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Assessing intrauterine retention according to microscopic stillbirth features: a cluster analysis approach

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Abstract

Background—Previous studies identified microscopic changes associated with intrauterine retention of stillbirths based on clinical time of death. The objective of this study was to utilize unsupervised machine learning (not reliant on subjective measures) to identify features associated with time from death to delivery.

Methods—Data were derived from the Stillbirth Collaborative Research Network. Features were chosen *a priori* for entry into hierarchical cluster analysis, including fetal and placental changes.

Results—A four-cluster solution (coefficient = 0.983) correlated with relative time periods of “no retention,” “mild retention,” “moderate retention,” and “severe retention.” Loss of nuclear basophilia within fetal organs were found at varying rates among these clusters.

Conclusions—Hierarchical cluster analysis is able to classify stillbirths based on histopathological changes, roughly correlating to length of intrauterine retention. Such clusters, which rely solely on objective fetal and placental findings, can help clinicians more accurately assess the interval from death to delivery.

Keywords

Perinatal pathology; Time of Death; Stillbirth/Intrauterine Fetal Demise; Unsupervised Machine Learning

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Introduction

Stillbirth rates are stable worldwide despite decreases in infant mortality; this results in a constant burden on providers to explain these unfortunate events (1). This is heightened in the setting of medicolegal claims, which are common following a stillbirth as patients seek to heal after this devastating event (2–4). Postmortem pathology has significant implications in legal cases since 25–60% of stillbirths do not have a clear etiology; knowing time of death can help elucidate these details (5).

Our current methods for determining time of death are based on knowledge of last known alive, usually derived from subjective reports of fetal movements and rarely from fetal heart rate or ultrasonographic evidence (6). Consensus has been established regarding pathologic findings indicative of differing lengths of intrauterine retention, but these findings are largely correlated to subjective measures (7). Algorithms have also been developed to estimate time from death to delivery based on clinical evidence (8).

Therefore, we sought to minimize such subjectivity by utilizing unsupervised machine learning to identify which features were associated with clinically relevant interval from time of death to delivery. This allows for grouping of relevant variables without bias of subjective last fetal movement. Such information is of great utility as it provides objective evidence of time from fetal death to delivery.

Methods

Data

The Stillbirth Collaborative Research Network is a comprehensive study of stillbirths and livebirths conducted from 2006 to 2009. Study procedures were approved by the Institutional Review Board at each clinical site and the Data Analysis Center. Written, informed consent was collected from each participant; all procedures have been described previously (9).

Data were derived from the complete study population; participants who delivered a singleton stillbirth of gestational age (GA) > 20 weeks and consented to complete postmortem examination were included. Clinical information was extracted via chart review and interview.

Postmortem examination

Study pathologists were trained in standard postmortem and placental examinations (10,11). Pathologists determined cause of death according to the Initial Causes of Fetal Death system (12). Histologic features were reported based on those determined by Genest et al (13–15). Loss of nuclear basophilia in the following areas was included: renal cortical tubules (isolated = 4 hours, all cells = 4 weeks), liver (isolated = 24 hours, all cells = 96 hours), myocardium (inner half = 24 hours, outer half = 48 hours), bronchial epithelium (isolated = 96 hours), tracheal cartilage (isolated = 1 week), gastrointestinal tract (all cells = 1 week), and adrenal glands (all cells = 1 week) (15). Placental findings included: villous

intravascular karyorrhexis = 6+ hours; luminal obliterations of stem villi (multifocal = 2+ days, extensive = 2+ weeks); and extensive fibrosis of terminal villi = 2+ weeks (13). Genest et al. (14) further estimated fetal death based on the grade of maceration: I = desquamation ≥1 cm and/or brown-red discoloration of umbilical stump; II = desquamation involving face/abdomen/back; III = desquamation involving ≥5% of body surface; IV = brown skin discoloration; and V = mummification.

