Feasibility Analysis of ECG-based pH estimation for Asphyxia Detection in Neonates

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May 6, 2022

Abstract

Birth asphyxia a potential cause of death is also associated with acute, and chronic morbidities. The traditional and immediate approach to monitor birth asphyxia (i.e., arterial blood gas analysis) is highly invasive and intermittent. Additionally, alternative non-invasive approaches such as pulse oximeter can be problematic, due to the possibility of false and erroneous measurements. Therefore, further research is needed to explore alternative non-invasive and accurate monitoring methods for asphyxiated neonates. This study aims to investigate prominent ECG features based on pH estimation that could potentially be used to explore non-invasive, accurate, and continuous monitoring of asphyxiated neonates. The dataset contains 274 segments of ECG and pH values recorded simultaneously. After pre-processing of data, principal component analysis and Pan-Tompkins algorithm are used for each segment, to determine the most significant ECG cycle, and to compute the ECG features. Descriptive statistics are performed to describe the main properties of the dataset. The Kruskal-Wallis nonparametric test is then used to analyse differences between the two groups. Finally, Dunn–Šidák post-hoc test is utilised for individual comparison among mean ranks of all groups. This study showed that ECG features (mainly QT, QTc, and Tslope/ T) based on pH estimation differed significantly in asphyxiated neonates.

1. Introduction: The neonatal period (i.e., the first 28 days of life) is a critical and vulnerable time for the newborn. The World Health Organization (WHO) reported the global number of neonatal deaths as 2.4 million in 2019. Of these deaths, 75% occur in the first week of life and approximately 42% (1 million) occur in the first 24 hours [1]. The WHO has identified a lack of quality medical care and appropriate interventional treatments during the intrapartum period and early days of life as being key risk factors for poor outcomes. Of specific concern are intrapartum-related complications, particularly birth asphyxia, which is recognized as a primary cause of death [1].

Birth asphyxia is defined by the WHO as a "failure to initiate and sustain breathing at birth" [1]. Birth asphyxia is the leading cause of neonatal deaths, accounting for 24% of neonatal deaths globally and 11% of child deaths under the age of 5 years [2]. A more precise definition of birth asphyxia is given by the American Journal of Obstetrics and Gynaecology (AJOBG), and the American Academy of Paediatrics. A neonate is categorized as asphyxiated if the umbilical arterial pH is < 7, the Apgar score is < 4 for 5 minutes, and there is evidence of neurological symptoms, and multiorgan dysfunction [2].

The most common causes of birth asphyxia are umbilical cord abnormalities (including umbilical cord compression and nuchal cord), uterine rupture during pregnancy or labour, placental abruption (premature detachment of the placenta from the uterus), placenta previa or low-lying placenta, and premature birth [3], [4].

Birth asphyxia is a potential cause of death; however, acute, and chronic morbidities are also associated with the condition. The immediate consequences of birth asphyxia may include hypoxia (lack of oxygen in tissues),

hypercapnia (excess of carbon dioxide in the bloodstream), metabolic or respiratory acidosis, ischemia, and hypotension. Neonates who survive this acute phase may develop long-term neurological sequelae including hypoxic-ischemic encephalopathy (HIE), cognitive impairment, speech and developmental delays, vision, hearing and feeding impairments, emotional and behavioural disorders, and learning disabilities. About 25% of survivors of birth asphyxia develop prolonged neurodevelopment disorders including cognitive and motor impairment, and cerebral palsy. These sequelae are associated with poor treatment options and prognoses [3], [5].

Traditionally, the primary and immediate modality used to assess birth asphyxia is arterial blood gas analysis in neonates. Assessing the birth asphyxia also includes Apgar scores and the manifestation of neurological disorders including sepsis and hypoxic-ischemic encephalopathy [6]. When monitored, birth asphyxia is managed by supplemental oxygen. In birth asphyxia, a low concentration of oxygen (hypoxia) results in metabolic acidosis and damage to the tissues. However, a high concentration of oxygen (hyperoxia) resulting in metabolic alkalosis may also damage the tissues [7], [8]. Blood gas analysis is an accurate monitoring method to assess neonatal conditions after birth asphyxia. Blood gas analysis measures oxygenation, and gas exchange acid-base disorder (metabolic acidosis or metabolic alkalosis). However, the highly invasive and intermittent nature of monitoring blood gas analysis has emphasized the need for the non-invasive and continuous monitoring of oxygenation in neonates [9], [10]. Pulse oximetry (PO) and transcutaneous oxygen monitoring are used for non-invasive continuous oxygenation monitoring in clinical practice. Pulse oximetry measures oxygen saturation in the blood (SpO2) but its accuracy (which is below 80%) is limited in determining the oxygen level in tissues. It may overestimate the neonatal oxygen saturation with fetal haemoglobin [11]. Transcutaneous oxygen monitoring measures the partial pressure of oxygen (PTcO2) through the skin and is influenced by the skin thickness, temperature, and how much contact gel is used [10]. In neonates experiencing low oxygenation, it is necessary to evaluate congenital heart disease. Electrocardiography (ECG) is also considered a definite clinical approach to assess cardiac disease; however, it offers poor sensitivity and low specificity [12].

Thus, an accurate, non-invasive, and continuous assessment of the neonatal condition is necessary and needed for the measurement of metabolic disorders in asphyxiated neonates. ECG is the gold standard for continuously monitoring an infant's HR in the neonatal intensive care unit (NICU). Further analysis of neonatal ECG signals may provide useful and accurate information on asphyxiated neonates. The study aims to investigate prominent ECG features in asphyxiated neonates that can be used for pH estimation (i.e., either neonatal condition is normal or abnormal). Such a capability in ECG would help the clinician in monitoring birth asphyxia non-invasively. Several ECG features including T-amplitude, T-amplitude/QRS-peak ratio, and the slope between T-amplitude and T-off are extracted from a dataset of 49 neonates. The dataset contains 274 segments of ECG and pH values recorded simultaneously. After pre-processing of data, 108 segments of good quality are identified. Principal component analysis (PCA) is used, to determine the most significant ECG cycle for each segment, and features are then computed from each segment using the Pan-Tompkins algorithm. To describe the main properties of the data utilized in this study, descriptive statistics are performed on ECG features using pH values. The Kruskal-Wallis nonparametric test is used to analyse differences between the two groups, followed by the Dunn–Šidák post-hoc test for individual comparison among mean ranks of all groups. The motivation behind this work is that to the best of our knowledge, this is the first time that the acid-base in asphyxiated neonates has been estimated with both ECG recordings and blood sample collection simultaneously. This paper is organized as follows: Section 2 describes the materials and methods used; Section 3 covers the results and discussion. And finally, section 4, ends with the conclusion and the future work.

2. Materials and methods

2.1. Dataset and Selection Criteria: The dataset used in this study has also been used in previous studies [13, 14] and is a private neonatal dataset. The dataset is collected in Neonatal Intensive Care Units (NICU) of the Cork University Maternity Hospital, Ireland between January 2003, and June 2005. The dataset is comprised of 49 neonates (under 28 days of their age, varying from 1 to 25 days) undergoing clinically

perinatal asphyxia. The neonates in this study were recruited if they fulfilled two or more of the following criteria: initial capillary or arterial pH <7.1, Apgar score <5 at 5 minutes, initial capillary, or arterial lactate >7 mmol/l. All recruited neonates were term infants (>= 37 weeks of gestation). The written parental consent of neonates was obtained under the ethical approval of the clinical research committee of Cork Teaching Hospitals. The dataset consists of recorded ECG signals in the time domain with a sampling rate of 256 Hz together with blood gas sample collection for blood gas analysis. Blood samples were evaluated for oxygenation state and acid-base disorders including pH, partial pressure of carbon dioxide (paCO2), and bicarbonate (HCO3). This is a unique dataset that contains raw ECG signals (ECG signals without any pre-processing steps), and simultaneous intermittent measurement of arterial pH using blood gas analysis. Therefore, the dataset allows for the evaluation of the potential of various ECG features to estimate the pH non-invasively.

