Anticipating Fainting: Real-Time Prediction of Vasovagal Syncope during Head-up Tilt Table Testing

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Abstract*— Vasovagal syncope (VVS) is the commonest cause of short-term loss of consciousness, which negatively impacts quality of life. To gather diagnostic information, medical professions often perform a head-up tilt test (HUTT) during direct observation. During this test, subjects may experience common symptoms such as nausea, pallor, sweating, palpitations, near faint and syncope. The purpose of the study was to develop an algorithm that uses electrocardiography (ECG) and blood pressure (BP) recordings from HUTT to predict VVS before its onset. In this study, the calculated cumulative risk based on the analysis of the three specific sets of features was compared to a pre-established VVS risk threshold. The purpose of this comparison was to determine if the cumulative risk was above or below the threshold and whether an alert should be generated. An alert would only be triggered when the cumulative risk exceeded the threshold. The prediction time was defined as the duration between the first alert and the actual syncope episode. A total of 137 subjects were recruited in this study. Our proposed model accurately predicted syncope onset in 87 out of 120 subjects. The model's sensitivity was 81.6% while its specificity was 66.2%. The precision was determined to be 62.5%, the F1 score was 70.8%. Additionally, the model was able to predict syncope before its onset with a median prediction time of 221.45 seconds (Interquartile range: 180.0 - 294.0 s). In conclusion, while predicting VVS can be challenging due to its complex nature, recognizing, and treating the underlying causes as well as implementing appropriate treatment methods, can significantly improve outcomes for individuals at risk. The proposed algorithm shows promise in reducing discomfort associated with symptom reproduction with HUTT.

Keywords*— Vasovagal syncope, head-up tilt test, autonomic nervous system, early prediction.

I. Introduction

Vasovagal syncope (VVS), which is a reflex syncope, is the most frequent cause of transient loss of consciousness [1]. When sympathetic tone is reduced and the parasympathetic nervous system briefly becomes overactive, arterial hypotension and cerebral hypoperfusion occur, which lead to VVS [2]. Over 40% of people experience a temporary loss of consciousness in their lifetime, and two-thirds of these cases are due to reflex syncope, also known as neurally mediated syncope [2]. Depending on the situation and the person's medical history, VVS might result in different outcomes. It typically doesn't have any major or lasting effects. However, in some circumstances, it can result in harm, especially if the person falls during the episode. Injuries can vary widely from minor cuts and bruises to more serious wounds like head trauma, fractures, or dislocations [3]. VVS could be crippling and have a negative impact on a person's quality of life, especially if it happens unexpectedly or while performing tasks that require concentration and focus, such as driving or operating large machinery [4]. In addition, VVS poses a risk to people in high-risk professions and older adults who do not exhibit any warning signs [5]. Therefore, early identification of syncope will lead to better outcomes, lower the risk of accidents, and provide the support needed to optimize management.

If typical symptoms are present, VVS can be diagnosed from the patient's history alone. In cases with atypical presentation, absence of a clear prodrome and frequent, disabling symptoms, head up tilt test (HUTT) is frequently conduction with direct medical observation to acquire diagnostic information. The objective of the HUTT would be to reproduce subjects' symptoms including nausea, sweating, pallor, palpitations, near faints and faints.

Heart rate (HR) and blood pressure (BP) are controlled by the autonomic nervous system (ANS), which is made up of the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) [6]. The two systems quickly switch off and on in healthy individuals to maintain the regulatory balance in physiological autonomic function. Potential key indicators towards prediction of pre-syncopal and syncopal symptoms before they occur are systolic blood pressure (SBP), a frequency domain variable of SBP, and heart rate (HR). These indicators are considered more important than heart rate variability (HRV) in predicting VVS. The goal of

this study was, therefore, to create an algorithm capable of forecasting VVS before it occurred using ECG and blood pressure recordings from the HUTT.

II. METHODS

A. System Overview

All processing steps were conducted on a laptop with Intel (R) Core (TM) i7-6600U 2.60 GHz CPUs and 8GB of RAM. To easily modify and visualize data and keep track of the code and investigation in a reproducible manner, an open-source web tool, Jupyter Notebook, was utilized. The python packages deployed were numpy, pandas, and matplotlib.

