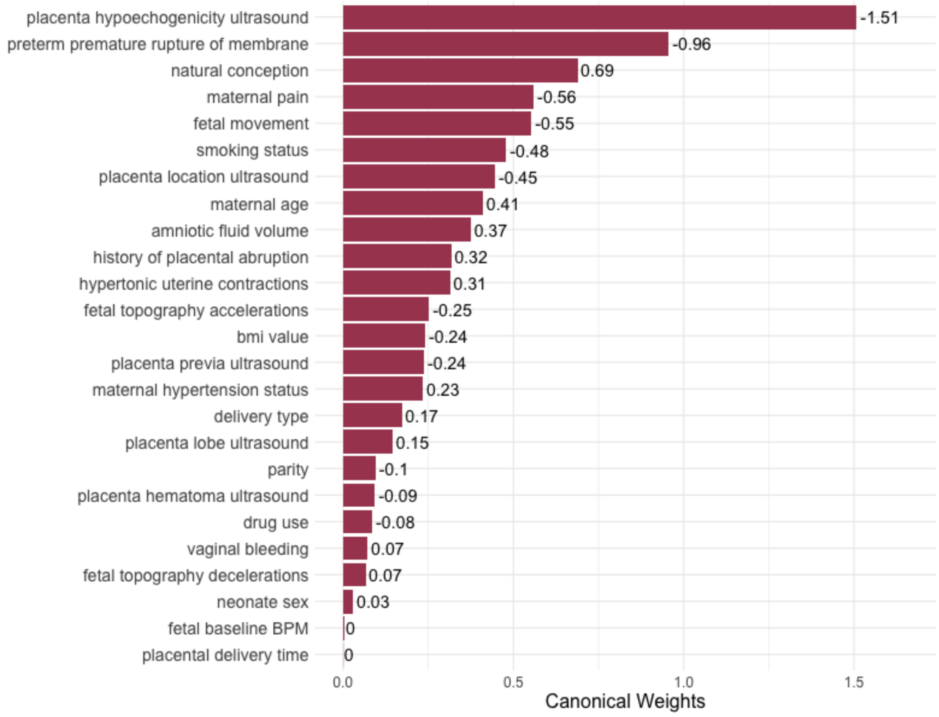

Figure 6.5: Canonical weights of clinical indicators corresponding to the first canonical variate obtained from CCA of clinical indicators and neonatal outcomes.

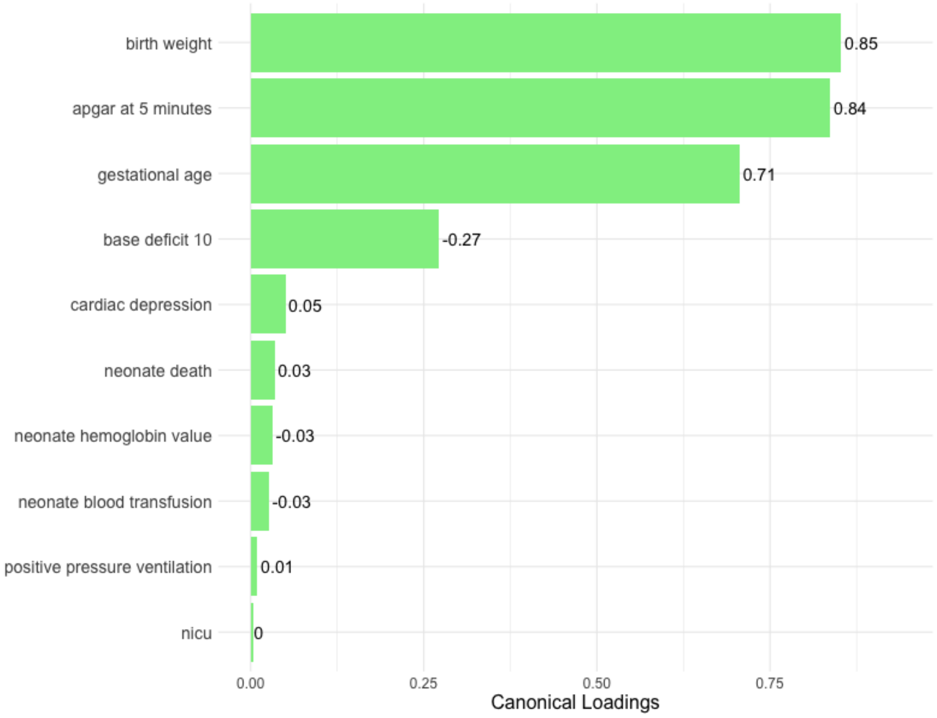

Figure 6.6: Canonical loadings for neonatal outcome variables in the first canonical correlation.

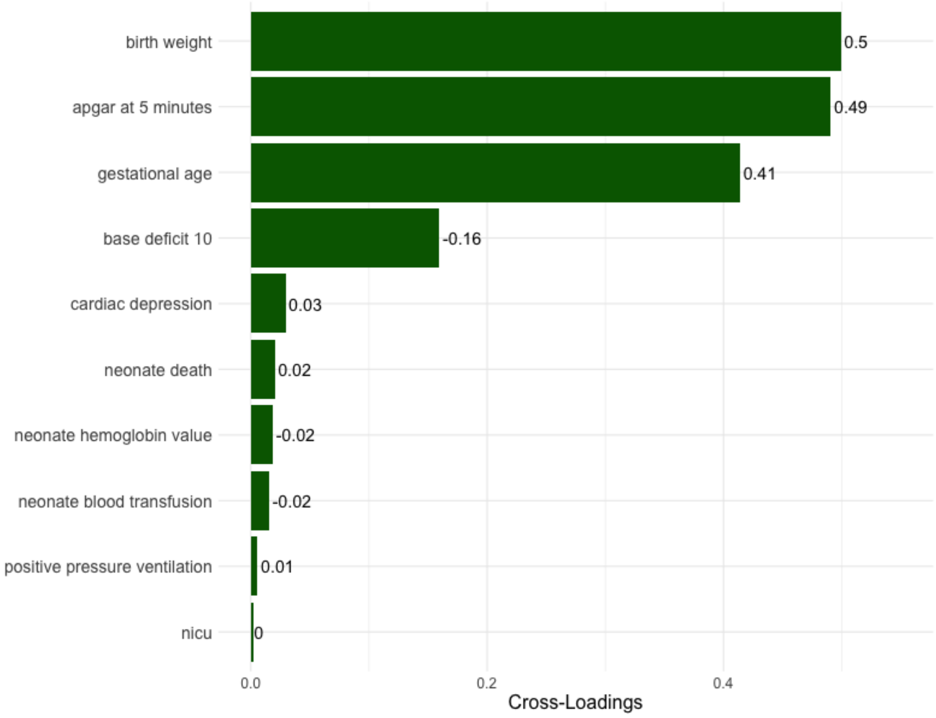

Figure 6.7: Canonical cross-loadings of neonatal outcomes corresponding to the first canonical variate obtained from CCA of neonatal outcomes and clinical indicators.

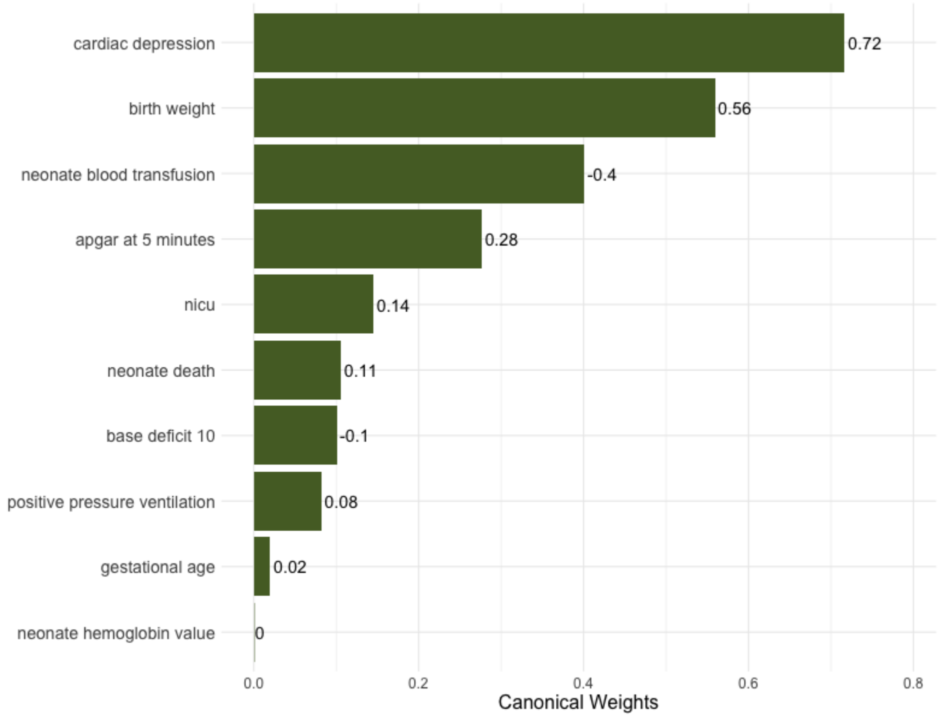

Figure 6.8: Canonical weights of neonatal outcomes corresponding to the first canonical variate obtained from CCA of neonatal outcomes and clinical indicators.

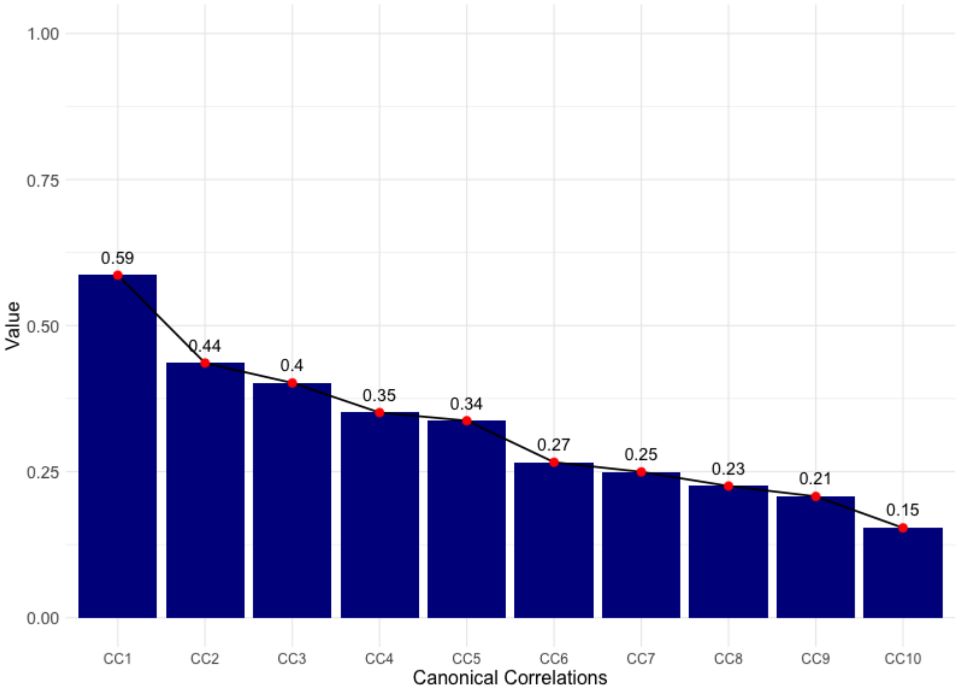

Figure 6.9: Scree plot showing decreasing canonical correlations between clinical indicators and outcome variables, with CC1 having the highest canonical correlation value of 0.59.