2.2. pH threshold in Neonates: Umbilical cord blood analysis is used to determine the risk of asphyxia in neonates. And arterial blood gas analysis is used in asphyxiated neonates to determine the threshold values of acid-base disorders. The first step to evaluate the direction of acid-base imbalance is pH estimation. However, the threshold values for fetal pH cannot be used in neonates due to changes in gas exchange right after delivery [15]. Thorborg et al explained the threshold ABG values based on the age of the neonates for pre-birth (pH > 7.20), at 5 minutes after birth (pH =7.20-7.34), and 1-7 days after birth (pH=7.35 – 7.45) [16]. According to Tan et al., the ideal environment for cellular metabolism accepts a range between 7.30 and 7.45 in neonates. This is lower than in older children (˜ 7.38 to-7.42) and there is an alkalosis if pH > 7.45 [17], while metabolic acidosis in neonates is considered if pH < 7.20 [18].

2.3. Signal pre-processing and Extraction of ECG Features: The neonatal ECG data were recorded using a two-lead ECG from chest electrodes. However, some of the neonatal ECG records had only single-channel recordings, so the single lead recordings are used for data segmentation. A ten-second segment is identified just before and after the blood collection time, so the total segment length is 20 seconds. From all available ECG records, a total of 274 segments are extracted where neonatal pH value and ECG were recorded at the same time.

A raw neonatal signal is pre-processed before extracting ECG features. Pre-processing steps involve signal baseline removal and high-frequency noise removal using a low pass Butterworth filter, mean removal, and amplitude normalization. The considerable frequency range to get useful ECG information is 0.05 Hz to 100 Hz. However, all relevant ECG information is considered to be preserved when an ECG signal is down sampled at 50 Hz. Then, a band-pass first-order Butterworth is implemented within the frequency range 0.67 Hz to 50 Hz. The 0.67 Hz threshold was chosen as a suitable frequency for removing the baseline completely without distorting the ECG signal [19]. Raw signal and pre-processed signals are shown in Fig. 1.

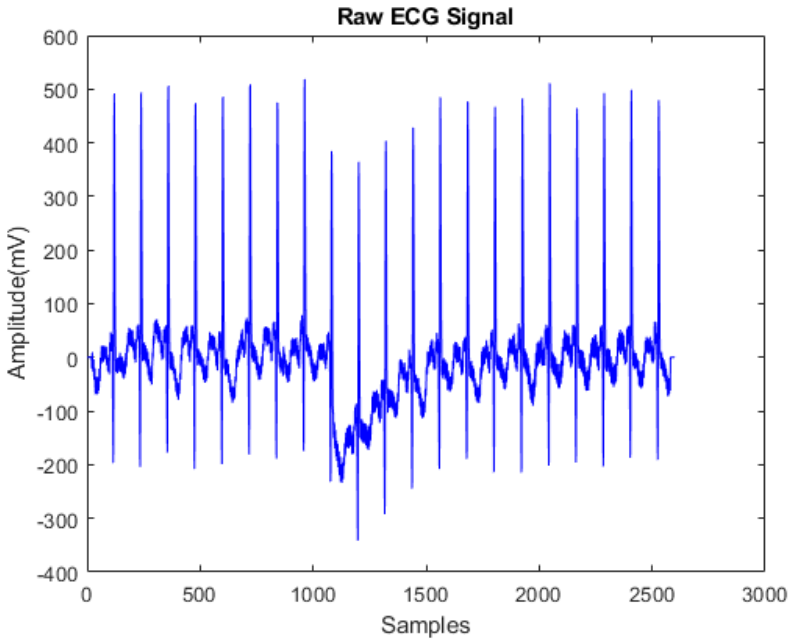


Fig. 1a *Raw ECG Signal*

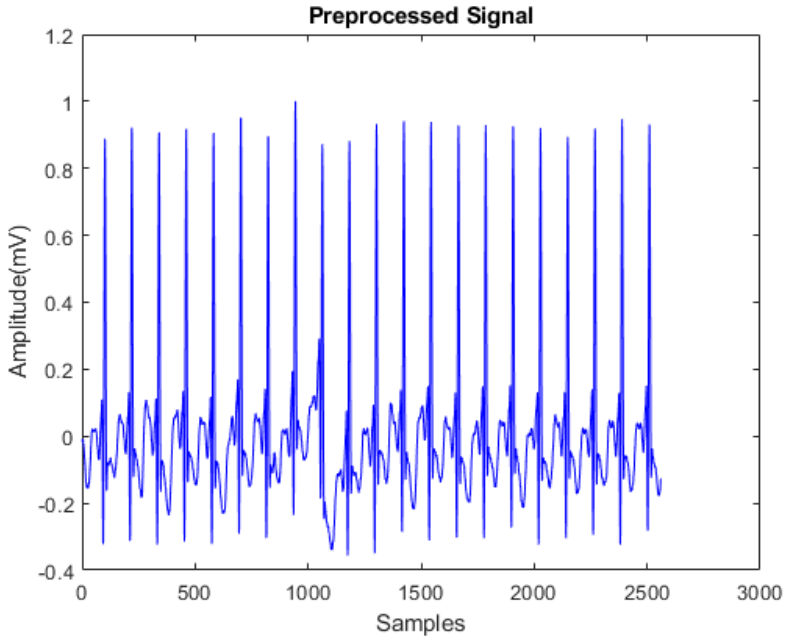


Fig. 1b *Pre-processed ECG Signal*

For feature extraction, the Pan-Tompkins algorithm is applied to pre-processed ECG signals to identify QRS-peaks detection. QRS-peaks detection includes four-stage filtering of the Pan-Tompkins algorithm: bandpass filter, differentiation, point squaring, and moving window integration [20] (Fig. 2). Then the location of QRS-peaks is used to calculate RR-average and heart rate. For T-wave features, a representative ECG

cycle is extracted from each segment and period normalization is performed. In the next step, principal component analysis is performed to get the most prominent ECG cycle for each segment. The principal component analysis is a statistical approach for extracting the most relevant principal components and normalizing them individually, by sliding a window over the data to reduce the non-stationarity effect [21]. Once the most prominent representative signal