Statistical analyses

Lesions were entered into hierarchical cluster analysis. Using this method, we identified distinct groups of stillbirths based on hierarchical relationships among lesions, thus constructing groups intended to correlate with increasing intrauterine retention time (16). Clusters were derived using agglomerative (“bottom-up”) or divisive (“top-down”) clustering, according to which method resulted in the highest clustering coefficient and were merged according to optimal cluster number (elbow method) (17–20) Clustering was completed in R (version 4.1.3); tested linkage methods for clustering included average, single, complete, and ward.

Once clusters were derived, sample characteristics were compared across and between clusters. Kruskall-Wallis and Mann-Whitney tests were used for continuous data; Chi-Square tests were used for categorical data. Significance was set at $p < 0.05$.

Results

Three-hundred and seventy-nine (379) patients met inclusion criteria for these analyses. A four-cluster agglomerative solution using the ward method yielded the highest clustering coefficient ($c = 0.983$). Comparisons across clusters are illustrated in Tables 1–3.

Characterizing clusters (Table 4)

Cluster 1 had limited post-mortem changes and the statistically highest rate of intrapartum cause of death, lowest GA at delivery, and lowest rates of grade IV-V maceration and reported reduced fetal movement. This group likely represents stillbirths with limited to no intrauterine retention (“No retention” cluster).

Cluster 2 had loss of nuclear basophilia within the GI tract, adrenal glands, and hepatocytes and higher rates of degenerative umbilical cord changes relative to cluster 1. Compared to cluster 1, this group had similar rates of maceration grade IV-V and obstetric cause of death but had significantly lower rates of intrapartum cause of death. Cluster 2 had significantly higher rates of reduced fetal movement compared to cluster 1 and lower compared to clusters 3 and 4. This group likely represents a short length of intrauterine retention that is longer than cluster 1 but shorter than 3 and 4 (“Mild retention” cluster).

Cluster 3 had intermediate rates of histologic changes; loss of nuclear basophilia was observed in the GI tract, adrenal glands, isolated renal cells, inner/outer myocytes, and bronchial epithelium. This group also had intermediate rates of maceration grade IV-V, high rates of reduced fetal movement, and low rates of intrapartum cause of death. This group

likely represents stillbirths with prolonged, though not the longest, intrauterine retention ("Moderate retention" cluster).

Cluster 4 had significant post-mortem changes, including complete inner myocyte loss of nuclear basophilia and high rates of loss of nuclear basophilia in the GI tract, adrenal glands, outer myocytes, and renal cells. This group also had statistically highest rates of maceration grade IV-V and reduced fetal movement and lowest rates of intrapartum cause of death. This group likely represents stillbirths with the longest length of intrauterine retention compared to the other three clusters ("Severe retention" cluster).

Discussion

In this study, we utilized hierarchical cluster analysis to identify four groups of stillbirths according to histologic features with the following relative intervals: No retention, Mild retention, Moderate retention, and Severe retention. Individuals in the clusters were well-correlated, indicated by the agglomerative clustering coefficient of 0.983. These clusters highlight that objective groups of stillbirths of differing intrauterine retention times can be derived without using subjective last known normal. These findings indicate which histologic findings are indeed associated with different times from death to delivery, building on those previously established (7,13–15,21). Isolated loss of renal tubular nuclear basophilia (≥4 hours) was a finding that increased in prevalence from Mild to Moderate retention. Further validating this finding, only *majority* renal cell loss of nuclear basophilia (≥4 weeks) was observed in Severe retention. Loss of nuclear basophilia in inner versus outer myocytes, (≥24 and ≥48 hours) followed a similar trend from Mild to Severe retention.

The clinical utility of such an approach lies in the ability for pathologies to match features found on postmortem examination with the relative cluster. Though there are overlapping features among clusters, those features listed above that are unique to clusters can signify a fetus may have been retained for that relative period of time. Furthermore, by relying solely on objective findings, including fetal and placental microscopic examination, pathologists and clinicians can determine relative time of retention without use of subjective fetal movements.