B. Data Collection

Data collection took place at the cardiorespiratory laboratories, Universiti Malaya Medical Centre (UMMC). Involving patients referred for HUTT due to syncope or near-syncope. Prior to the test, patients were provided with the necessary information, and informed consent was obtained. The study received approval from both Universiti Tunku Abdul Rahman (UTAR) Scientific and Ethical Review Committee (U/SERC/218/2020) and the UMMC Medical Research Ethics Committee (MREC ID NO: 2020913-9066). The HUTT was performed in a controlled environment and involved the administration of 800 micrograms of glyceryl trinitrate (GTN) under the tongue to provoke a pharmacological response. The patients were tilted at a 70-degree angle using a tilt-table with a footplate and remained in that position for 20 minutes after a 10-minute supine rest period [7]. During the test, non-invasive monitoring equipment (Task Force Monitor, CNSystem, Austria) was used to measure hemodynamic parameters such as ECG and beat-to-beat BP signals. The test is considered positive if physical changes, such as decrease in heart rate, cardiac interruptions, and low blood pressure. Conversely, if neither physical changes nor symptoms are present during the test, the results are considered negative [8].

C. Early Vasovagal Syncope Prediction Algorithm

The sampling rate for the beat-to-beat BP signal was 100Hz, and 1000Hz for the non-intrusive continuous ECG data. Twenty-four beat-to-beat variables from the HUT test, which included both supine and 70-degree tilting positions. HR, SBP, DBP, and their frequency domain characteristics are among the twenty-four beat-to-beat variables collected or derived. High frequency normalized power, low frequency normalized power, and the ratio of low-frequency to high-frequency systolic blood pressure variability normalized power are illustrations of frequency domain measurements. The study employed numerous iterations of the trial-and-error process to select the elements of the early VVS prediction algorithm. Feature combinations for our early VVS prediction system are listed below:

1. SBP, HR and LFHF_SBPV
2. SBP, HR and HFnu_SBPV
3. HR, SBP, LFnu_HRV and Lfnu_SBPV

The study took the past three minutes' worth of supine position signal in order to obtain a steady signal. Then, from the chosen features, we derived the mean and standard deviation. The values of SBP, HR, Lfnu_SBPV (normalized low-frequency power of systolic blood pressure variability), LFHF_SBPV (ratio of low-frequency to high-frequency systolic blood pressure variability), HFnu_SBPV (normalized high-frequency power of systolic blood pressure variability) were standardized with respect to the baseline because the ranges of the attributes vary, bringing them to comparable levels. Formula (1) as shown below was used to normalize the tilting position signals:

$$Normalization = \frac{X_i - X_{baseline}}{baseline\ standard\ deviation} \quad (1)$$

$$1.\ G\_risk = -(wfSBP * NorSBP) + (wfHR * NorHR) - (wf\text{LFHF\_SBPV} * NorLFHF\_\text{SBPV}) \quad (2)$$

$$2.\ G\_risk = -(wfSBP * NorSBP) + (wfHR * NorHR) + (wf\text{HFnu\_SBPV} * Nor\text{HFnu\_SBPV}) \quad (3)$$

$$3.\ G\_risk = (wfHR * NorHR) - (wfSBP * NorSBP) - (wfLFnu\_HRV * NorLFnu\_HRV) - (wf\text{Lfnu\_SBPV} * Nor\text{Lfnu\_SBPV}) \quad (4)$$

Calculated values of below 1 were represented as -1. Calculated values above 1 were indicated by the number 1. The resulting normalized values fall into the range of -1 to 1, with -1 denoting a strong reduction from baseline, 0 a no change, and 1 a high rise. The sum of the weighting factors for the various features, which were also chosen by trial and error, should not be greater than 1. Then, using the formulas below, the cumulative sum of the global risk was determined. Here G_risk was represented as global risk, wf as weighting factor and nor as normalized. The total global risk was the result of adding the corresponding features' normalized sums and weighting factors. The computation for the normalized heart rate and HFnu_SBPV only considers positive signs because it raises the overall risk. SBP, LFHF_SBPV, LFnu_HRV, and Lfnu_SBPV all exhibit normalized values with negative signs in VVS test positive patients, indicating a reduction in those specific parameters while an increase in these components lowers the total risk. A fall in blood pressure causes VVS, which also causes a slowing of the heartbeat and pulse. VVS would also be caused by a malfunction in the autonomic control of the circulatory system. Studies evaluating the impact of HUTT on frequency domain analyses of HRV and BPV in healthy people have shown a notable rise in the LF power spectrum in addition to the withdrawal of the high frequency or parasympathetic tone.