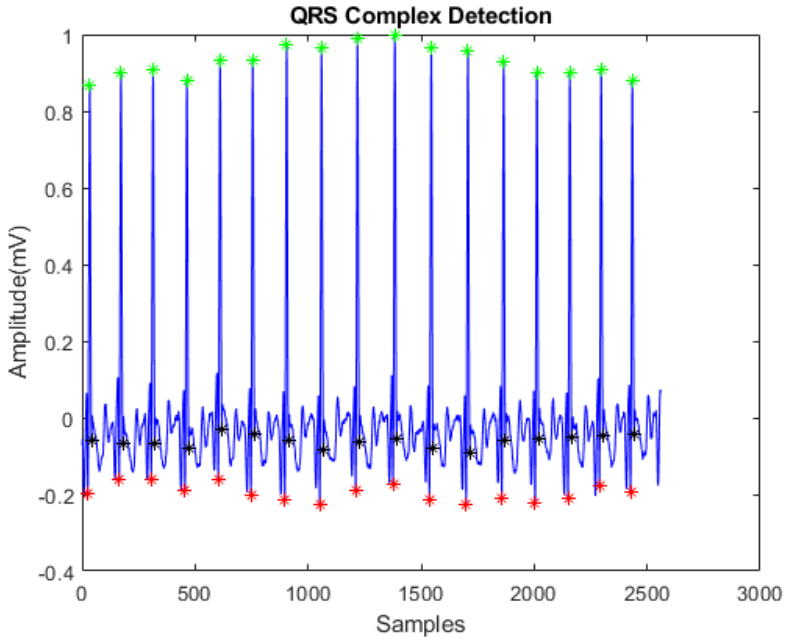


Fig. 2 *QRS-peaks detection*

is identified, QRS-peaks is detected again to use as a reference ECG feature. With the identified reference QRS-peaks, other T-wave features are extracted from the post PCA representative signal [22]. In the next step, ECG features used in this study are calculated. These features include, T Amplitude, Tslope, Tslope/T, HR, QT, QTc, RRAvg, Tslope/sqrt|T| and Tslope/|T| (Fig. 3). The T wave features may provide useful information about metabolic disorders [23], so T-wave features have been given more emphasis to evaluate metabolic disorders in asphyxiated neonates.

2.4. Statistical Analysis of ECG Features: The first step is to determine the direction of the acid-base imbalance by evaluating the neonatal pH value. The acid-base imbalance gives information about the acidosis and alkalosis disorders based on neonatal blood gas analysis. [24]. The dataset used in this study has 274 segments recorded from 49 neonates. On excluding the poor signals, 108 segments of good quality remain, where ECG waveform and pH values are recorded simultaneously. Moreover, based on the pH value the data is further categorized into three groups: 9 segments occur where the pH value is less than 7.20 (metabolic acidosis or acidosis) and 83 segments occur where the pH ranges between 7.20 and 7.45 (this range is considered normal), and 16 segments where pH is greater than 7.45(metabolic alkalosis or alkalosis). Using pH threshold values, in this study neonatal condition is categorized into three groups acidosis, normal, and alkalosis.

2.4.1. Descriptive Analysis: Descriptive statistics is conducted on ECG features using pH values in MATLAB Software to summarize the basic features of the data used in this study. Various statistical methods are based on assumptions about the normality of the data, so assessing the normality of data is considered an important prerequisite for many statistical methods. Graphical and numerical methods offer unbiased judgment to assess data normalization; however, graphical methods have the advantage over the numerical

method. Such as, in assessing the normality of data, a numerical method may be under-sensitive to low sized sample dataset (n <50, n = number of samples) and oversensitive to a large ample-sized dataset (n > 300) [25]. For graphical representation, box and whisker plots are used for the summarization and distribution of data between groups [25].

2.4.2. Statistical Analysis: Statistical analysis using a non-parametric test was performed on MATLAB software. Data measurements were expressed as median [inter quartile range (IQR)] to compare the groups. Given a small and imbalanced dataset, a multiple group comparison test was used to analyse the difference between groups. A post hoc test was performed after the multiple group comparison test, and statistically significant differences were found based on the p-value ($p < 0.05$).

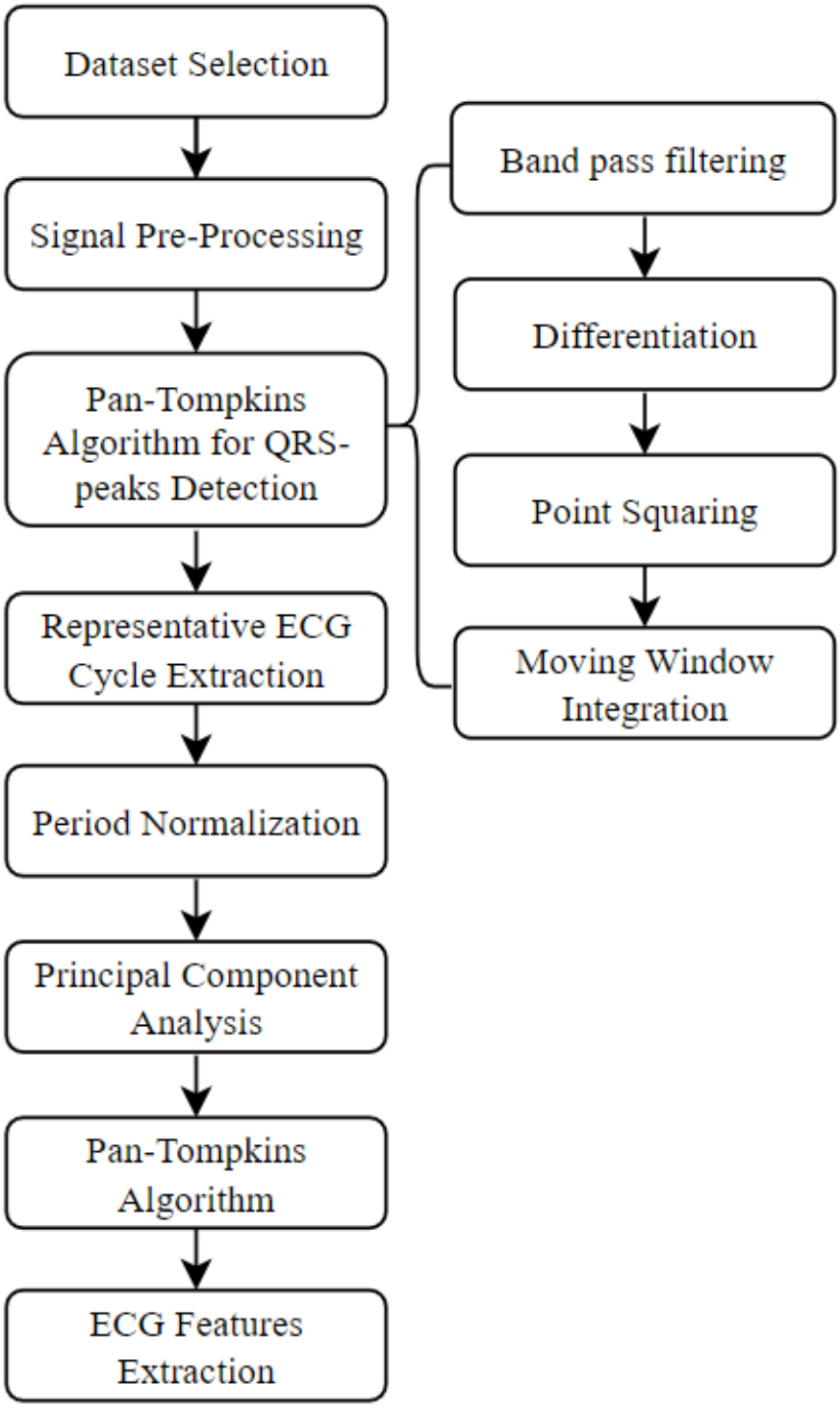


Fig. 3 *Flow chart of ECG Features Extraction*

The difference between groups was analysed by the Kruskal-Wallis Test. Dunn–Šidák post-hoc test was used to validate the Kruskal-Wallis Test for comparing measurement data between the groups. When the data

on which the tests are based are reranked pairwise, the ranks of the data change. Dunn's test demonstrated how to deal with this problem using a Bonferroni adjustment, which involves dividing the p-value (p-value 0.05) by the total number of tests and requiring a considerably smaller p-value (here p-value 0.05*1/3) to reject any test. This modification keeps the p-numerical value but multiplies it [26]. The familywise error rate (FWER) is based on this modification i.e., a re-definition of p-value to indicate the possibility of falsely rejecting the null hypothesis in one test out of all the testing done. The FWER was introduced by the Bonferroni adjustment. However, the Šidák adjustment is a little more powerful, yet equivalent, approach. This adjustment considers subsequent pairwise hypothesis testing as part of distinct families and depends on whether prior tests were rejected [26]. Hence, to keep the rank sums from the chi-square test after a Kruskal–Wallis test, Dunn's-Šidák post-hoc test is the suitable approach. Two groups' mean ranks are significantly different if their intervals are disjointed; they are not significantly different if their intervals overlap. The p-value ($p < 0.05$) was treated as statistically significant [27].