These patterns suggest that factors influencing a longer gestation may align with higher birth weight and Apgar scores in this cohort. Some outcome variables with relatively lower loadings (eg. as base deficit 10, NICU admission, or neonate hemoglobin value) show minimal cross-loadings and canonical weights (Figure 6.7 to 6.8), suggesting they play a more peripheral role in the relationship between the leading canonical variates. Even though these factors may be clinically relevant in specific contexts, they are not the main drivers of the association captured by this first canonical function. Although the second canonical variate was examined (Figure A11 to A12, Appendix), these variables did not emerge among the principal contributors in the subsequent dimension, suggesting that some potentially important factors in both data sets may not be fully captured by focusing on the leading canonical function.

6.3 Summary and Discussions

The analysis in this chapter indicates a moderate but consistent multivariate association between maternal clinical indicators and neonatal outcomes, aligning with the observations presented in Chapters 4 and 5. In Chapter 4, placental weight and certain histological markers of vascular or inflammatory disruption were associated with poorer neonatal metrics, suggesting that placental compromise may contribute to lower fetal growth and greater neonatal vulnerability. Many of these histological markers are also linked to abruption but are only identifiable post-delivery, limiting their utility for early diagnosis and highlighting the importance of clinical and imaging variables.

In Chapter 5, maternal clinical factors—including vascular conditions, lifestyle behaviors, and ultrasound findings—were shown to correlate with the same histological markers, suggesting that particular maternal profiles may predispose the placenta to structural and functional abnormalities. The results of this chapter connect those clinical factors to neonatal outcomes associated with placental integrity in Chapter 4. For example, while Chapter 4 noted a link between placental weight and birth weight, and Chapter 5 showed that maternal smoking and abnormal ultrasound findings relate to reduced placental mass or lesions, the current chapter reveals that these maternal indicators also coincide with variation in neonatal outcomes. This consistency raises the possibility that maternal clinical profiles might help identify pregnancies at elevated risk of abruption, although larger studies with comparison groups are needed to assess predictive value and diagnostic accuracy.

Maternal behaviors such as smoking and drug use, as well as conditions like hypertension, remain particularly influential. Chapter 5 detailed their effects on placental morphology, and here, they appear negatively associated with neonatal health. Birth weight reemerges as a critical outcome variable, suggesting potential benefits from interventions aimed at improving vascular health or reducing harmful exposures. Apgar scores, which were linked to placental function in Chapter 5, also show sensitivity to maternal clinical patterns that may compromise uteroplacental perfusion. Variables like maternal age and amniotic fluid volume display subtler relationships, potentially becoming more pronounced when analyzed alongside other factors. This finding mirrors the broader theme in Chapters 4 and 5, where canonical correlation analysis proved useful in detecting complex interactions that simpler pairwise methods might overlook. Overall, these results underscore the multifactorial nature of the maternal–fetal environment and the need for integrated analyses that consider a range of nutritional, vascular, mechanical, and behavioral factors together.

Chapter 7

Summary and Discussions

In this thesis, we investigated the complex relationships among maternal clinical indicators, placental histological features, and neonatal outcomes in pregnancies with placental abruption. The objective was to understand the histological characteristics of abruption and its associations with clinical indicators including complications that can be seen on ultrasound. We aimed to explore the inherent multidimensional relationships in the data beyond what simple pairwise correlations can show, hence we employed Canonical Correlation Analysis (CCA). By doing so, we sought to identify early predictors of placental abruption and highlight candidate clinical markers and ultrasound-based measurements to guide a more proactive and nuanced prenatal care strategies. Timely identification and management of abruption not only improve maternal and neonatal outcomes but may also reduce the risk of legal and ethical consequences that arise when adverse events lead to potential litigation. Finally, we also sought to understand how maternal conditions shape placental health and identify potential risk factors associated with abruption.

7.1 Summary

Placental weight is a critical determinant of its functional capacity for nutrient and gas exchange. Abnormal weights, whether low or high, may impair fetal growth and development, leading to adverse perinatal outcomes. According to the hypothesis put forward by the developmental origins of health and disease (DOHaD), suboptimal placental development can have long-term health implications for the offspring, including an increased risk of hypertension and cardiovascular diseases in adulthood [73, 95].

Other placental dimensions, such as width and thickness, are also important indicators of the surface area available for nutrient and gas exchange between mother and fetus [71]. Width represents the lateral span of the placenta, providing an indication of its horizontal growth, while thickness reflects the depth of the placental tissue and its capacity to house functional units such as villi and intervillous spaces. Larger surface areas facilitate more efficient transfer, which is essential for fetal growth and development. Variations in placental size may result because of differences in gestational age, as well as due to other factors, including nutrition and health status of the mother, as well as fetal factors such as growth potential, which has a genetic component. In cases of placental abruption, abnormal dimensions may reflect compromised placental development, potentially exacerbating the risk of adverse fetal outcomes. In the absence of normative values for a healthy placenta, the degree of compromise in fetal development and growth cannot be fully understood. Hence, highlighting the need for research to establish normal ranges for the biometric placental measurements, which can then be compared to our findings.

The observed variability in placental biometric measurements emphasizes the complexity of the various factors influencing placental growth and development. Maternal nutritional status, BMI, comorbidities, and environmental exposures can all impact placental growth and morphology. These factors affect the placenta's capacity to support fetal development, with potential implications for both immediate perinatal outcomes and long-term health, as posited in the hypothesis by the DOHaD.

Abnormal biometric measurements may serve as markers for underlying pathologies contributing to placental abruption. For example, insufficient placental growth due to chronic hypoxia or poor maternal nutrition may weaken placental attachment, increasing the risk of abruption [1]. Conversely, excessively large placentas associated with maternal diabetes may lead to vascular abnormalities predisposing to detachment. Considering the importance of the physical and biometric characteristics of the placenta, it is important for the normal ranges to be established and examined with respect to maternal factors (eg. age, BMI, nutrion), maternal health (eg. diabetes, hypertension) and various pregnancy complications, including placental abruption.

The findings presented from Chapter 3 to Chapter 6 of this thesis underscore that placental abruption emerges from a web of interconnected factors rather than from a single, isolated cause. Maternal health and behaviours—such as hypertension, smoking, and metabolic imbalances—intersect with placental pathologies (e.g., chorioamnionitis, infarctions, retroplacental clots) at the maternal-fetal interface [2,3]. The placenta itself is a dynamic, responsive organ whose histological features provide a tangible record of these associations. Variations in placental weight, thickness, and histological lesions all reflect the cumulative impact of maternal health and lifestyle behaviors on the intrauterine environment, ultimately influencing fetal growth and adaptation [80,96]. From a clinical perspective, this framework offers crucial insights.

Currently, diagnosing placental abruption often relies on clinical suspicion, maternal symptomatology, and sometimes inconclusive ultrasonographic findings [2,14] . Definitive confirmation generally occurs clinically (during delivery, which often is through caesarean section) and postdelivery through histopathological examination, at which point opportunities to intervene early and mitigate harm are limited. Such a postpartum approach inherently constrains the clinician's ability to prevent adverse maternal and neonatal outcomes. The potential to identify maternal clinical indicators and ultrasound findings (preferably in early stages of pregnancy), through their association with placental pathology, allows early diagnosis.. The findings presented in this thesis indicated that the detection of placental hematomas on ultrasound, hypoechogenicity shown in ultrasound, or other abnormal growth patterns seen on prenatal ultrasound are potential indicators of abruption. These results are consistent with other literature showing associations of these variables with increased risk of adverse outcomes [56,59,97]. Similarly, literature shows that maternal hypertension or evidence of compromised maternal vascular health can signal an at-risk placental environment [65,98]. Our analysis also identified these maternal factors to be the leading contributors driving the multivariate associations between clinical variables and histology as well as associations between clinical variables and neonatal outcomes. As such, recognizing these patterns early allows clinicians to intensify fetal surveillance, enhance maternal monitoring for early detection of a possible abruption (or other pregnancy complications) or initiate preventive measures—such as improved blood pressure control, smoking cessation programs, or targeted nutritional and lifestyle interventions [53, 89]. Such proactive strategies can directly influence neonatal well-being.

The findings presented in Chapters 4 and 5 highlight that placental lesions and inadequate placental function correlate strongly with unfavorable neonatal metrics such as low birth weight, reduced gestational age, and low Apgar scores, which is a measure of general wellbeing of a newborn [74, 81, 87]. By identifying and addressing risk factors that are associated with these histological markers during pregnancy—through closer ultrasound follow-ups, antibiotic prophylaxis for suspected intrauterine infections, or immediate attention to maternal pain and bleeding—clinicians may prevent or reduce the severity of placental compromise and thus mitigate the chain reaction leading to fetal hypoxia, preterm birth, and long-term neurodevelopmental challenges [22, 86]. These findings also carry broader implications for prenatal care models and guidelines. A shift from reactive to anticipatory management aligns with a more integrative model of obstetric care, encouraging collaboration among obstetricians, maternal-fetal medicine specialists, pathologists, neonatologists, and ancillary healthcare providers [93, 94]. For example, abnormal placental development patterns detected via routine second-trimester ultrasounds could trigger a multidisciplinary review. This team might consider adjusting antenatal visits, adding non-stress tests or biophysical profiles, recommending dietary improvements or stress reduction techniques, and, when warranted, planning earlier delivery to avert full-blown abruption and severe neonatal compromise.

The results across Chapters 4, 5, and 6 also highlight that interventions need not be limited to the immediate pregnancy in question. Histopathological findings from one pregnancy can inform counseling and management in subsequent pregnancies [96, 97]. For instance, women with a history of abruption or with placentas exhibiting certain histological characteristics (e.g., fibrin deposition, meconium staining) may benefit from preconception counseling, tighter prenatal surveillance in future pregnancies, and lifestyle adjustments (such as smoking cessation or weight management) to reduce recurrence risk [53,99]. Moreover, acknowledging that placental pathology is often a reflection of systemic maternal health underscores the public health importance of addressing modifiable risk factors at the population level. Improvements in maternal healthcare—such as better management of chronic hypertension, accessible nutrition counseling, smoking cessation support, and prevention of intrauterine infections—could collectively enhance placental health and improve neonatal outcomes on a wider scale [71, 100]. In essence, recognizing that the placenta is an active integrator of maternal conditions and that its pathology can be inferred from clinical and ultrasound parameters sets the stage for an earlier, more nuanced approach to prenatal care. By identifying at-risk pregnancies before histological abnormalities become critical, clinicians can intervene pre-emptively.. Such interventions promise not only to improve immediate neonatal outcomes by reducing hypoxia and preterm birth but also to lessen long-term morbidity, thereby improving lifelong health trajectories for both mother and child.