Several findings were not consistent with consensus, most strikingly loss of nuclear basophilia in hepatocytes (both isolated and majority, ≥96 hours) only in the Mild retention cluster. If such a finding were indeed related to intrauterine retention, we would expect it to be present in all longer retention clusters. Loss of nuclear basophilia is relatively uncommon in this cohort (11.1% of the total cohort); these cases may represent a subset of fetuses who experienced intrauterine hepatic changes affecting both fetal liver size and postmortem hepatic degeneration. The original studies by Genest et al. did not thoroughly assess maternal conditions such as gestational diabetes or acute fatty liver of pregnancy or fetal myelopoiesis, anemia, biliary atresia, or infection, which may also contribute (15,22,23). Future external validation of these clusters will help elucidate the cause of this unexpected finding.

Placental lesions in our clusters may correlate with both intrauterine retention times and cause of death. Intravascular karyorrhexis in Mild through Severe clusters, correlated well with consensus, with reported retention ≥6 hours. Vascular karyorrhexis and chorionic vascular lesions both can be attributed to intrauterine retention and fetal vascular malperfusion, which may result from umbilical cord accidents (24). Our moderate and severe retention clusters had the highest rates of umbilical-cord related cause of death, and the severe retention cluster had the highest rate of villous karyorrhexis; these findings may be related in attributing cause of death.

Our study has several strengths, principally the quality of our pathological data, derived from a study with standardized training and protocols, which allows us to state our findings with confidence. Our methodology is singular in being able to objectively identify findings correlated with different lengths of intrauterine retention. We also are cognizant of the limitations of this study; while we were able to correlate clusters with clinical variables and estimate time from death to delivery, we are unable to give an exact time frame from our analyses. We would have liked to have utilized an objective measurement to estimate this interval, such as determining the difference between clinical GA at delivery and GA according to postmortem examination; however, we do not have this capability in our data at this time. We also did not assess further confounding factors such as organ weights, fetal conditions, and maternal factors that may influence findings. Such factors will be included in further studies of these clusters.

In conclusion, we were able to identify four clusters of stillbirths stratified by time from death to delivery based on histopathologic findings using hierarchical cluster analysis. This information will be of great clinical utility for those caring for and identifying causes of these patients' stillbirths. Further analysis will seek to correlate clusters with quantifiable time of death utilizing methods from adult forensic sciences (25).

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Table 1:

Maternal characteristics

	Cluster 1 (n = 122)	Cluster 2 (n = 39)	Cluster 3 (n = 106)	Cluster 4 (n = 112)	p-value	Post-hoc comparisons					
						1 v 2	1 v 3	1 v 4	2 v 3	2 v 4	3 v 4
Age (years)	26.4 ± 6.4	29.5 ± 6.3	27.6 ± 6.9	28.4 ± 6.9	**0.047**	**0.012**	0.2	**0.04**	0.14	0.3	0.4
Race (minority)	60 (49.2)	14 (35.9)	42 (39.6)	36 (32.1)	0.059	0.15	0.15	**0.008**	0.7	0.7	0.2
Ethnicity (Hispanic)	34 (27.9)	17 (43.6)	37 (34.9)	42 (37.8)	0.2	0.07	0.3	0.1	0.3	0.5	0.7
Education (years)	12.5 ± 3.0	13.6 ± 2.5	12.8 ± 3.1	13.2 ± 3.0	0.15	0.05	0.5	0.09	0.13	0.5	0.3
Pre-pregnancy history											
Diabetes	6 (5.4)	2 (5.3)	8 (8.1)	5 (4.7)	0.8	0.9	0.4	0.8	0.7	0.9	0.3
Hypertension	15 (13.4)	5 (13.2)	16 (16.2)	13 (12.1)	0.9	0.9	0.6	0.8	0.7	0.9	0.4
Prenatal history											
Had prenatal care	99 (88.4)	37 (97.4)	94 (94.9)	101 (95.3)	0.14	0.12	0.09	0.065	0.9	0.9	0.9
Reduced fetal movement	41 (37.3)	18 (47.4)	66 (66.7)	71 (67.6)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.038**	**0.027**	0.9
Alcohol in pregnancy	46 (41.1)	13 (34.2)	41 (41.4)	38 (35.5)	0.7	0.5	0.9	0.4	0.4	0.9	0.4
Smoking in pregnancy	29 (25.9)	4 (10.5)	19 (19.2)	13 (12.1)	**0.035**	**0.048**	0.2	**0.01**	0.2	0.9	0.2