3. Results and discussion: The first step in determining the direction of the acid-base imbalance is to evaluate the pH in blood gas analysis [24]. The dataset used in our study has datapoints of only 25 patients with 108 segments where ECG waveform and pH values are recorded simultaneously. The data is further limited by the fact that only 9 segments exist in the dataset where pH value is less than 7.20 (metabolic acidosis), 83 segments where pH ranges between 7.20 and 7.45 (this range is considered normal) and only 16 segments where pH is greater than 7.45(metabolic alkalosis) (Fig. 4). All ECG features used in this study are grouped (acidosis, normal, and alkalosis) by pH values.

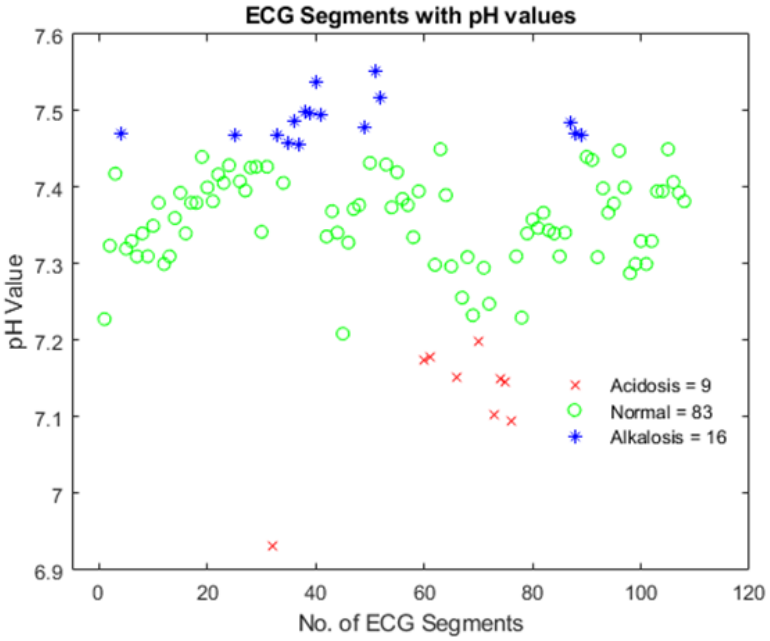


Fig. 4 *ECG Segments vs pH value*

3.1. Results from descriptive analysis: The distribution pattern of the data (parametric or non-parametric) was observed by examining the results of the box and whisker plots. A box plot with a median line approximately at the centre is considered symmetric and with symmetric whiskers indicate that the data may have come from anormal distribution. Where outliers are present in our dataset, removal of the outlier is required, or the data is treated as not normally distributed [23]. If data follows the normal distribution, then

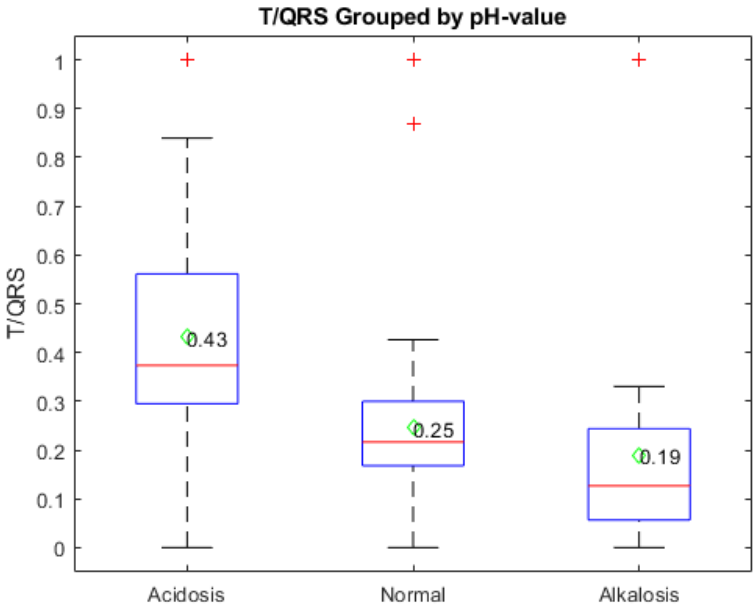


Fig. 5*a* *T/QRS*

the mean value of the data is considered as a representative value of the data/ In the case of non-normal, skewed, or unknown