Abnormal autonomic balance may contribute to activation of the Bezold-Jarisch reflex contributing to the mechanism leading to syncope [9]. In normal physiological conditions, when a individual has postural change from lying down to standing up, the body's internal regulating

mechanism begins to operate to prevent large changes in cerebral blood flow (CBF) during the action.

In postural hypotension, individuals may experience a short period of dizziness or syncope because of rapid reduction in cerebral perfusion when getting up quickly, particularly if both abnormalities cerebral autoregulation and ANS are present. HUTT can be used to simulate a similar situation and provide comprehensive information including the possible causes and severity of postural hypotension. During the process of posture change, biophysiological signals such as HR, BP and CBF can be changed dependently or independently, and HUTT can make the correct diagnosis from analysis of the signals during the test and raise the alarm if patients' systemic or cerebral haemodynamic changes crosses the risk threshold and mark them as syncope positive; or otherwise, mark them as syncope negative.

Our early syncope prediction system's cumulative risk gauges how likely it is that the patient will experience a syncope episode. It is measured and put up against a warning threshold that has been determined through adoption of gridsearch concept, 0.01 for each increment, within the range of 0 – 1. The system predicts a syncope episode upon exceeding the threshold and generates an alert (Fig. 2.).

D. Performance Evaluation

The evaluation of the early prediction algorithm included the use of several performance evaluation metrics including recall, specificity, precision and F1 score. The following formulas were used to calculate our proposed models.

$$\text{Recall (Sensitivity)} = \frac{\text{TP}}{\text{TP} + \text{FN}} \tag{5}$$

$$\text{Specificity} = \frac{\text{TN}}{\text{FP} + \text{TN}} \tag{6}$$

$$\text{Precision} = \frac{\text{TP}}{\text{TP} + \text{FP}} \tag{7}$$

$$\text{F1 scor} = 2 * \frac{\text{Precision} * \text{Recall}}{\text{Precision} + \text{Recall}} \tag{8}$$

Where, true positive (TP), false positive (FP), false negative (FN), and true negative (TN) are all included in the calculation of the confusion matrix. A test positive patient is designated as TP when the model predicts them as test positive. FP is used to indicate a test negative patient that has been predicted as a test positive. A test negative patient, on the other hand, is identified as TN. A test positive patient is predicted as test negative and is indicated by FN.

III. Results and Discussion

A total of 137 participants were selected in the study. However, due to missing beat-to-beat data, only 120 patients' data were used for the early prediction algorithm analysis. The average age of test individuals who were positive was 66.87 ± 20.44 years, while test negative subjects were aged 65.34 ± 20.0 years.

The mean was calculated by taking the total number of values in a dataset and dividing it by the number of values, which represents the data's dominant trend. The standard deviation is an indicator of how much variety there is in a set of data. It is determined by averaging the squared deviations between each value in the dataset and the mean, which is the variance, then dividing that result by the square root of the variance. One way to understand the typical gap between data points and the mean is to imagine it as the regular distance that separates the data points from the central value. A low standard deviation implies that the data points are within a restricted range of the mean, whereas a high standard deviation suggests that the data points are dispersed throughout a wide range of values. If the data are distributed normally, the standard deviation may be less than, equal to, or larger than the mean depending on how the data are distributed specifically. Our standard deviation is higher than the mean due to the occurrence of extreme values at both ends (Table I). In some cases, skewed or artificially exaggerated standard deviations may have resulted from the way data was collected or measured. These extreme numbers can have a significant impact on the data's variability.

In datasets with unbalanced classes, accuracy may be misleading when one class has disproportionately large numbers of instances compared to the other. Sensitivity is a better choice in these circumstances. The three feature combinations SBP, HR, and LFHF_SBPV produce the best outcomes. Therefore, the most efficient pairings include SBP = 0.89, HR = 0.1, LFHF_SBPV = 0.01and risk threshold = 0.6. Our model correctly predicted 87 subjects. With a sensitivity of 81.6%, a specificity of 66.2%, a precision of 62.5%, and a F1 score of 70.8%, the proposed methodology successfully predicted VVS patients before its onset. The VVS prediction time was 544.2 ± 545.6 seconds. TABLE I presents the early syncope prediction outcomes. It is important to note that while all three sets of features are combined, the intention is to capture a more holistic representation of the complex physiological processes underlying early VVS. However, as our analysis found that the combined all three feature set performed worse than individual set, potentially due to leveraging the strength of some important parameters.