7.2 Strengths and Limitations

The major strength of this thesis is the data itself. Our analysis benefits from a rich dataset with several important variables including very time consuming and expensive histological analysis performed nearly in all pregnancies leading to abruption between the year 2013 and 2020. This histological analysis includes markers that are important in postpartum diagnosis of placental abruption. The descriptive statistics provided in Chapter 3, characterizing placental abruption, is a novel contribution, which allowed us to fill important gap in the literature. A key strength of this thesis also lies in its use of a multivariate approach to explore the complex and multidimensional relationships between multiple sets of variables. By examining entire variable sets simultaneously, the analysis revealed relationships that simpler pair-wise correlation analysis did not adequately describe. This approach enabled a more comprehensive understanding of how maternal conditions, placental changes seen on histology, and neonatal outcomes are interlinked. However, several limitations must be acknowledged. First and foremost, data consists of only abruption cases. Hence, we could not make any comparisons with health pregnancy or pregnancy with other complications. Data also did not allow confirmatory analysis, which is needed to establish the predictive power and diagnosis accuracy of the markers which we identified as potential risk factors associated with placental abruption and its impacts on neonatal outcomes. Another potential limitation is the focus primarily on neonatal outcomes, leaving maternal health (postpartum) trajectories less explored. Understanding the maternal long-term effects of abruption, and how they relate to placental pathology would provide a more comprehensive perspective. Data did not allow long-term impacts of abruption on child health to be explored.

The study was conducted in a Canadian healthcare context, and generalizability to other populations may be limited. The retrospective design and reliance on medical records led to considerable percentage of missing data in some of the variables, and some other relevant variables may have also been missed (because they may not be routinely collected from pregnant women). This may have introduced biases in the analysis. The use of CCA as an exploratory tool, although informative, requires careful interpretation; the results are sensitive to data quality, variable selection, and sample size. For example, certain variables were excluded due to strong correlations that risked singularity in the CCA model. Extensive sensitivity analysis to explore the impact of these excluded variables is valuable, potentially clarifying their influence on the findings. While the analysis identified promising clinical and ultrasound indicators, further research is needed to validate these findings through a confirmatory analysis, and translate them into clinically meaningful guidelines or decision-support tools.

7.3 Future Directions

One of the most important pieces of evidence gaps we identified in the literature is the normative values of healthy placenta. Without a comprehensive description of healthy placenta, including the normal ranges of its biometric measurements, the characteristic of abruption can not be fully explored. First and foremost, a systematic review of the literature is required to fully understand the characteristics of healthy placenta. Data from healthy placenta is also needed to estimate normal ranges (also referred to as reference intervals), and to describe its other histological signatures. Clinical and ultrasound data from healthy pregnancy is also needed to compare the various characteristics of abruption cases with healthy pregnancy. The insights gained here also open several other avenues for future research. Prospective, longitudinal studies with standardized data collection and objective assessment protocols would allow inferences to be made and causal relationships to be identified. Confirmatory statistical methodologies, such as regression analysis, predictive modeling, structural equation models and path analysis, could better delineate the various pathways linking maternal indicators, placental histology, and neonatal outcomes. For this to be possible, data from women with healthy pregnancy, women with complications other than abruption, and women with abruption need to be collected. Advancements in prenatal imaging technologies—such as Doppler flow studies, three-dimensional ultrasound, or even MRI—may enhance early detections of subtle placental abnormalities, increasing (or complimenting) the predictive value of ultrasound findings. Incorporating molecular biomarkers, including inflammatory mediators or genetic markers, could deepen our understanding of the pathogenesis of abruption and lead to targeted interventions. Developing predictive scoring systems that integrate maternal risk factors, ultrasound findings, and possibly biochemical markers would equip clinicians with practical tools for early risk stratification and tailored management strategies. Such tools could inform decisions about the frequency of prenatal visits, the intensity of fetal surveillance, or the timing of delivery, ultimately improving maternal and neonatal health outcomes.

7.4 Conclusions

This thesis indicates that maternal clinical factors, placental histology, and neonatal outcomes may be interconnected in pregnancies complicated by placental abruption in Ottawa. While these findings are exploratory, they suggest that certain clinical and ultrasound indicators could help identify higher-risk pregnancies before advanced placental pathology develops. Early detection and targeted interventions may reduce adverse outcomes for mothers and newborns. Further confirmatory research is required to evaluate the predictive value of these markers and to guide evidence-based clinical decisions. A more proactive prenatal care model—featuring systematic risk assessment and multidisciplinary collaboration—could potentially mitigate the effects of placental abruption.

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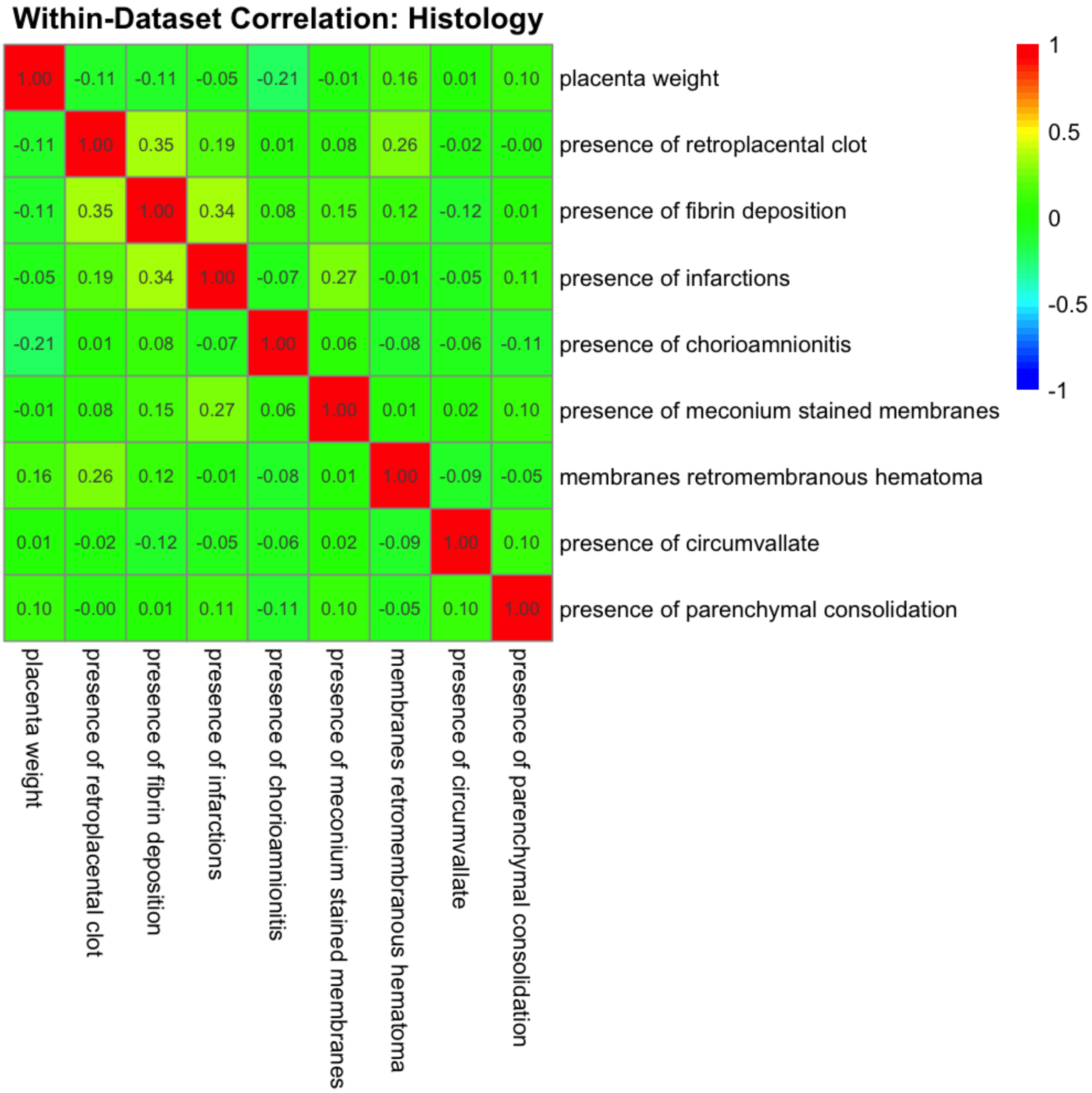
Appendix A

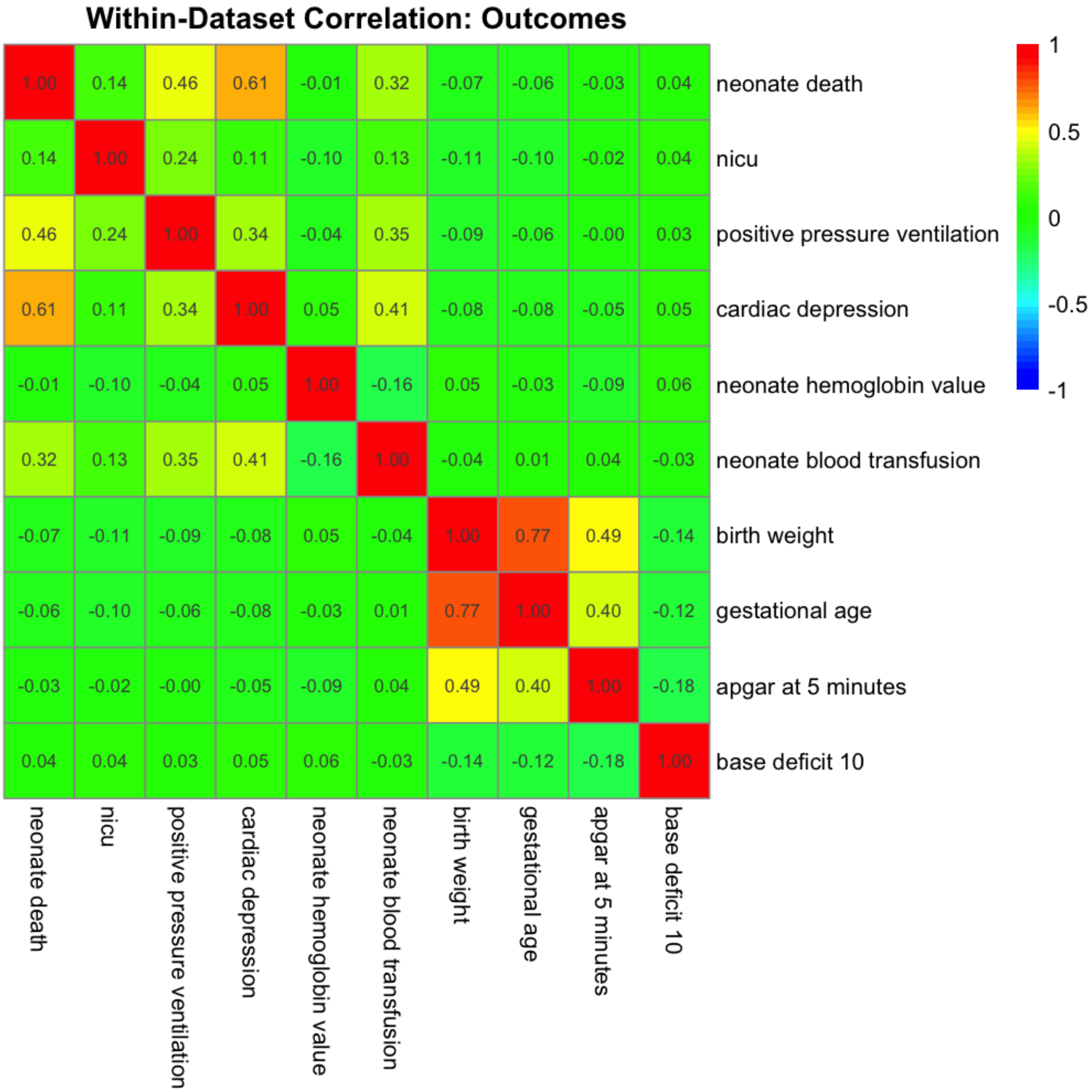
Appendix



Within-Dataset Correlation: Histology

	placenta weight	presence of retroplacental clot	presence of fibrin deposition	presence of infarctions	presence of chorioamnionitis	presence of meconium stained membranes	membranes retromembranous hematoma	presence of circumvallate	presence of parenchymal consolidation
placenta weight	1.00	-0.11	-0.11	-0.05	-0.21	-0.01	0.16	0.01	0.10
presence of retroplacental clot	-0.11	1.00	0.35	0.19	0.01	0.08	0.26	-0.02	-0.00
presence of fibrin deposition	-0.11	0.35	1.00	0.34	0.08	0.15	0.12	-0.12	0.01
presence of infarctions	-0.05	0.19	0.34	1.00	-0.07	0.27	-0.01	-0.05	0.11
presence of chorioamnionitis	-0.21	0.01	0.08	-0.07	1.00	0.06	-0.08	-0.06	-0.11
presence of meconium stained membranes	-0.01	0.08	0.15	0.27	0.06	1.00	0.01	0.02	0.10
membranes retromembranous hematoma	0.16	0.26	0.12	-0.01	-0.08	0.01	1.00	-0.09	-0.05
presence of circumvallate	0.01	-0.02	-0.12	-0.05	-0.06	0.02	-0.09	1.00	0.10
presence of parenchymal consolidation	0.10	-0.00	0.01	0.11	-0.11	0.10	-0.05	0.10	1.00

Figure A.1: Within-dataset correlation matrix for histology markers.

