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Towards Predicting Polycystic Ovary Syndrome with a Novel Smartphone-based Biomedical Application Lyfas

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Abstract

Background: Polycystic Ovary Syndrome (PCOS) adversely affects reproductive and metabolic health. It mandates early detection. Lyfas is a mHealth instrument, which is a personalized, fast, non-invasive, and pervasive smartphone-based application. It captures Heart rate variability and its biomarkers (HRVBs) by finger touch on the phone camera. HRVBs are a surrogate for cardiac autonomic modulation that occurs in PCOS.

Objective: Early prediction of PCOS by Lyfas HRVBs and its validation by gynecologists.

Methods and Material: A retrospective double-blind control trial has been conducted on a mixed population of PCOS (N=218) and healthy (N=153) participants. The cohort is further divided into a) 'Forward miners or FM' (N=210: PCOS 135, healthy 75), where Lyfas has been used to mine the 'significant' HRVBs of PCOS, and b) 'Reverse mappers or RM' (N=161), where Lyfas decisions, based on the 'significant' HRVBs are validated by a panel of gynecologists.

Statistical analysis: Cronbach's alpha, Descriptive statistics, Q-Q plots, Spearman's correlation, and classification metric (recall, specificity, precision, accuracy, fscore, and Youden's index), and Bland-Altman's reliability test (BART).

Results: LF/HF and SD1/SD2 shows significant positive correlation (ρ = 0.60 and 0.45 and p-value = 0.009 and 0.02, respectively). Lyfas shows 82% recall, 84% specificity, 85% precision, 83% accuracy, 84% fscore, and 74% Youden's index when compared to the diagnoses of gynecologists. BART shows Lyfas has a 2% of proportional bias, i.e., 98% reliable when compared to gynecologists' prediction.

Conclusions: Lyfas HRVBs (LF/HF and SD1/SD2) can be assistive to gynecologists to predict the possibility of PCOS in the suspected population in 3-5 minutes.

Keywords: Lyfas; Polycystic Ovary Syndrome; Cardiovascular optical biomarkers; Heart rate variability

1. Introduction

Sound reproductive health is a sign of autonomic-endocrine homeostasis. Polycystic Ovary Syndrome (PCOS) has adverse effects on reproductive and metabolic health. The risk of infertility is very high in PCOS, which is about 70-80% of the population [1]. The global prevalence of PCOS is 6-26% in the population [2], while in India, it is 3.7-22.5% [3] and showing an increased trend mostly due to unhealthy lifestyle, food habits, and lack of physical exercise [4]. A large-scale study on the Indian population has revealed that about 16% of the population in the age group of 20-29 years suffer from PCOS [5]. PCOS cases are seen even in teenagers in recent times and at a much higher rate than what is expected [6]. PCOS also has a genetic basis, e.g., cytochrome P1A1 (CYP1A1), CYP11A, CYP17A1, CYP19, and many others [2]. PCOS poses risks of infertility [7], hypertension (HTN) [8], cardiovascular diseases (CVD) [9], dyslipidemia (DL) -obesity and early atherosclerosis [10], type-II diabetes mellitus (T2DM) [11], and so forth as cascading effects. Insulin resistance (IR) and compensatory hyperinsulinemia are associated in 44%-70% of PCOS cases and are considered to be the key factors to cause T2DM [12]. PCOS also has tremendous effects on the health-related quality of life (HRQOL), e.g., high body mass index (BMI) due to obesity, marriage due to infertility, and more prevalent in the higher educated cohort [13]. PCOS cases also suffer from mental illnesses, such as anxiety disorders, depression, obsessive-compulsive disorders, and bipolar disorders [14]. This concerning scenario of PCOS mandates early prediction, therefore, starting the early intervention.