When data is skewed and not normally distributed, relying on the minimum prediction time could not be the best option, as it is greatly influenced by outliers and may not represent the typical prediction time for most cases. To ensure timely and accurate VVS prediction, the use of the median prediction time is recommended instead. This provides a more realistic estimate of the time required for the majority of cases and is less sensitive to outliers, reducing the risk of delayed or missed diagnoses.

The emphasis of this study differed from previous studies through its focus on predicting the occurrence of a condition based on specific physiological data (TABLE II). Previous studies, except Eickolt et al. 2013 [11], achieved higher sensitivity values in early VVS prediction using labelled data, which our algorithm did not use. However, our algorithm was able to predict VVS earlier than the previous studies (TABLE II). Labelled data can improve model accuracy, leading to

differences in sensitivity values. Nevertheless, our algorithm's ability to predict VVS disease earlier is a valuable advantage in real-time situations where early diagnosis is essential. VVS can limit patients' ability to participate in normal activities, affecting their quality of life. Real-time prediction of VVS would help patients from experiencing the syncope pain again while reducing assessment time.

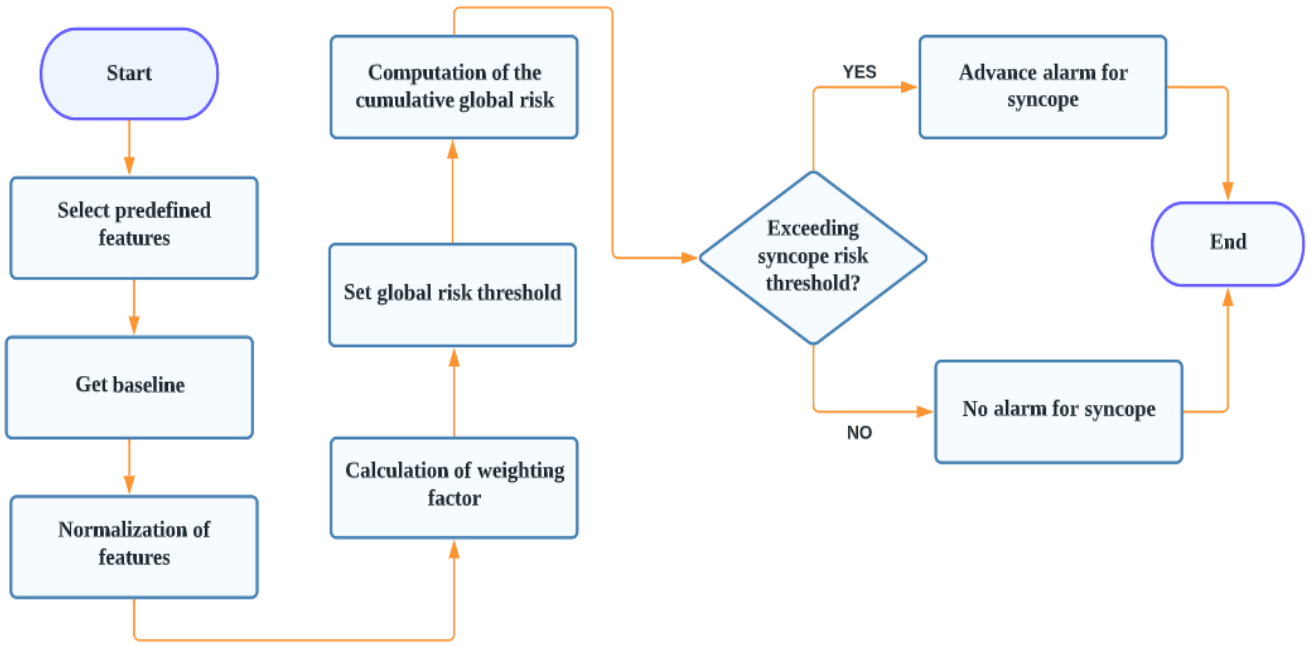

Fig. 1. The flowchart of the proposed model. It begins with carefully selection of important features that are relevant to cardiovascular parameters and their connections to autonomic nervous system activity. These features are divided into three sets and evaluated to determine their potential contributions in the prediction system. A baseline duration of 180 seconds is set as a reference point. The selected features are then normalized to ensure consistency and comparability. Multiple combinations of weighting factors are examined to assess their impact on the prediction process. A crucial step in the model involves determining a threshold for the risk of VVS. This threshold value is fine-tuned through a trial-and-error process using the dataset, indicating its adaptation to the study. Once the threshold is established, the model proceeds to calculate the VVS risk for each individual. Finally, if an individual's VVS risk surpasses the determined threshold, the algorithm issues an alarm, signaling the potential occurrence of a syncope episode.