All values given as mean ± standard deviation (continuous measures) or number (percentage of cluster) (categorical measures). P-values derived from Kruskall-Wallis or Chi-Square tests (continuous and categorical, respectively) for omnibus tests and Mann-Whitney and Chi-Square tests for post-hoc comparisons. P-values < 0.05 are considered significant (bolded).

Table 2:

Stillbirth characteristics

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	p-value	Post-hoc comparisons					
						1 v 2	1 v 3	1 v 4	2 v 3	2 v 4	3 v 4
Gestational age at delivery	26.6 ± 6.7	28.4 ± 7.0	31.1 ± 6.3	29.1 ± 6.5	**<0.001**	0.12	**<0.001**	**0.001**	**0.03**	0.5	**0.033**
Vaginal delivery	98 (80.3)	33 (84.6)	90 (84.9)	99 (88.4)	0.4	0.5	0.4	0.1	0.9	0.6	0.4
External exam											
Weight (g)	1142 ± 1148	1328 ± 1102	1653 ± 1174	1308 ± 1229	**0.001**	0.2	**<0.001**	0.6	0.13	0.5	**0.005**
Sex (female)	50 (41.0)	19 (48.7)	46 (43.4)	53 (47.3)	0.7	0.4	0.7	0.3	0.6	0.9	0.6
Maceration grade IV-V	6 (4.9)	2 (5.1)	13 (12.3)	32 (28.6)	**<0.001**	0.9	0.8	**<0.001**	0.4	**0.003**	**0.003**
Cause of death (INCODE)											
Obstetric	72 (59.5)	22 (56.4)	29 (27.4)	28 (25.0)	**<0.001**	0.7	**<0.001**	**<0.001**	**0.001**	**<0.001**	0.7
Intrapartum	44 (36.4)	7 (17.9)	5 (4.7)	4 (3.6)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.017**	**0.007**	0.7
Umbilical cord	12 (9.9)	7 (17.9)	27 (25.5)	27 (24.1)	**0.011**	0.3	**0.002**	**0.004**	0.3	0.4	0.8
Placental	54 (44.6)	21 (53.8)	69 (65.1)	65 (58.0)	**0.018**	0.3	**0.002**	**0.041**	0.2	0.6	0.3
Genetic/syndromic	33 (27.3)	9 (23.1)	27 (25.5)	22 (19.6)	0.6	0.6	0.8	0.2	0.8	0.6	0.3
Hypertensive disorders	19 (15.7)	2 (5.1)	17 (16.0)	18 (16.1)	0.4	0.09	0.9	0.9	0.08	0.08	0.9
Maternal medical complication	43 (35.5)	12 (30.8)	37 (34.9)	36 (32.1)	0.9	0.6	0.9	0.6	0.6	0.9	0.7
Infection	43 (35.5)	13 (33.3)	35 (33.0)	43 (38.4)	0.9	0.8	0.7	0.7	0.9	0.6	0.4

All values given as mean ± standard deviation (continuous measures) or number (percentage of cluster) (categorical measures). P-values derived from Kruskall-Wallis or Chi-Square tests (continuous and categorical, respectively) for omnibus tests and Mann-Whitney and Chi-Square tests for post-hoc comparisons. P-values < 0.05 are considered significant (bolded).