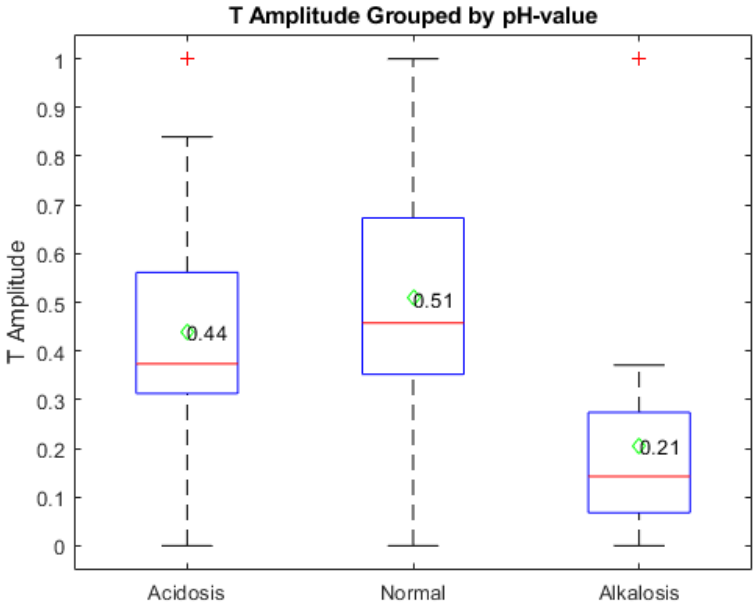


Fig. 5*b* *T Amplitude*

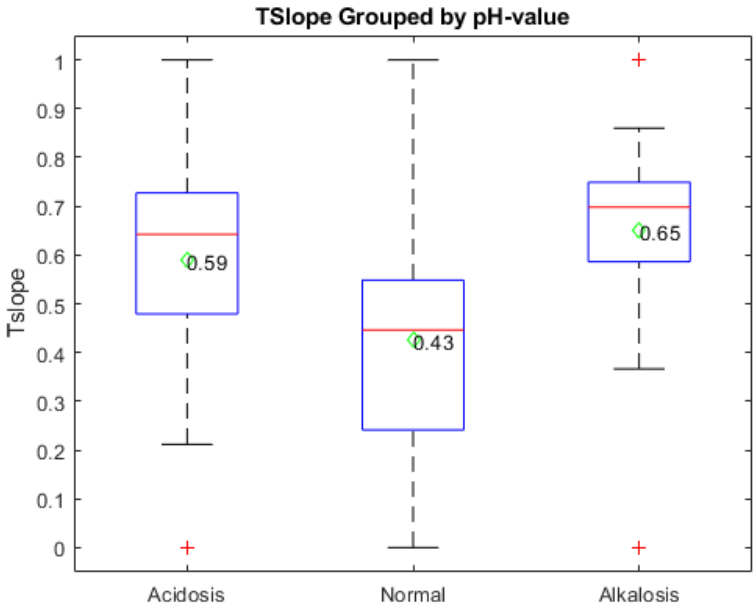


Fig. 5*c T Slope*

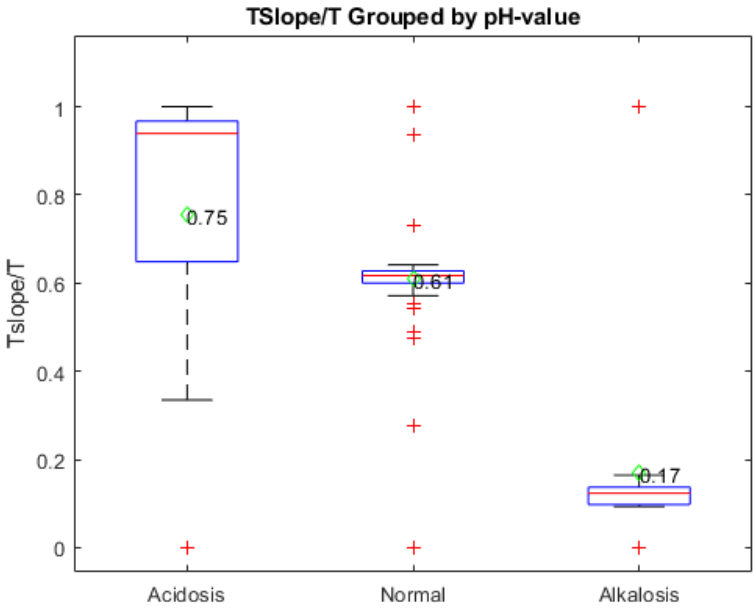


Fig. 5*d T Slope/T*

distribution, the median value is used as a representative value of the data. For normal data, parametric tests are used. Otherwise, non- parametric tests are used to compare the groups, even with a small