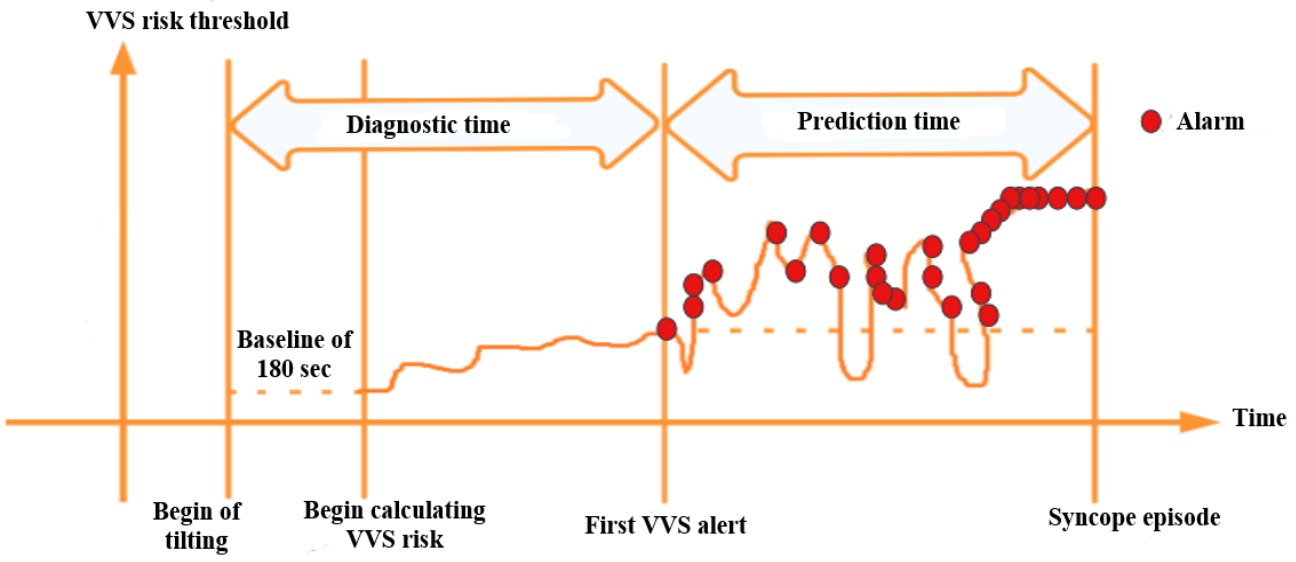

Fig 2. An illustration of the calculation of forecast time using the vasovagal syncope (VVS) risk. The VVS risk threshold is crucial in determining when to issue notifications, indicating an increased likelihood of syncope. When the VVS risk exceeds the threshold, VVS notifications are generated. Prediction time is calculated from the first notification to the actual episode, providing an estimate of available time. The baseline calculation establishes a reference point, enabling identification of trends unrelated to VVS risk and enhancing accurate prediction by considering both underlying patterns and deviations.

TABLE I. SUMMARY OF OUR PROPOSED MODEL PERFORMANCES'