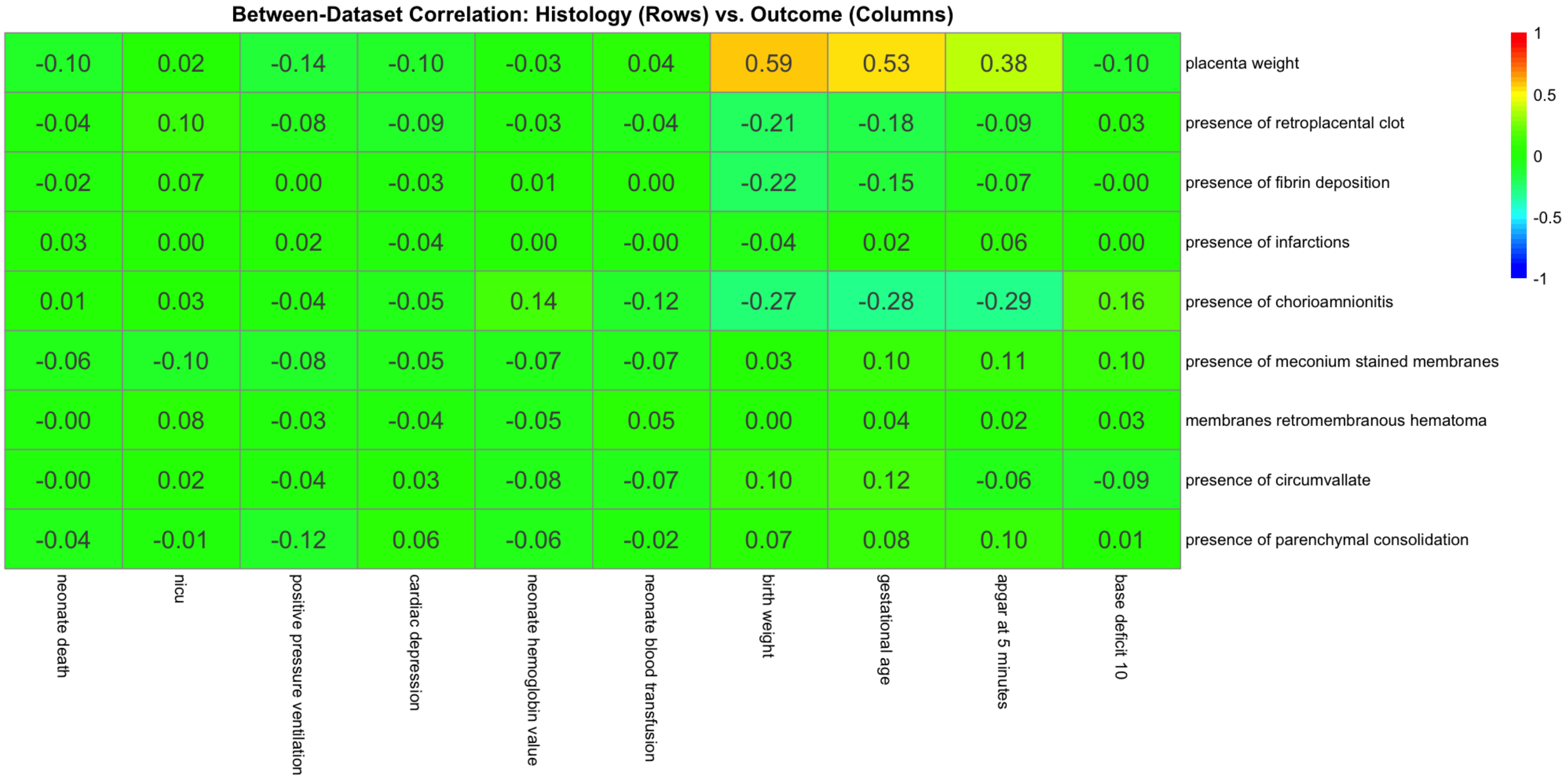


	neonate death	nicu	positive pressure ventilation	cardiac depression	neonate hemoglobin value	neonate blood transfusion	birth weight	gestational age	apgar at 5 minutes	base deficit 10
neonate death	1.00	0.14	0.46	0.61	-0.01	0.32	-0.07	-0.06	-0.03	0.04
nicu	0.14	1.00	0.24	0.11	-0.10	0.13	-0.11	-0.10	-0.02	0.04
positive pressure ventilation	0.46	0.24	1.00	0.34	-0.04	0.35	-0.09	-0.06	-0.00	0.03
cardiac depression	0.61	0.11	0.34	1.00	0.05	0.41	-0.08	-0.08	-0.05	0.05
neonate hemoglobin value	-0.01	-0.10	-0.04	0.05	1.00	-0.16	0.05	-0.03	-0.09	0.06
neonate blood transfusion	0.32	0.13	0.35	0.41	-0.16	1.00	-0.04	0.01	0.04	-0.03
birth weight	-0.07	-0.11	-0.09	-0.08	0.05	-0.04	1.00	0.77	0.49	-0.14
gestational age	-0.06	-0.10	-0.06	-0.08	-0.03	0.01	0.77	1.00	0.40	-0.12
apgar at 5 minutes	-0.03	-0.02	-0.00	-0.05	-0.09	0.04	0.49	0.40	1.00	-0.18
base deficit 10	0.04	0.04	0.03	0.05	0.06	-0.03	-0.14	-0.12	-0.18	1.00

Figure A.2: Within-dataset correlation matrix for neonatal outcomes.

Table A.1: Clinical indicators, histological markers, and neonatal outcomes used in CCA performed from chapter 4 to chapter 6.

Clinical Indicators	Histological Markers
Maternal Age	Placenta Weight
Parity	Presence of Retroplacental Clot
Natural Conception	Presence of Fibrin Deposition
BMI Value	Presence of Infarctions
Smoking Status	Presence of Chorioamnionitis
Drug Use	Presence of Meconium Stained Membranes
History of Placental Abruption	Membranes Retromembranous Hematoma
Maternal Hypertension Status	Presence of Circumvallate
Preterm Premature Rupture of Membrane	Presence of Parenchymal Consolidation
Amniotic Fluid Volume	
	Neonatal Outcomes
Placenta Hypoechogenicity	Neonate Death
Placenta Hematoma Ultrasound	NICU
Placenta Previa Ultrasound	Positive Pressure Ventilation
Placenta Lobe Ultrasound	Cardiac Depression
Placenta Ultrasound Location	Neonate Hemoglobin Value
Vaginal Bleeding	Neonate Blood Transfusion
Hypertonic Uterine Contractions	Birth Weight
Maternal Pain	Gestational Age
Fetal Movement	Apgar at 5 Minutes
Delivery Type	Base Deficit 10
Placental Delivery Time	
Fetal Baseline BPM	
Fetal Topography Accelerations	
Fetal Topography Decelerations	
Neonate Sex	



Between-Dataset Correlation: Histology (Rows) vs. Outcome (Columns)

	neonate death	nicu	positive pressure ventilation	cardiac depression	neonate hemoglobin value	neonate blood transfusion	birth weight	gestational age	apgar at 5 minutes	base deficit 10
placenta weight	-0.10	0.02	-0.14	-0.10	-0.03	0.04	0.59	0.53	0.38	-0.10
presence of retroplacental clot	-0.04	0.10	-0.08	-0.09	-0.03	-0.04	-0.21	-0.18	-0.09	0.03
presence of fibrin deposition	-0.02	0.07	0.00	-0.03	0.01	0.00	-0.22	-0.15	-0.07	-0.00
presence of infarctions	0.03	0.00	0.02	-0.04	0.00	-0.00	-0.04	0.02	0.06	0.00
presence of chorioamnionitis	0.01	0.03	-0.04	-0.05	0.14	-0.12	-0.27	-0.28	-0.29	0.16
presence of meconium stained membranes	-0.06	-0.10	-0.08	-0.05	-0.07	-0.07	0.03	0.10	0.11	0.10
membranes retromembranous hematoma	-0.00	0.08	-0.03	-0.04	-0.05	0.05	0.00	0.04	0.02	0.03
presence of circumvallate	-0.00	0.02	-0.04	0.03	-0.08	-0.07	0.10	0.12	-0.06	-0.09
presence of parenchymal consolidation	-0.04	-0.01	-0.12	0.06	-0.06	-0.02	0.07	0.08	0.10	0.01

Figure A.3: Pairwise correlation heatmap between histology markers and neonatal outcomes.