Table 3:

Histologic findings

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	p-value	Post-hoc comparisons					
						1 v 2	1 v 3	1 v 4	2 v 3	2 v 4	3 v 4
Fetal findings (loss of nuclear basophilia) – clustering measures											
Renal cells											
Isolated	1 (0.8)	19 (48.7)	61 (57.5)	0 (0.0)	**<0.001**	**<0.001**	**<0.001**	0.9	0.3	**<0.001**	**<0.001**
Majority	1 (0.8)	10 (25.6)	16 (15.1)	106 (94.6)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.14	**<0.001**	**<0.001**
Hepatocytes											
Isolated	0 (0.0)	38 (97.4)	4 (3.8)	0 (0.0)	**<0.001**	**<0.001**	**0.045**	--	**<0.001**	**<0.001**	0.054
Majority	0 (0.0)	38 (97.4)	4 (3.8)	0 (0.0)	**<0.001**	**<0.001**	**0.045**	--	**<0.001**	**<0.001**	0.054
Myocytes											
Inner	0 (0.0)	15 (38.5)	70 (66.0)	112 (100.0)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.003**	**<0.001**	**<0.001**
Outer	0 (0.0)	6 (15.4)	65 (61.3)	103 (92.0)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Bronchial epithelium	4 (3.3)	5 (12.8)	54 (50.9)	78 (69.6)	**<0.001**	**0.039**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.005**
GI tract (majority)	1 (0.8)	26 (66.7)	96 (90.6)	109 (97.3)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.035**
Adrenal glands (majority)	3 (2.5)	21 (53.8)	92 (86.8)	108 (96.4)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.01**
Placental findings											
Villous karyorrhexis	12 (9.8)	15 (38.5)	34 (32.1)	63 (56.2)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.5	0.05	**<0.001**
Fetal blood cell karyorrhexis	9 (7.4)	8 (20.5)	21 (19.8)	37 (33.0)	**<0.001**	**0.033**	**0.006**	**<0.001**	0.9	0.14	**0.027**
Chorionic vascular lesions	29 (23.8)	17 (43.6)	20 (18.9)	46 (41.1)	**<0.001**	**0.017**	0.4	**0.005**	**0.002**	0.8	**<0.001**
Disc calcifications	1 (0.8)	1 (2.6)	4 (3.8)	3 (2.7)	0.5	0.4	0.2	0.4	0.9	0.9	0.7
Umbilical cord											
Degenerative changes	7 (5.7)	10 (25.6)	13 (12.3)	22 (19.6)	**0.002**	**0.001**	0.082	**0.001**	0.05	0.4	0.14
Wharton's substance calcifications	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0.7	--	--	0.5	--	0.9	0.9

All values given number (percentage of cluster). P-values derived from Chi-Square tests. P-values < 0.05 are considered significant (bolded).

Table 4:

Cluster Characterization (Summary)

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Cluster name	No retention	Mild retention	Moderate retention	Severe retention
Fetal lesions (loss of nuclear basophilia)*	None	Isolated/majority renal cells, isolated/ majority hepatocytes, inner myocytes, GI tract, adrenal glands	Isolated renal cells, inner/outer myocytes, bronchial epithelium, GI tract, adrenal glands	Majority renal cells, inner/outer myocytes, bronchial epithelium, GI tract, adrenal glands
Placental lesions*	Chorionic vascular lesions	Villous & fetal blood cell karyorrhexis, chorionic vascular lesions	Villous karyorrhexis	Villous & fetal blood cell karyorrhexis, chorionic vascular lesions
Umbilical cord lesions*	None	Degenerative changes	None	None
Maceration Grade IV-V	4.9%	5.1%	12.3%	28.6%
Reduced fetal movement	37.3%	47.4%	66.7%	67.6%
Cause of death				
Intrapartum	36.4%	17.9%	4.7%	3.6%
Obstetric	59.5%	56.4%	27.4%	25.0%

*Present in >20% of this group. See Tables 1–3 for statistical tests and p-values.