1st set of selected features and their values							
SBP	**HR**	**LFHF-SBPV**	Risk Threshold	Performance (%)	Prediction Time (sec) (mean ± SD)	Min Time (sec)	Median Time (sec)
0.89	0.1	0.01	0.6	Sen: 81.6; Spe: 66.2; Pre: 62.5; F1 score: 70.8	544.2 ± 545.6	120.6	221.45
0.8	0.1	0.1	0.5	Sen: 81.6; Spe: 63.4; Pre: 60.6; F1 score: 69.6	549.8 ± 541.9	120.6	216.70
0.84	0.1	0.06	0.5	Sen: 81.6; Spe: 62.0; Pre: 59.7; F1 score: 69.0	563.8 ± 543.4	120.6	210.90
1	0	0	0.5	Sen: 81.6; Spe: 62.0; Pre: 59.7; F1 score: 69.0	567.6 ± 551.8	120.6	211.07
0	1	0	0.5	Sen: 73.5; Spe:14.1; Pre: 37.1; F1 score: 49.3	562.6 ± 438.2	99.8	143.65
0	0	1	0.5	Sen: 42.9; Spe: 57.7; Pre: 41.2; F1 score: 42.0	493.9 ± 402.1	120.6	277.90
0.5	0.5	0	0.5	Sen: 67.3; Spe: 49.3; Pre: 47.8; F1 score: 55.9	603.7 ± 557.0	120.6	201.37
0.5	0	0.5	0.5	Sen: 34.7; Spe: 81.7; Pre: 56.7; F1 score: 43.0	430.2 ± 342.9	146.32	384.50
2nd set selected features and their values							
SBP	**HR**	**HFnu_SBPV**	Risk Threshold	Performance (%)	Prediction Time (sec) (mean ±S D)	Min Time (sec)	Median Time (sec)
0.89	0.1	0.01	0.6	Sen: 81.6; Spe: 66.2; Pre: 62.5; F1 score: 70.8	546.2 ± 548.1	120.6	221.45
0.82	0.1	0.08	0.6	Sen: 77.6; Spe: 67.6; Pre: 62.3; F1 score: 69.1	553.7 ± 537.1	120.6	222.37
0.8	0.1	0.1	0.5	Sen: 81.6; Spe: 63.4; Pre: 60.6; F1 score: 69.6	604.84 ± 602.1	120.6	255.70
3rd set of selected features and their values							
HR	**SBP**	**LFnu_HRV**	**Lfnu_SBPV**	Risk Threshold	Performance (%)	Prediction Time (sec) (mean ± SD)	Min Time (sec)	Median Time (sec)
0.125	0.5	0.125	0.25	0.5	Sen: 51.0; Spe: 83.1; Pre: 67.6; F1 score: 58.1	532.3 ± 432.2	120.6	249.30
0.125	0.5	0.11	0.265	0.5	Sen: 42.9; Spe: 83.1; Pre: 70.0; F1 score: 53.2	504.7 ± 401.1	120.6	249.30
0.125	0.5	0.11	0.265	0.43	Sen: 51.0; Spe: 80.3; Pre: 64.1; F1 score: 56.8	653.7 ± 599.5	120.6	234.30

Note: HR, heart rate; SBP, systolic BP; SBPV, SBP variability; HFnu, normalized high frequency power; LFHF, normalized ratio of HF and LF; LFnu, normalized low frequency power; Sen, sensitivity; Spe, specificity; Pre, precision

TABLE II. COMPARISON WITH OTHERS REAL-TIME EARLY SYNCOPE PREDICTION TECHNIQUES

Authors'	Signals	No. of samples	Prediction Time (sec) (mean ± SD)	Performance (%)
Virag et al 2008 [5]	ECG, BP	1155	128 ± 216	Sen: 95.0; Spe: 93.0
Meyer et al 2011 [10]	ECG, PPG	14	99 ±108	Sen: 100; Spe: 100
Eickolt et al. 2013 [11]	ECG, PPG	44	203 ± 227	Sen: 81; Spe:85
Mereu et al 2013 [12]	ECG, BP	145	44.1±6.6	Sen: 86.2; Spe:89.1
Muhlsteff et al. 2013 [13]	ECG, PPG	43	77.71 ± 71.78	Sen: 90.5; Spe: 83.3
R. Couceiro et al 2016 [14]	ECG, PPG	43	116.4 ± 155.5	Sen: 95.2; Spe: 95.4
Proposed	ECG, BP	120	544.18 ± 545.58	Sen: 81.6; F1 Score: 70.8; Spe: 66.2 Pre: 62.5

N.B: ECG, electrocardiography; ICG, impedance cardiography; BP, blood pressure; sensitivity; Spe, specificity; Pre, precision; N, syncope negative subjects; P, syncope positive subjects.

IV. Conclusion

Our findings suggest that combining the extracted features could be crucial in predicting impending VVS. The proposed methodology was able to predict VVS patients before its onset with a sensitivity of 81.6%, specificity of 66.3%, precision of 62.5% and F1 score of 70.8%. The median prediction time was 221.5 seconds (Interquartile range = 180.0 - 294.0 seconds). The proposed algorithm could possess a great deal of promise to reduce the discomfort associated with reproduction of distressing symptoms in individuals with VVS.

V. Limitation and Future works

For the investigation, only ECG and BP signals were analysed. Impedance Cardiography (ICG) signal could also be used to predict test positive subjects. A few cardiodynamic parameters, such as stroke volume, cardiac output, ventricular ejection time, and pre-ejection interval, are processed continuously by the ICG, a safe technique that measures the total electrical conductivity of the thorax and changes in that conductivity over time. It is used to detect impedance changes brought on by a high-frequency, low- amplitude current passing between two additional pairs of electrodes outside the measured area in the thorax.

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