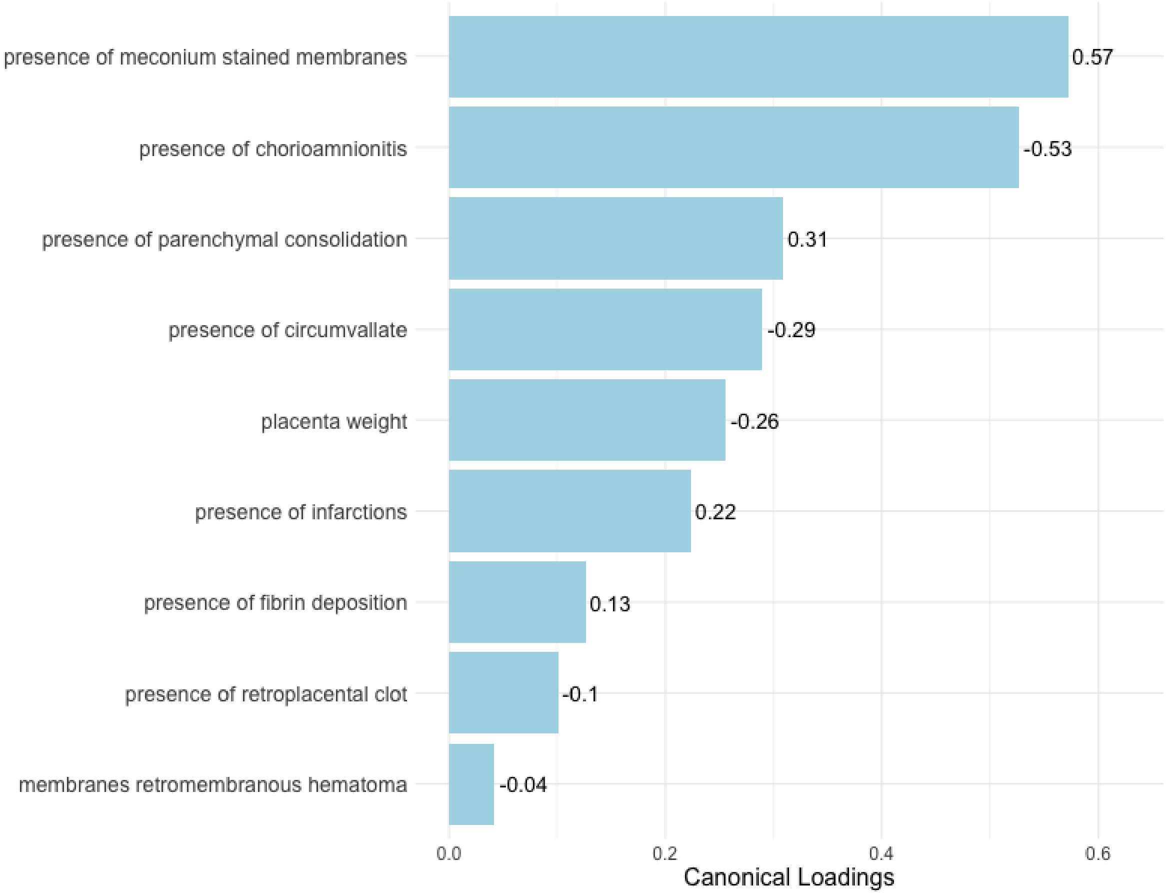


Figure A.4: Canonical loadings of histology markers corresponding to the second canonical variate obtained from Canonical Correlation Analysis (CCA) of histology markers and outcomes.

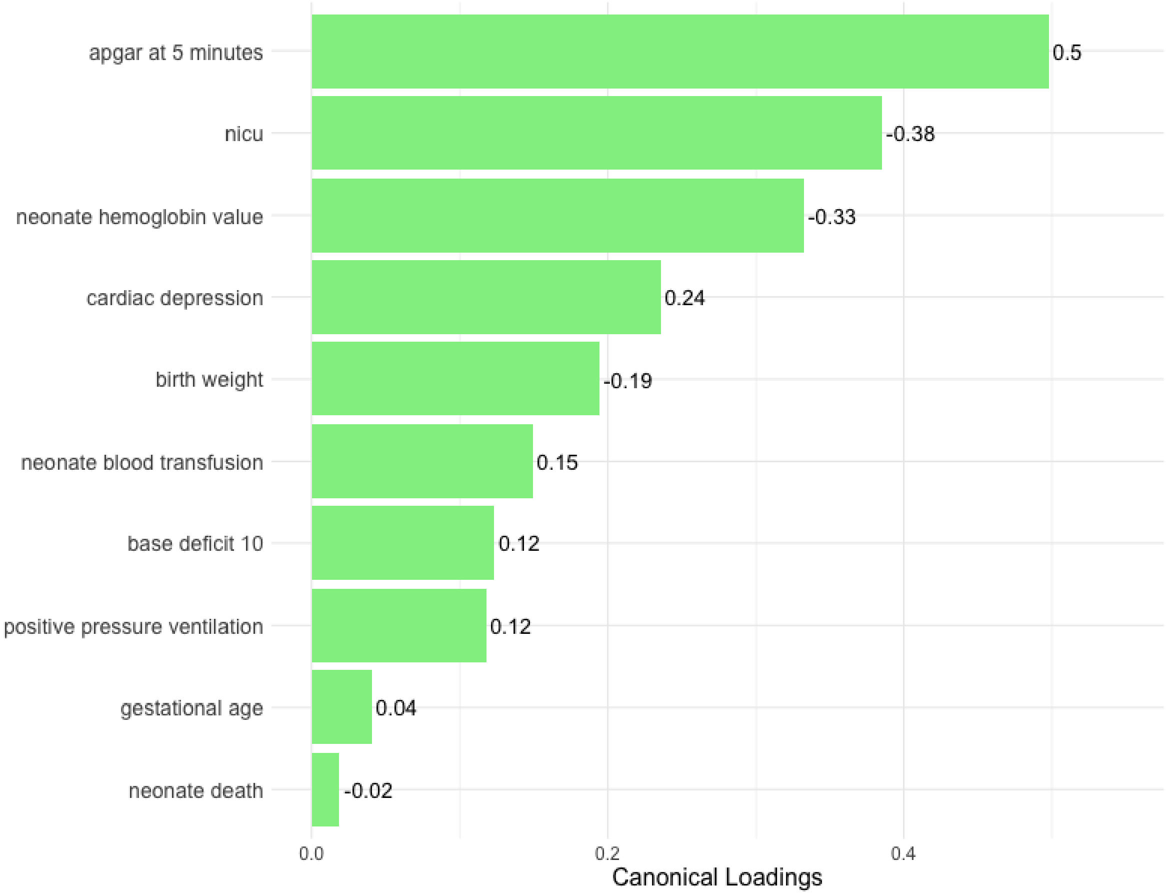
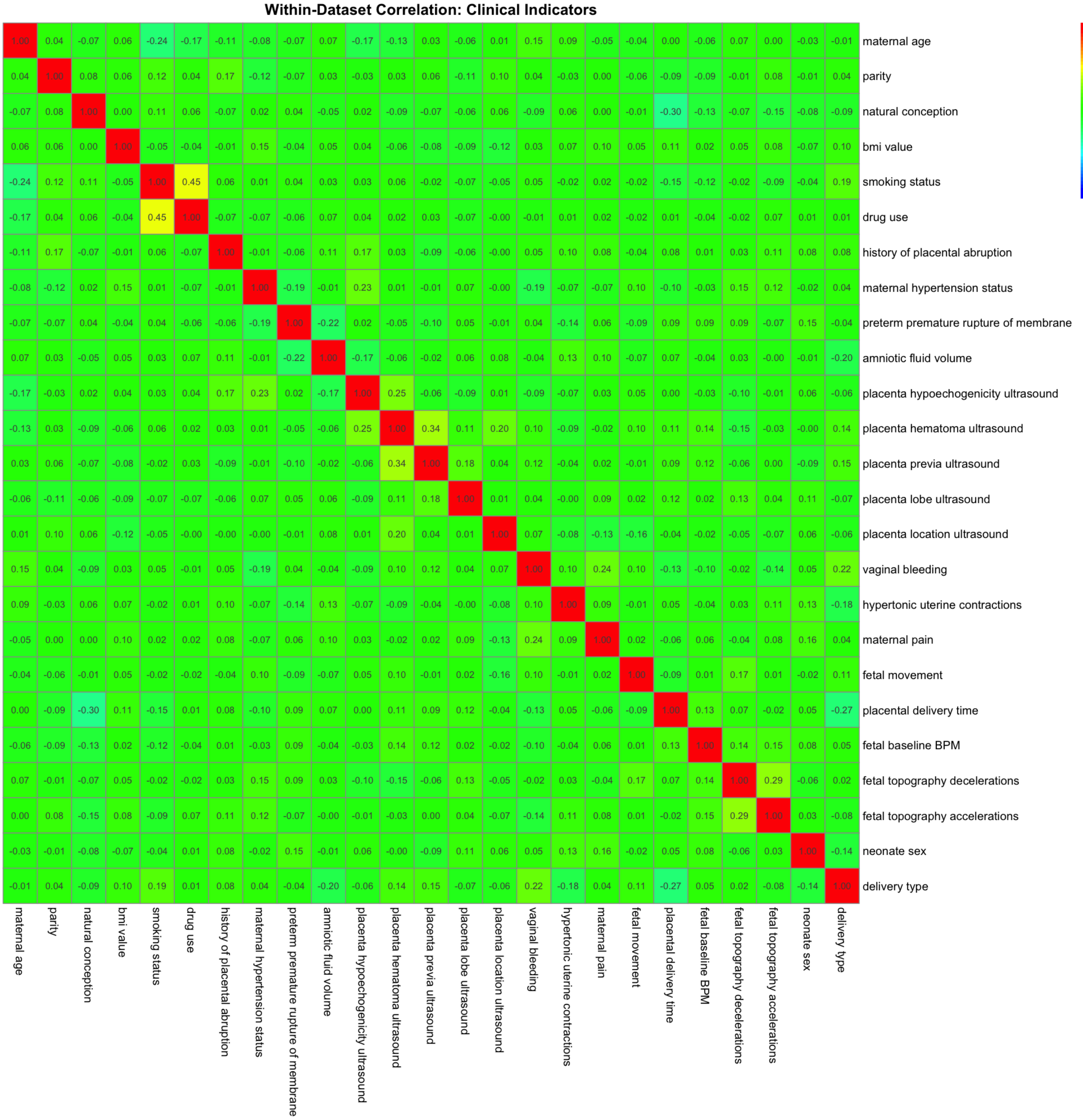


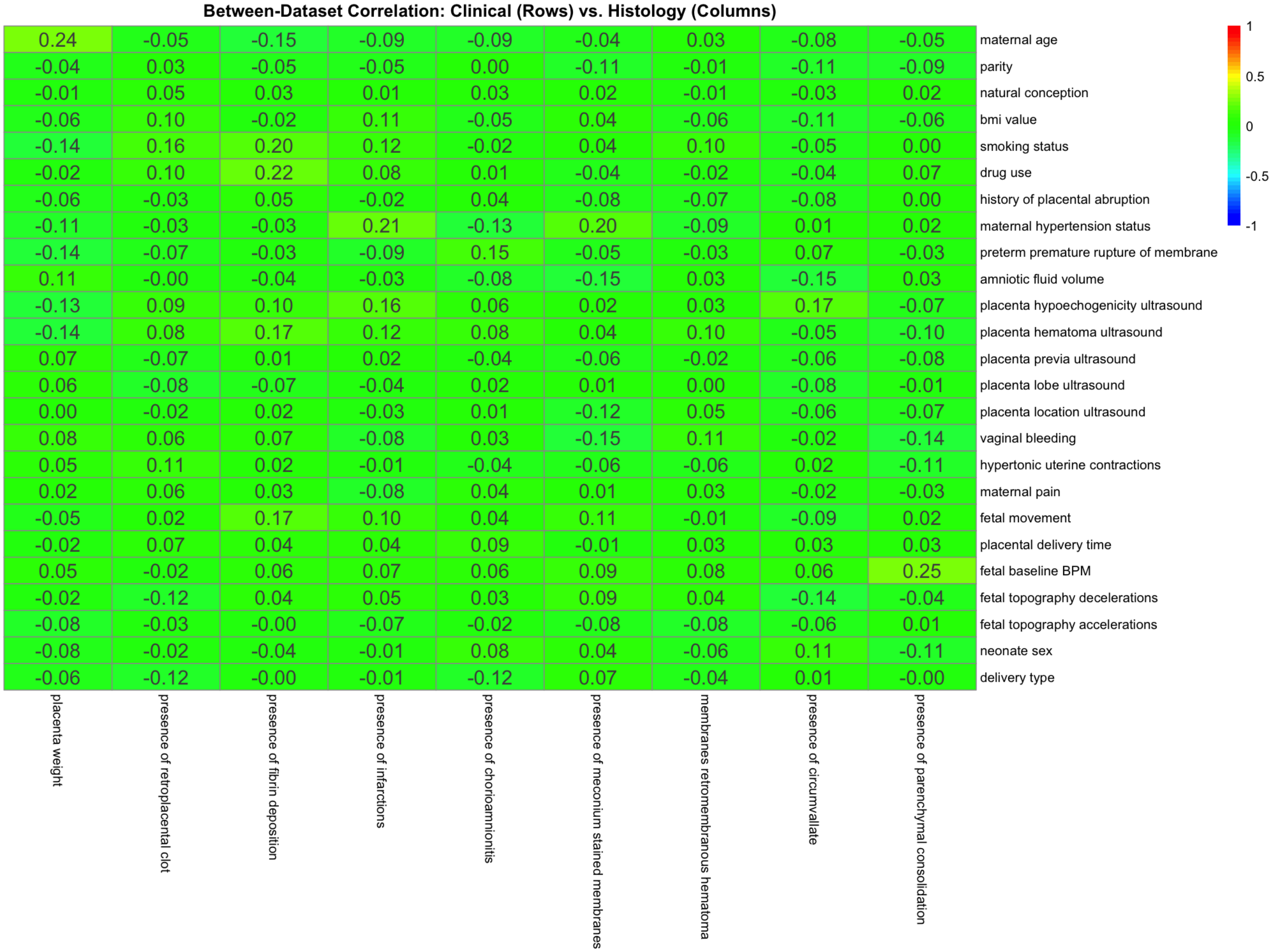
Figure A.5: Canonical loadings of neonatal outcome variables for the second canonical variate obtained from the Canonical Correlation Analysis (CCA) between neonatal outcomes and associated predictors.