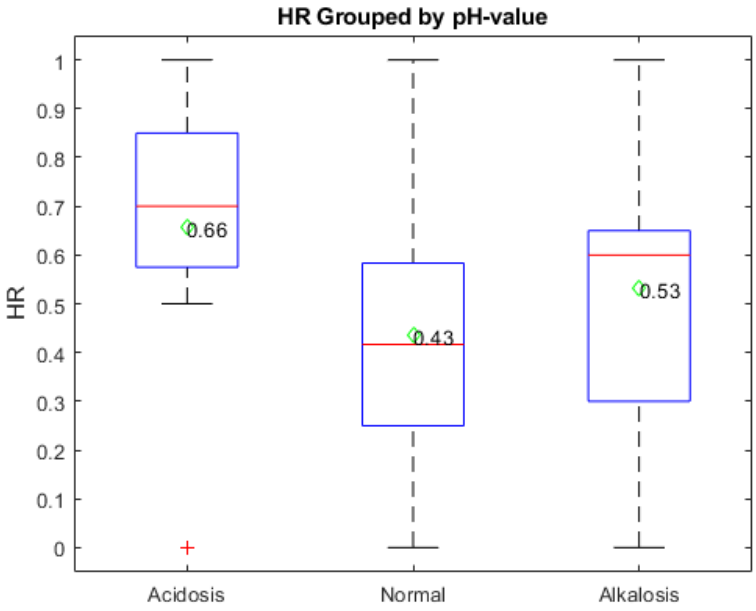


Fig. 5*e HR*

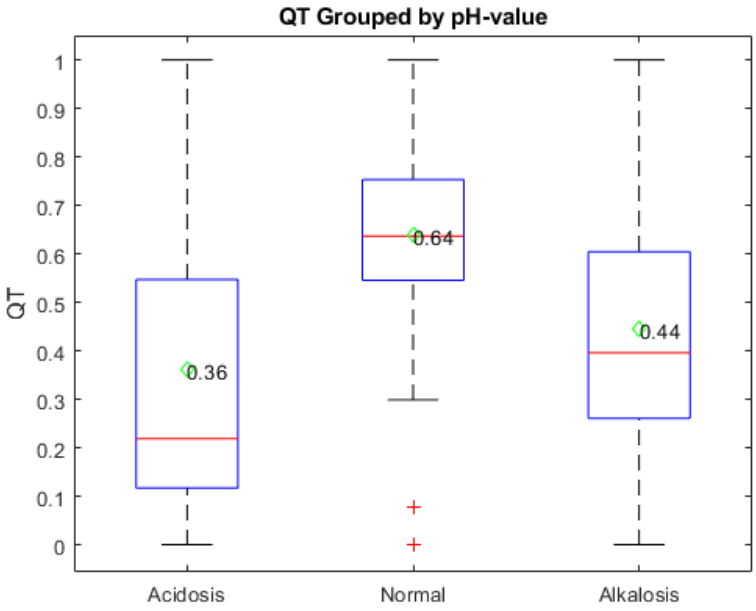


Fig. 5*f QT interval*

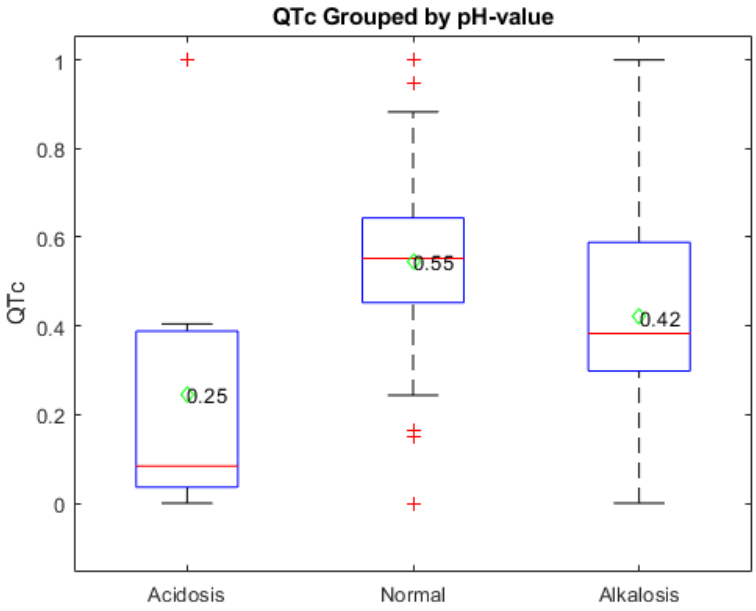


Fig. 5*g QTc Interval*

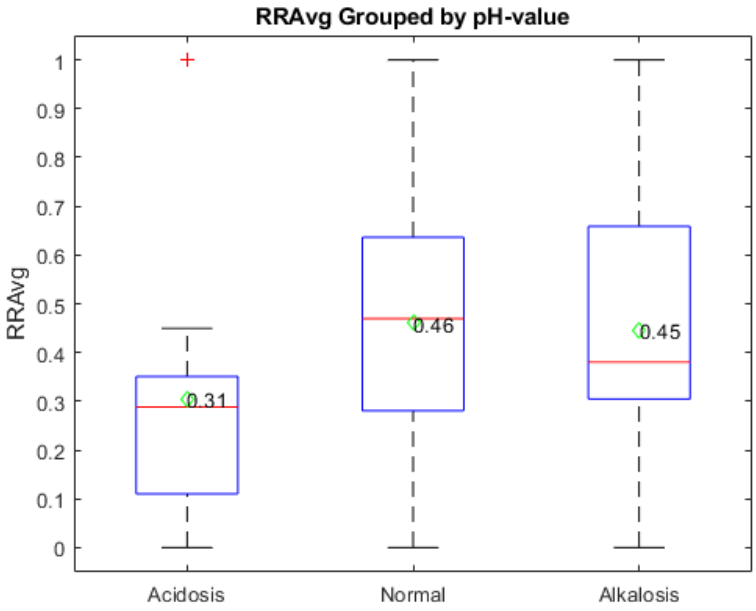


Fig. 5*h RR Average*

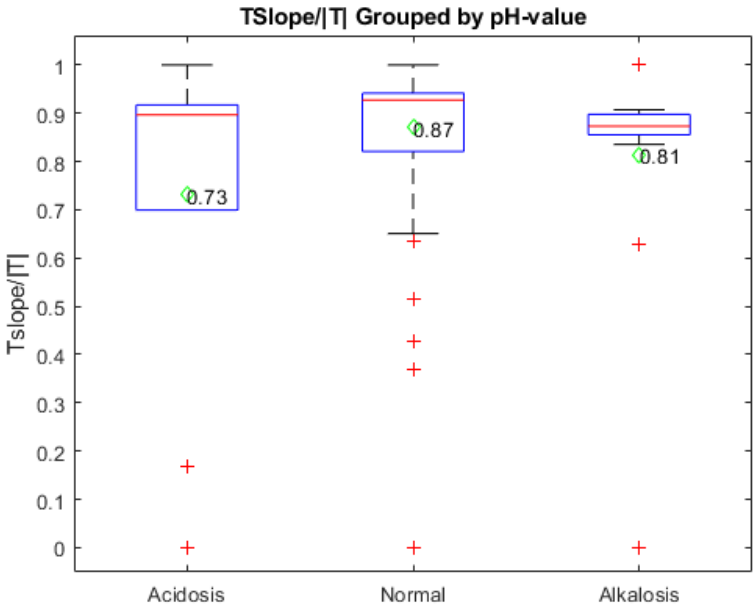


Fig. 5*i* *Tslope//T|*

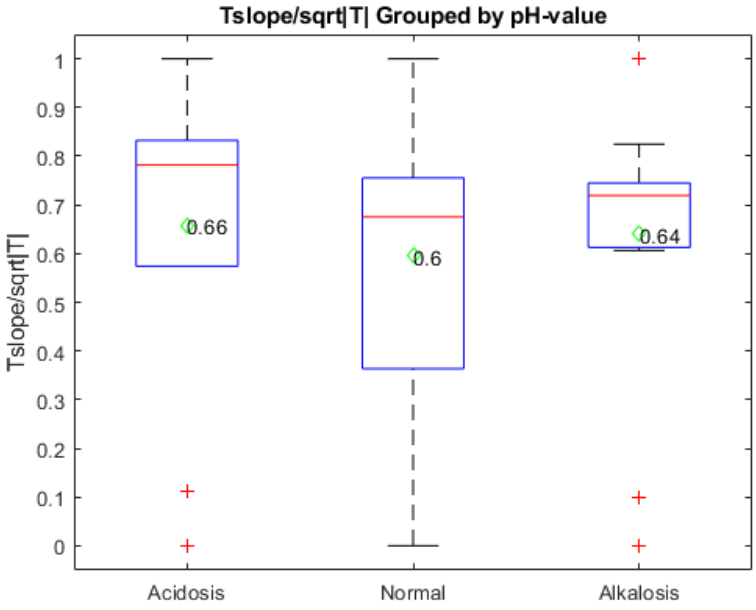


Fig. 5*j* Tslope/[?]|T|

Fig. 5 (5*a* -5*j*) *Descriptive analysis using box plots has shown that data is not normalized*

sample size (n $<$ 50) [22]. From the boxplots (Fig. 5), the inner 50% of the data do not appear symmetric about the median, a characteristic that we would expect from normal data. Therefore, the data may not be

normally distributed. The data used in this study for each group is small to medium-sized sampled (50 [?] n < 300) data and is strongly unbalanced (acidosis = 9, normal = 83, and alkalosis = 16). The boxplots suggest that the data is not normal; therefore, the non-parametric test was selected for further statistical analysis.

4.2. Results from Statistical Analysis: The Kruskal-Wallis test is performed to determine whether differences between groups exist. It is used to test the null hypothesis that ECG Features medians are equal in all groups, versus the alternative that there is a difference between at least two of the groups. The test statistics for the Kruskal-Wallis test approximate the chi-square distribution, if the number of observations in each group is [?] 5, with k-1 degrees of freedom. k is the number of comparison groups. If the calculated value of the Kruskal-Wallis test is less than the critical chi-square value, then the null hypothesis cannot be rejected. If the calculated value of the Kruskal-Wallis test is greater than the critical chi-square value, then the null hypothesis is rejected: that is at least one of the groups comes from a different population [23].

The output of the Kruskal-Wallis test in our dataset, for example, for T/QRS gives the p-value of 0.0076. Importantly, the chi-square is less than the calculated value of the Kruskal-Wallis test, indicating that at least one of the groups is different from the others. The results for other features including T Amplitude, Tslope, Tslope/T, HR, QT, and QTc) are also significant, indicating that at least one of the groups in all these features is significantly different from the others. Three features (RRAvg, Tslope/sqrt|T| and Tslope/|T|) are excluded from further analysis, as the output values for the Kruskal-Wallis test indicated that none of the groups is significantly different from other groups. The statistical outputs are shown in Table 1.

Table 1: Kruskal-Wallis test

ECG Features	Chi-square value	p-Value
T/QRS	9.77	0.0076
T Amplitude	22.23	0.0000
Tslope	18.64	0.0001
Tslope/T	32.93	0.0000
HR	7.8	0.0202
QT	16.24	0.0003
QTc	16.32	0.0003
RRAvg	4.05	0.1319
Tslope/|T|	6.89	0.0318
Tslope/[?]|T|	2.6	0.2719

When the null hypothesis that ECG Features medians are equal in all groups are equal is rejected, there is a need to determine where the difference among the medians is. To determine which pairs of medians are significantly different, and which are not, Dunn–Šidák post-hoc test is used. Pairwise comparisons using Dunn's test for T/QRS indicated that the acidosis group's (group 1) mean ranks were observed to be significantly different (p = 0.0066) from those of the alkalosis group (group 3). No other differences were statistically significant for T/QRS Feature. Similarly, results for T Amplitude indicated that normal group's (group 2) mean ranks differed significantly from the alkalosis group (p= 0.0000) and no other differences were statistically significant. The statistical outputs are shown in Table 2.