Within-Dataset Correlation: Clinical Indicators

	maternal age	parity	natural conception	bmi value	smoking status	drug use	history of placental abruption	maternal hypertension status	preterm premature rupture of membrane	amniotic fluid volume	placenta hypoechogenicity ultrasound	placenta hematoma ultrasound	placenta previa ultrasound	placenta lobe ultrasound	placenta location ultrasound	vaginal bleeding	hypertonic uterine contractions	maternal pain	fetal movement	placental delivery time	fetal baseline BPM	fetal topography decelerations	fetal topography accelerations	neonate sex	delivery type
maternal age	1.00	0.04	-0.07	0.06	-0.24	-0.17	-0.11	-0.08	-0.07	0.07	-0.17	-0.13	0.03	-0.06	0.01	0.15	0.09	-0.05	-0.04	0.00	-0.06	0.07	0.00	-0.03	-0.01
parity	0.04	1.00	0.08	0.06	0.12	0.04	0.17	-0.12	-0.07	0.03	-0.03	0.03	0.06	-0.11	0.10	0.04	-0.03	0.00	-0.06	-0.09	-0.09	-0.01	0.08	-0.01	0.04
natural conception	-0.07	0.08	1.00	0.00	0.11	0.06	-0.07	0.02	0.04	-0.05	0.02	-0.09	-0.07	-0.06	0.06	-0.09	0.06	0.00	-0.01	-0.30	-0.13	-0.07	-0.15	-0.08	-0.09
bmi value	0.06	0.06	0.00	1.00	-0.05	-0.04	-0.01	0.15	-0.04	0.05	0.04	-0.06	-0.08	-0.09	-0.12	0.03	0.07	0.10	0.05	0.11	0.02	0.05	0.08	-0.07	0.10
smoking status	-0.24	0.12	0.11	-0.05	1.00	0.45	0.06	0.01	0.04	0.03	0.03	0.06	-0.02	-0.07	-0.05	0.05	-0.02	0.02	-0.02	-0.15	-0.12	-0.02	-0.09	-0.04	0.19
drug use	-0.17	0.04	0.06	-0.04	0.45	1.00	-0.07	-0.07	-0.06	0.07	0.04	0.02	0.03	-0.07	-0.00	-0.01	0.01	0.02	-0.02	0.01	-0.04	-0.02	0.07	0.01	0.01
history of placental abruption	-0.11	0.17	-0.07	-0.01	0.06	-0.07	1.00	-0.01	-0.06	0.11	0.17	0.03	-0.09	-0.06	-0.00	0.05	0.10	0.08	-0.04	0.08	0.01	0.03	0.11	0.08	0.08
maternal hypertension status	-0.08	-0.12	0.02	0.15	0.01	-0.07	-0.01	1.00	-0.19	-0.01	0.23	0.01	-0.01	0.07	-0.00	-0.19	-0.07	-0.07	0.10	-0.10	-0.03	0.15	0.12	-0.02	0.04
preterm premature rupture of membrane	-0.07	-0.07	0.04	-0.04	0.04	-0.06	-0.06	-0.19	1.00	-0.22	0.02	-0.05	-0.10	0.05	-0.01	0.04	-0.14	0.06	-0.09	0.09	0.09	0.09	-0.07	0.15	-0.04
amniotic fluid volume	0.07	0.03	-0.05	0.05	0.03	0.07	0.11	-0.01	-0.22	1.00	-0.17	-0.06	-0.02	0.06	0.08	-0.04	0.13	0.10	-0.07	0.07	-0.04	0.03	-0.00	-0.01	-0.20
placenta hypoechogenicity ultrasound	-0.17	-0.03	0.02	0.04	0.03	0.04	0.17	0.23	0.02	-0.17	1.00	0.25	-0.06	-0.09	0.01	-0.09	-0.07	0.03	0.05	0.00	-0.03	-0.10	-0.01	0.06	-0.06
placenta hematoma ultrasound	-0.13	0.03	-0.09	-0.06	0.06	0.02	0.03	0.01	-0.05	-0.06	0.25	1.00	0.34	0.11	0.20	0.10	-0.09	-0.02	0.10	0.11	0.14	-0.15	-0.03	-0.00	0.14
placenta previa ultrasound	0.03	0.06	-0.07	-0.08	-0.02	0.03	-0.09	-0.01	-0.10	-0.02	-0.06	0.34	1.00	0.18	0.04	0.12	-0.04	0.02	-0.01	0.09	0.12	-0.06	0.00	-0.09	0.15
placenta lobe ultrasound	-0.06	-0.11	-0.06	-0.09	-0.07	-0.07	-0.06	0.07	0.05	0.06	-0.09	0.11	0.18	1.00	0.01	0.04	-0.00	0.09	0.02	0.12	0.02	0.13	0.04	0.11	-0.07
placenta location ultrasound	0.01	0.10	0.06	-0.12	-0.05	-0.00	-0.00	-0.00	-0.01	0.08	0.01	0.20	0.04	0.01	1.00	0.07	-0.08	-0.13	-0.16	-0.04	-0.02	-0.05	-0.07	0.06	-0.06
vaginal bleeding	0.15	0.04	-0.09	0.03	0.05	-0.01	0.05	-0.19	0.04	-0.04	-0.09	0.10	0.12	0.04	0.07	1.00	0.10	0.24	0.10	-0.13	-0.10	-0.02	-0.14	0.05	0.22
hypertonic uterine contractions	0.09	-0.03	0.06	0.07	-0.02	0.01	0.10	-0.07	-0.14	0.13	-0.07	-0.09	-0.04	-0.00	-0.08	0.10	1.00	0.09	-0.01	0.05	-0.04	0.03	0.11	0.13	-0.18
maternal pain	-0.05	0.00	0.00	0.10	0.02	0.02	0.08	-0.07	0.06	0.10	0.03	-0.02	0.02	0.09	-0.13	0.24	0.09	1.00	0.02	-0.06	0.06	-0.04	0.08	0.16	0.04
fetal movement	-0.04	-0.06	-0.01	0.05	-0.02	-0.02	-0.04	0.10	-0.09	-0.07	0.05	0.10	-0.01	0.02	-0.16	0.10	-0.01	0.02	1.00	-0.09	0.01	0.17	0.01	-0.02	0.11
placental delivery time	0.00	-0.09	-0.30	0.11	-0.15	0.01	0.08	-0.10	0.09	0.07	0.00	0.11	0.09	0.12	-0.04	-0.13	0.05	-0.06	-0.09	1.00	0.13	0.07	-0.02	0.05	-0.27
fetal baseline BPM	-0.06	-0.09	-0.13	0.02	-0.12	-0.04	0.01	-0.03	0.09	-0.04	-0.03	0.14	0.12	0.02	-0.02	-0.10	-0.04	0.06	0.01	0.13	1.00	0.14	0.15	0.08	0.05
fetal topography decelerations	0.07	-0.01	-0.07	0.05	-0.02	-0.02	0.03	0.15	0.09	0.03	-0.10	-0.15	-0.06	0.13	-0.05	-0.02	0.03	-0.04	0.17	0.07	0.14	1.00	0.29	-0.06	0.02
fetal topography accelerations	0.00	0.08	-0.15	0.08	-0.09	0.07	0.11	0.12	-0.07	-0.00	-0.01	-0.03	0.00	0.04	-0.07	-0.14	0.11	0.08	0.01	-0.02	0.15	0.29	1.00	0.03	-0.08
neonate sex	-0.03	-0.01	-0.08	-0.07	-0.04	0.01	0.08	-0.02	0.15	-0.01	0.06	-0.00	-0.09	0.11	0.06	0.05	0.13	0.16	-0.02	0.05	0.08	-0.06	0.03	1.00	-0.14
delivery type	-0.01	0.04	-0.09	0.10	0.19	0.01	0.08	0.04	-0.04	-0.20	-0.06	0.14	0.15	-0.07	-0.06	0.22	-0.18	0.04	0.11	-0.27	0.05	0.02	-0.08	-0.14	1.00

Figure A.6: Within-dataset correlation matrix for clinical indicators.



Between-Dataset Correlation: Clinical (Rows) vs. Histology (Columns)

	placenta weight	presence of retroplacental clot	presence of fibrin deposition	presence of infarctions	presence of chorioamnionitis	presence of meconium stained membranes	membranes retromembranous hematoma	presence of circumvallate	presence of parenchymal consolidation
maternal age	0.24	-0.05	-0.15	-0.09	-0.09	-0.04	0.03	-0.08	-0.05
parity	-0.04	0.03	-0.05	-0.05	0.00	-0.11	-0.01	-0.11	-0.09
natural conception	-0.01	0.05	0.03	0.01	0.03	0.02	-0.01	-0.03	0.02
bmi value	-0.06	0.10	-0.02	0.11	-0.05	0.04	-0.06	-0.11	-0.06
smoking status	-0.14	0.16	0.20	0.12	-0.02	0.04	0.10	-0.05	0.00
drug use	-0.02	0.10	0.22	0.08	0.01	-0.04	-0.02	-0.04	0.07
history of placental abruption	-0.06	-0.03	0.05	-0.02	0.04	-0.08	-0.07	-0.08	0.00
maternal hypertension status	-0.11	-0.03	-0.03	0.21	-0.13	0.20	-0.09	0.01	0.02
preterm premature rupture of membrane	-0.14	-0.07	-0.03	-0.09	0.15	-0.05	-0.03	0.07	-0.03
amniotic fluid volume	0.11	-0.00	-0.04	-0.03	-0.08	-0.15	0.03	-0.15	0.03
placenta hypoechogenicity ultrasound	-0.13	0.09	0.10	0.16	0.06	0.02	0.03	0.17	-0.07
placenta hematoma ultrasound	-0.14	0.08	0.17	0.12	0.08	0.04	0.10	-0.05	-0.10
placenta previa ultrasound	0.07	-0.07	0.01	0.02	-0.04	-0.06	-0.02	-0.06	-0.08
placenta lobe ultrasound	0.06	-0.08	-0.07	-0.04	0.02	0.01	0.00	-0.08	-0.01
placenta location ultrasound	0.00	-0.02	0.02	-0.03	0.01	-0.12	0.05	-0.06	-0.07
vaginal bleeding	0.08	0.06	0.07	-0.08	0.03	-0.15	0.11	-0.02	-0.14
hypertonic uterine contractions	0.05	0.11	0.02	-0.01	-0.04	-0.06	-0.06	0.02	-0.11
maternal pain	0.02	0.06	0.03	-0.08	0.04	0.01	0.03	-0.02	-0.03
fetal movement	-0.05	0.02	0.17	0.10	0.04	0.11	-0.01	-0.09	0.02
placental delivery time	-0.02	0.07	0.04	0.04	0.09	-0.01	0.03	0.03	0.03
fetal baseline BPM	0.05	-0.02	0.06	0.07	0.06	0.09	0.08	0.06	0.25
fetal topography decelerations	-0.02	-0.12	0.04	0.05	0.03	0.09	0.04	-0.14	-0.04
fetal topography accelerations	-0.08	-0.03	-0.00	-0.07	-0.02	-0.08	-0.08	-0.06	0.01
neonate sex	-0.08	-0.02	-0.04	-0.01	0.08	0.04	-0.06	0.11	-0.11
delivery type	-0.06	-0.12	-0.00	-0.01	-0.12	0.07	-0.04	0.01	-0.00

Figure A.7: Pairwise correlation heatmap between histology markers and clinical indicators.

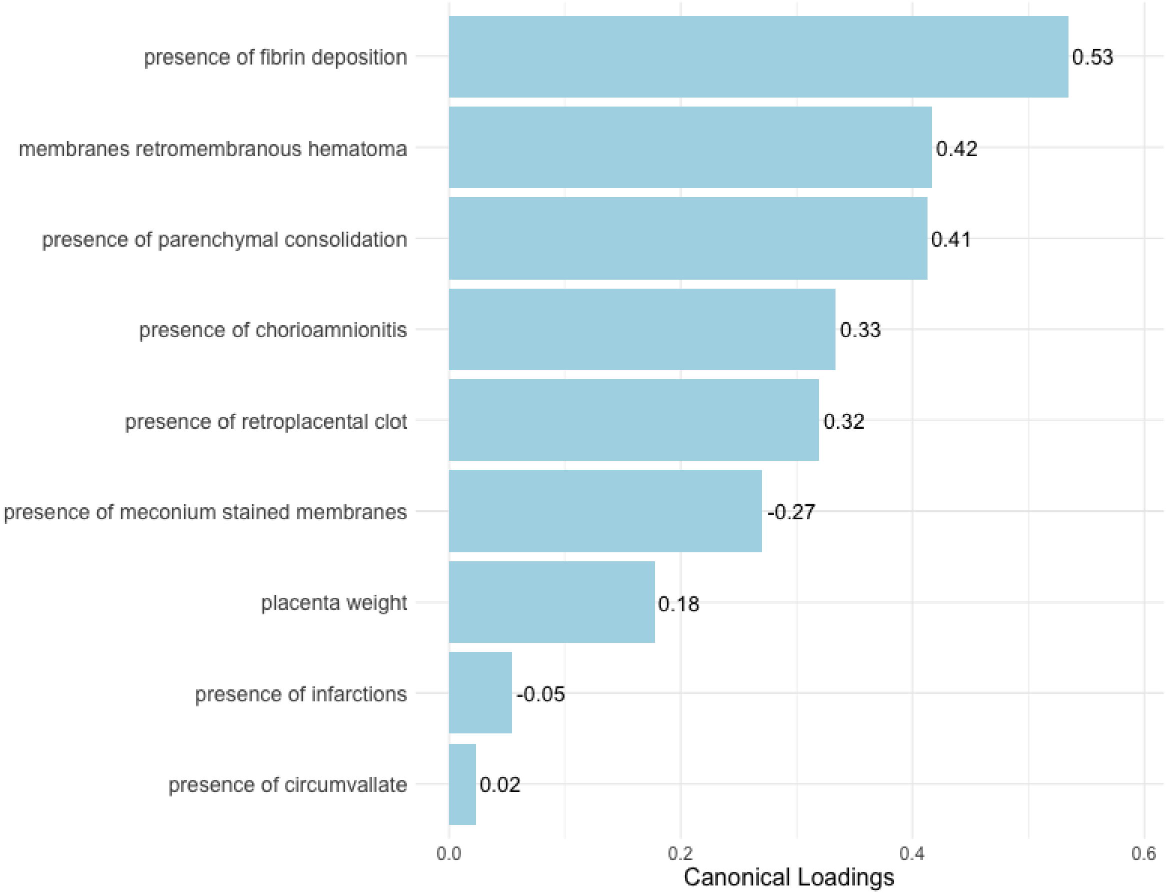


Figure A.8: Canonical loadings for the second canonical variate corresponding to histological markers in the analysis of histological markers and clinical indicators.

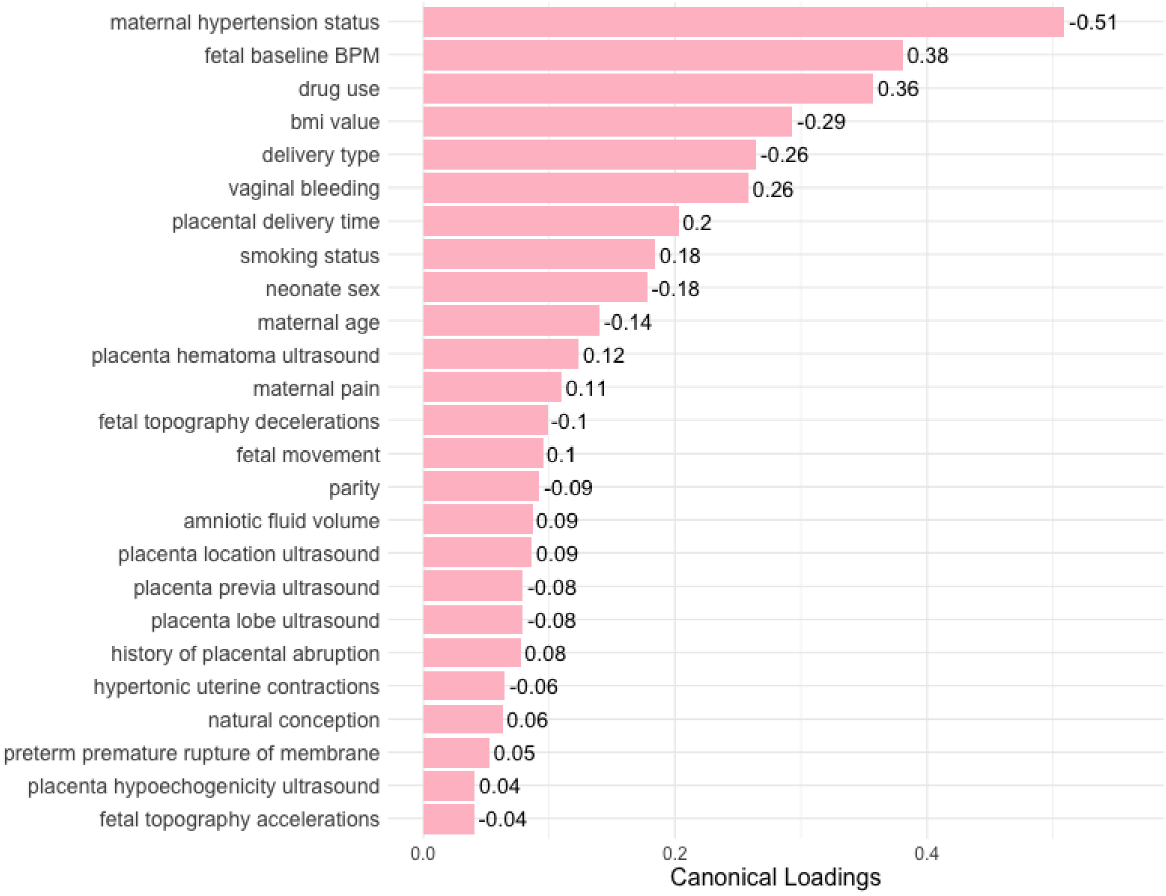
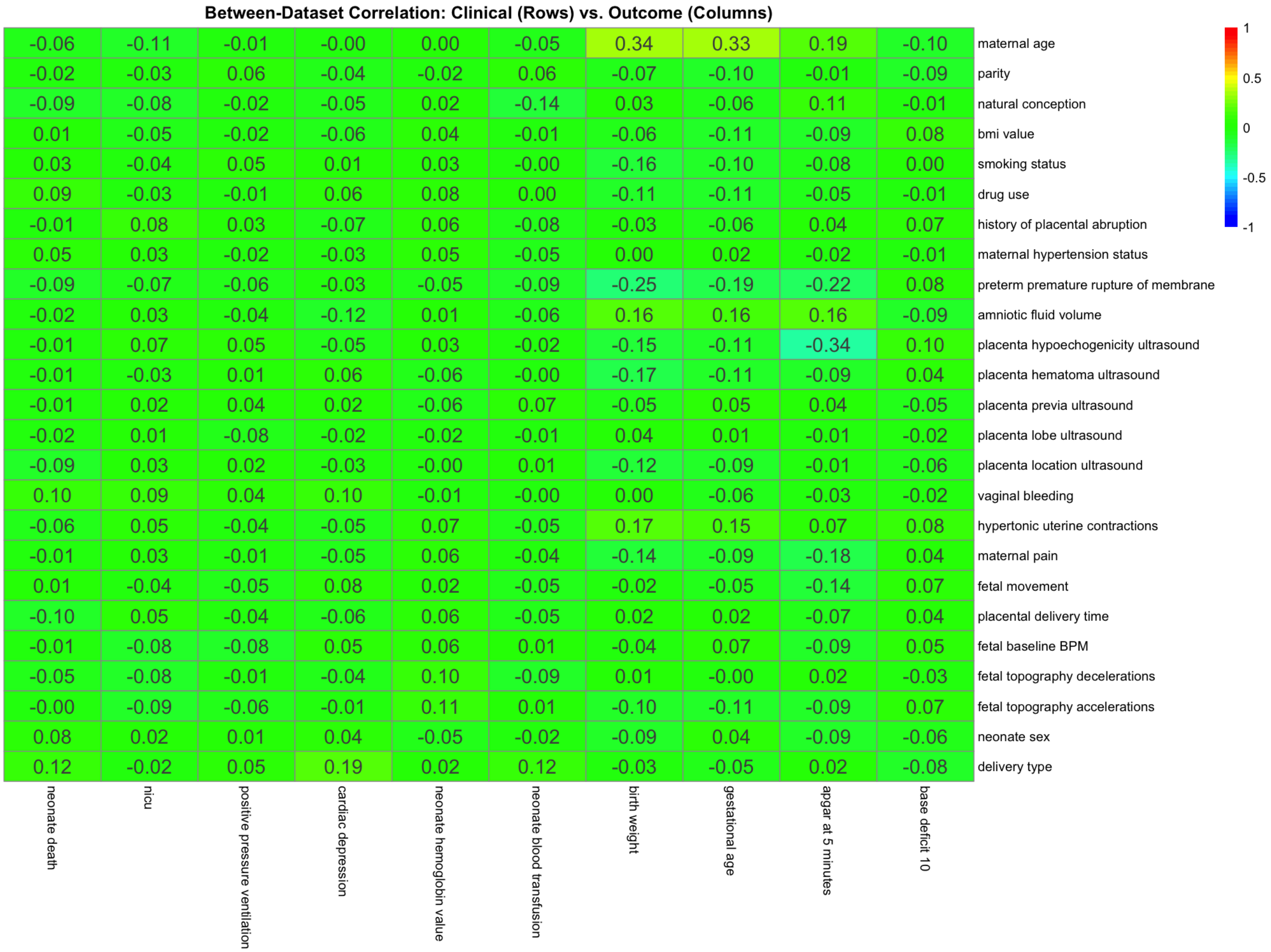