Table 2: Dunn–Šidák post-hoc Test

ECG Features	Groups	Groups	Mean ranks	Interval	Interval	p-Value
T/QRS	1	3	8.7705	39.9306	71.0906	0.0066
T Amplitude	2	3	19.6905	40.1092	60.5279	0.0000
Tslope	2	3	-54.7252	-34.3065	-13.8878	0.0002
Tslope/T	1	3	35.1733	66.3333	97.4934	0.0000

ECG Features	Groups	Groups	Mean ranks	Interval	Interval	p-Value
	2	3	22.4849	42.9036	63.3223	0.0000
HR	1	2	2.1611	28.3186	54.4761	0.0289
QT	1	2	-57.4931	-31.2557	-5.0183	0.0133
	2	3	6.8566	27.2696	47.6826	0.0043
QTc	1	2	-64.4095	-38.1647	-11.9199	0.0015
	2	3	0.8501	21.2688	41.6875	0.0381

The interactive graph of mean ranks estimates and compares interval for ECG features. The mean ranks in Fig.6*a for* T/QRS show that the comparison interval for the acidosis group and alkalosis group do not intersect. This lack of intersection suggests that the mean rank of the acidosis group is significantly different than the mean rank of the alkalosis group. The interactive graphs are used to plot the means ranks of groups for all ECG features. And the interactive graphs with significantly different mean ranks are shown in Fig. 6.

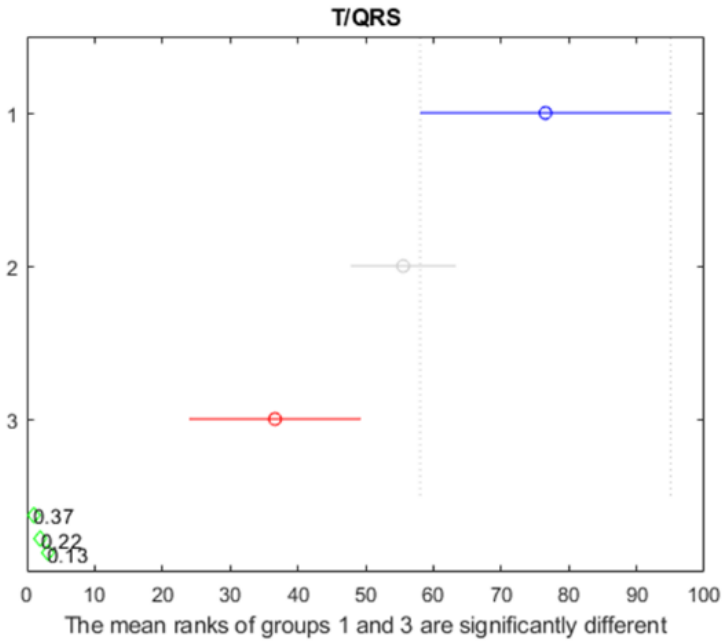


Fig. 6*a T/QRS*

The significant difference in metabolic disorders in asphyxiated neonates compared to the normal group was investigated. If the neonate is experiencing a hypoxic condition leading towards asphyxia, the results have shown that proper clinical management results in the normal condition of the neonate. However, poor management may result in metabolic disorders that can be assessed by pH value, using invasive blood sampling collection. Significant differences were evident between the normal condition of the neonate and metabolic disorders when ECG Analysis was performed. QT, QTc, and Tslope/ T are the three main ECG features that are significantly different in all three groups (acidosis, normal, and alkalosis). The strength of this study is the study design for pH estimation on an ECG dataset, with blood gas measurements recorded and analysed in asphyxiated neonates.