Figure A.9: Canonical loadings of clinical indicators corresponding to the second canonical variate obtained from CCA of histology markers and clinical indicators



	neonate death	nicu	positive pressure ventilation	cardiac depression	neonate hemoglobin value	neonate blood transfusion	birth weight	gestational age	apgar at 5 minutes	base deficit 10
maternal age	-0.06	-0.11	-0.01	-0.00	0.00	-0.05	0.34	0.33	0.19	-0.10
parity	-0.02	-0.03	0.06	-0.04	-0.02	0.06	-0.07	-0.10	-0.01	-0.09
natural conception	-0.09	-0.08	-0.02	-0.05	0.02	-0.14	0.03	-0.06	0.11	-0.01
bmi value	0.01	-0.05	-0.02	-0.06	0.04	-0.01	-0.06	-0.11	-0.09	0.08
smoking status	0.03	-0.04	0.05	0.01	0.03	-0.00	-0.16	-0.10	-0.08	0.00
drug use	0.09	-0.03	-0.01	0.06	0.08	0.00	-0.11	-0.11	-0.05	-0.01
history of placental abruption	-0.01	0.08	0.03	-0.07	0.06	-0.08	-0.03	-0.06	0.04	0.07
maternal hypertension status	0.05	0.03	-0.02	-0.03	0.05	-0.05	0.00	0.02	-0.02	-0.01
preterm premature rupture of membrane	-0.09	-0.07	-0.06	-0.03	-0.05	-0.09	-0.25	-0.19	-0.22	0.08
amniotic fluid volume	-0.02	0.03	-0.04	-0.12	0.01	-0.06	0.16	0.16	0.16	-0.09
placenta hypoechogenicity ultrasound	-0.01	0.07	0.05	-0.05	0.03	-0.02	-0.15	-0.11	-0.34	0.10
placenta hematoma ultrasound	-0.01	-0.03	0.01	0.06	-0.06	-0.00	-0.17	-0.11	-0.09	0.04
placenta previa ultrasound	-0.01	0.02	0.04	0.02	-0.06	0.07	-0.05	0.05	0.04	-0.05
placenta lobe ultrasound	-0.02	0.01	-0.08	-0.02	-0.02	-0.01	0.04	0.01	-0.01	-0.02
placenta location ultrasound	-0.09	0.03	0.02	-0.03	-0.00	0.01	-0.12	-0.09	-0.01	-0.06
vaginal bleeding	0.10	0.09	0.04	0.10	-0.01	-0.00	0.00	-0.06	-0.03	-0.02
hypertonic uterine contractions	-0.06	0.05	-0.04	-0.05	0.07	-0.05	0.17	0.15	0.07	0.08
maternal pain	-0.01	0.03	-0.01	-0.05	0.06	-0.04	-0.14	-0.09	-0.18	0.04
fetal movement	0.01	-0.04	-0.05	0.08	0.02	-0.05	-0.02	-0.05	-0.14	0.07
placental delivery time	-0.10	0.05	-0.04	-0.06	0.06	-0.05	0.02	0.02	-0.07	0.04
fetal baseline BPM	-0.01	-0.08	-0.08	0.05	0.06	0.01	-0.04	0.07	-0.09	0.05
fetal topography decelerations	-0.05	-0.08	-0.01	-0.04	0.10	-0.09	0.01	-0.00	0.02	-0.03
fetal topography accelerations	-0.00	-0.09	-0.06	-0.01	0.11	0.01	-0.10	-0.11	-0.09	0.07
neonate sex	0.08	0.02	0.01	0.04	-0.05	-0.02	-0.09	0.04	-0.09	-0.06
delivery type	0.12	-0.02	0.05	0.19	0.02	0.12	-0.03	-0.05	0.02	-0.08

Figure A.10: Pairwise correlation heatmap between clinical indicators and neonatal outcomes

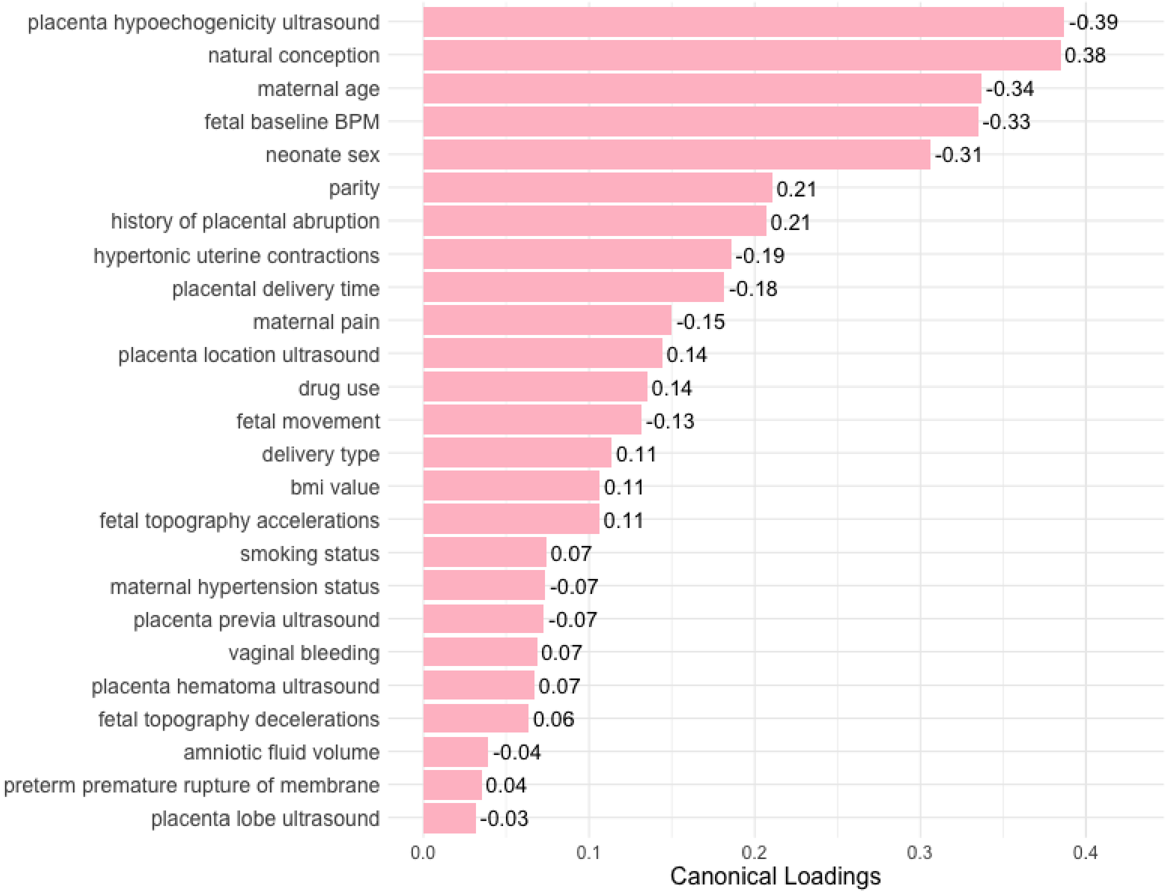


Figure A.11: Canonical loadings for the second canonical variate corresponding to clinical indicators in the analysis of clinical indicators and neonatal outcomes.

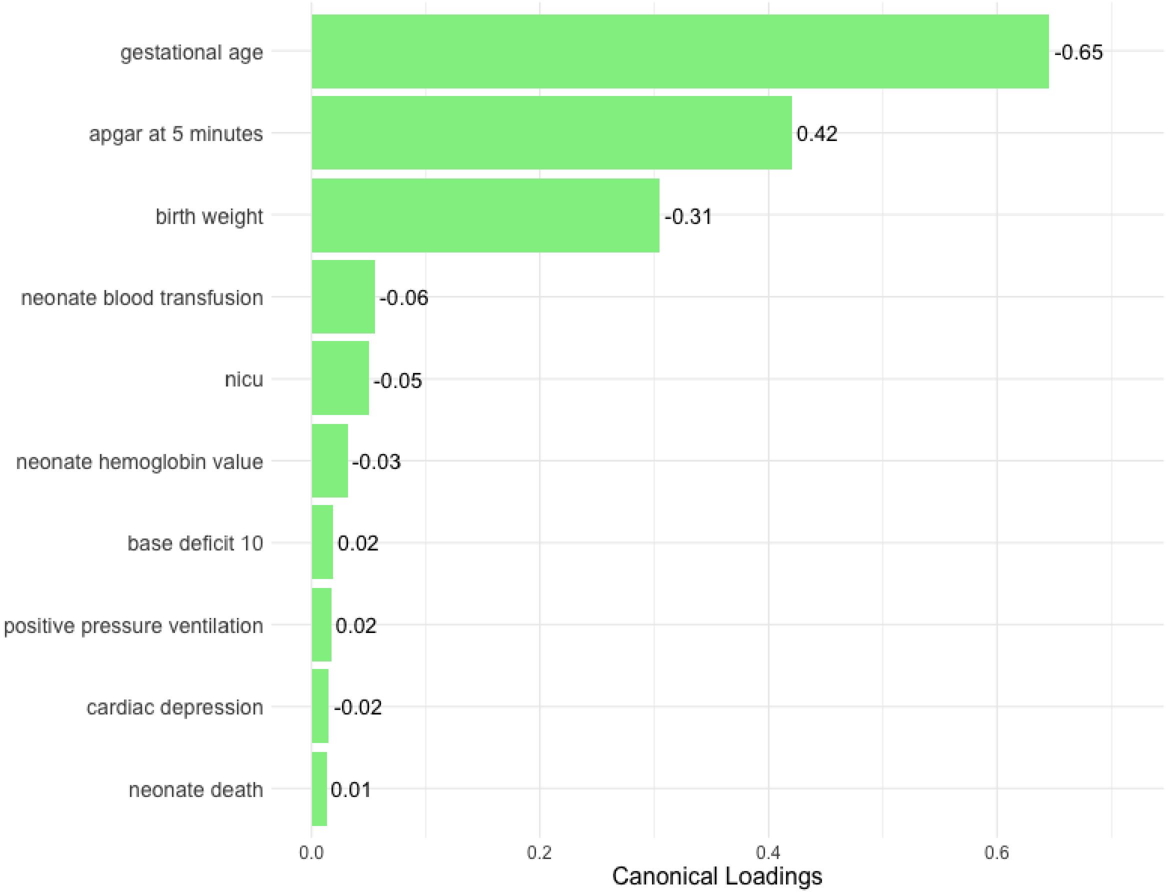


Figure A.12: Canonical loadings for the second canonical variate corresponding to neonatal outcomes in the analysis of clinical indicators and neonatal outcomes.