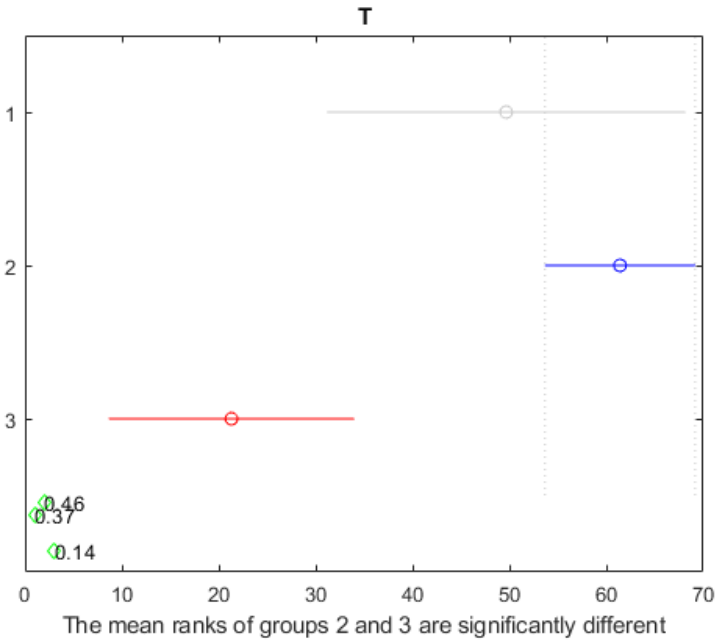


Fig. 6*b* *T Amplitude*

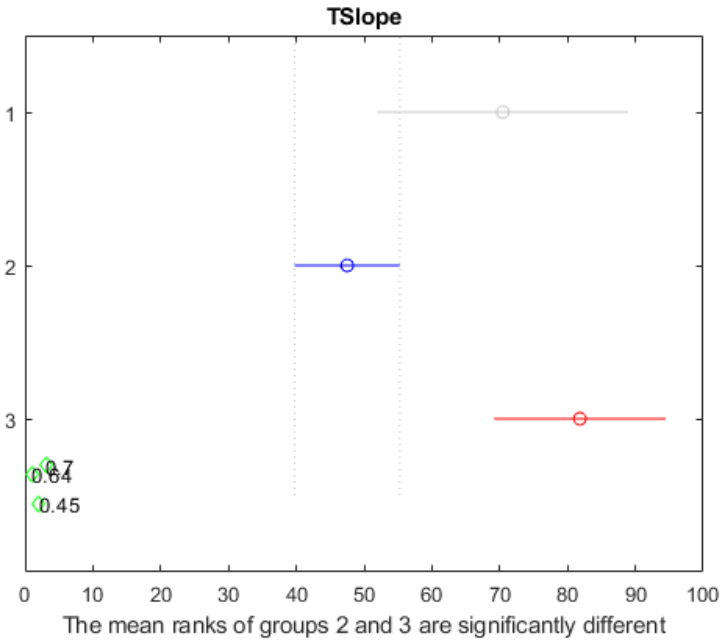


Fig. 6*c* *T Slope*

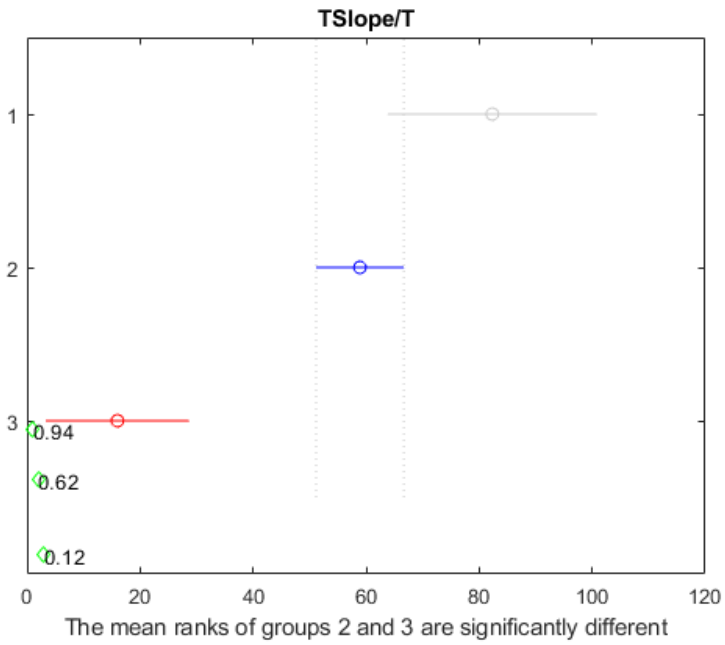
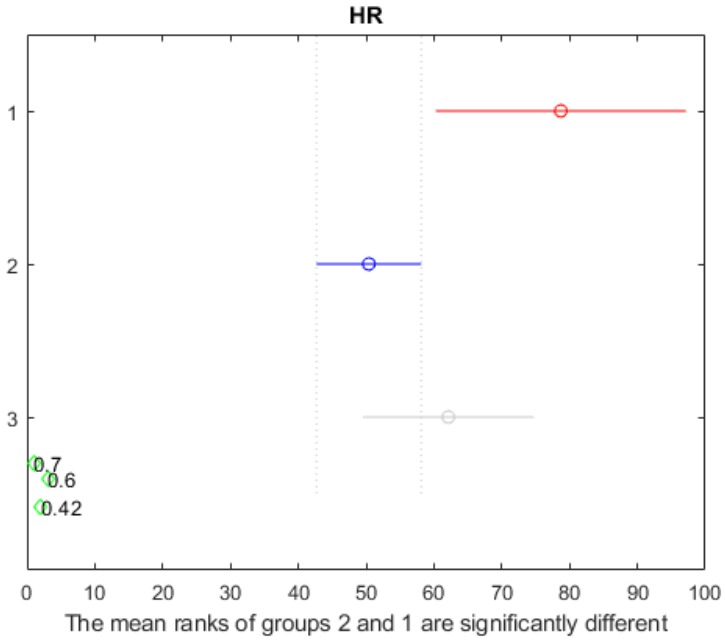


Fig. 6*d* *Tslope/T*



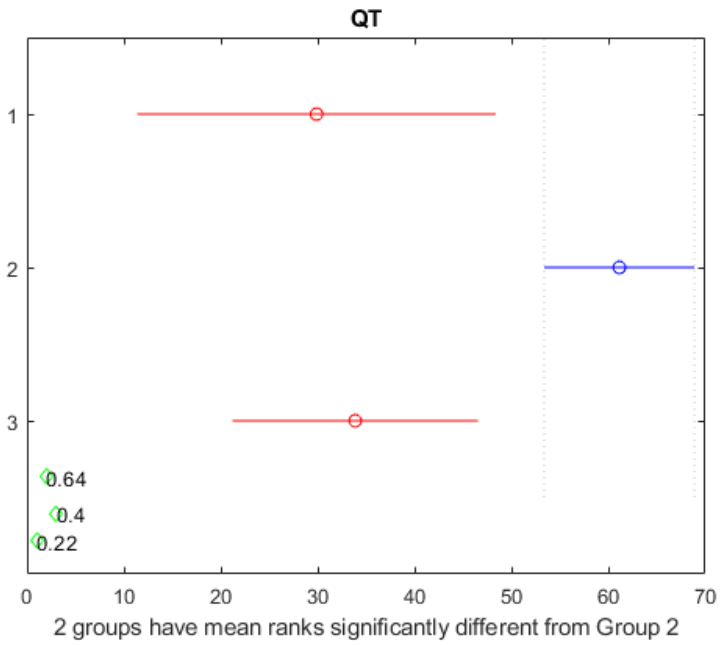


Fig. 6*e* *HR*

Fig. 6*f* *QT*

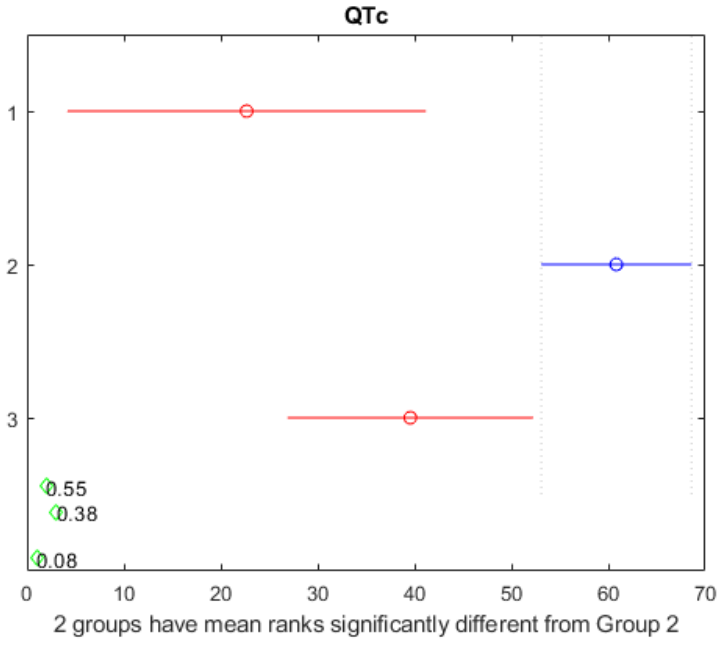


Fig. 6*g* *QTc*

Fig 6 (6a-6g). The interactive graphs for the significantly different ECG features among all three groups (acidosis, normal, and alkalosis).

A major limitation of this study is the size of the study population and that all three groups have a different number of data points, which limits the ability to identify rare, serious, adverse events. The imbalanced and small-sized study also limits the test applied for the statistical analysis. Additionally, in this study only one parameter (pH value) is considered for acid-base estimation. However, other parameters including base excess (BE), partial pressure of O2 (pO2), partial pressure of CO2 (pCO2), and bicarbonate (HCO3-) can play an important role while determining the metabolic disorders in neonates [28]. Another main challenge during analysis is the poor quality of the ECG recordings, which may be interfered with by neonatal motion artifacts and variations in electrode placement. These low and high-frequency noises may have an impact on signal pre-processing, QRS peaks detection, ECG features extraction, and further analysis of ECG features. For example, after pre-processing 274 ECG segments were extracted. However, upon applying features extraction algorithms more than half of these segments were rejected due to poor signal quality, and features were extracted from only 108 good quality segments. A large prospective study in the context of asphyxiated patients with optimized ECG features processing algorithms may overcome the limitations of this study.

5. Conclusion and future work: This paper, for the first time, evaluated the behaviour of ECG Features in asphyxiated neonates while measuring the blood gas analysis simultaneously. This study showed that ECG features (Tslope/T, QT, QTc, T/QRS, T Amplitude, Tslope, and HR) significantly differ in neonates with asphyxia. Additionally, QT, QTc, and Tslope/ T are the three main ECG features that are significantly different in all three groups (acidosis, normal, and alkalosis), before and after the management of asphyxia in neonates. Therefore, using all these significant ECG features or a combination of these, this study might aid the investigation of non-invasive, accurate, and continuous monitoring techniques for asphyxiated neonates. Although we have used a small and imbalanced dataset to measure ECG features that are the important markers to predict the neonatal condition after birth asphyxia, our study may guide clinicians to consider the significant ECG features in the clinical management of asphyxiated neonates. Further studies in larger cohorts will extend these results toward non-invasive and accurate monitoring of asphyxia.

5. Acknowledgments: The authors gratefully acknowledge the contribution of Prof. Geraldine Boylan and her team (University College Cork, Ireland) for providing the private dataset of asphyxiated neonates to conduct this study.

6. Funding and Declaration of Interests:

This work is funded by the Science Foundation Ireland (Grant Number: 17/RC-PhD/3482) and the Irish Centre for Fetal and Neonatal Translational Research (INFANT) Cork, Ireland.

The authors declare no conflict of interest.

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