Screening of PCOS is done by the gynecologists based on menstrual history (oligomenorrhea or amenorrhea, infertility), physical examination (obesity, acne, hair growth in the unusual areas of the body commonly on the face, around naval, and nipples), and laboratory tests e.g., hormone assay, diabetic and lipid profile, and pelvic ultrasound (USG) to check multiple follicles in the ovaries, which is costly for an average income Indian family. Laboratory tests are quite costly and invasive as well. Moreover, test reports are positive only when the pathology is well-set. Another disadvantage lies with coming to contact with the phlebotomists or sonologists while giving the blood samples or undergoing the USG, which are not so safe during the pandemic time. To address these logistic issues, digital health has come into play, and mobile health (m-health) is a novel extension of it due to its potential in capturing the cardiac autonomic modulation due to metabolic syndromes non-invasively and ubiquitously.

Lyfas is a clinically validated novel biomedical application that runs on Android smartphones [15]. It captures Heart rate variability and its biomarkers (HRVB) from the index finger capillaries using arterial photoplethysmography (PPG) and photochromatography (PCG) by finger touch on the rear phone camera. The camera sensor and torchlight, phone processor, and memory chip have made Lyfas hardware cost-free and hence is economic to its users. HRVBs are a surrogate for cardiac autonomic modulation that occurs in metabolic syndromes. Lyfas AI/ML-enabled heuristics evaluate the HRVB scores and its proprietary analytics provides a comprehensive snapshot of mind-body analytics, which could throw light on forecasting the chances of PCOS and its allied metabolic risks. It is also important to note that the m-health market size is increasing at a CAGR of 22.3% from 2020 to 2027 from USD 46 Million in 2016 to USD 230 Million in 2027 [16]. Also, it is worth noting that the number of smartphone users is expected to raise from 748 Million in 2020 to 1500 Million by 2040, and can adopt m-health easily [17].

The *objective* of this study is to screen PCOS cases using Lyfas and validate them by a panel of gynecologists.

2. Material and Method

In this section, the approach and techniques used in this study have been elaborated.

2.1 Ethical statement

The study protocol has been approved by the Vagus Institutional Ethics Committee, Bengaluru, Malleswaram, Karnataka, India review board, registered with the Central Drugs Standard Control Organization, Ministry of Health and Family Welfare, Govt. of India (No. ECR/1181/Inst/KA/2019, dated 30-01-2020).

Signed informed consents of all participants' have been taken on the organization letterhead according to the declaration of Helsinki by the research team prior test.

2.2 Experimental design

2.2.1 Definitions of the study groups

This section starts with two important definitions such as (a) Forward miners (FM) which comprise the mixture of PCOS and health subjects on which Lyfas has been tested at first to mine the significant HRVBs (having high correlation and p-values <0.05) and (b) Reverse mappers (RM), which represents another mixed group of PCOS and healthy subjects with whom the significant HRVBs are mapped for the prediction purpose and the prediction is then validated by a panel of gynecologists. Thus, FM gives the pool of significant HRVBs while RM validates the clinical mapping with the help of gynecologists.

2.2.2 Inclusion criteria (sign-symptoms) and % of the population observed in this study

Amenorrhea (25%)

Hirsutism and Acne (21%)

Obesity (14%)

Infertility (10%)

Multiple ovarian cystic lesions in USG (9%)

Mood dysregulations (anxiety 4% and anger 3% anger and anxiety both 7%), and

High testosterone level in serum (7%).

2.2.3 Exclusion criteria (mimicking disorders) [18]

Thyroid disorders by checking serum T3, T4, and TSH levels, Dysregulations may cause amenorrhea and menorrhagia, infertility, obesity, hirsutism, and so forth.

Hyperprolactinemia by investigating serum prolactin levels and history of amenorrhoea and galactorrhoea (milky discharge through nipples), infertility, etc.

Congenital adrenal hyperplasia (CAH), is a genetic disorder where hyperandrogenism is the hallmark trait, and patients present with amenorrhea, hirsutism, male pattern in baldness, etc. It is diagnosed by genetic study.

Cushing syndrome is a condition where adrenal glands produce excessive cortisol and androgens giving rise to phenotypes similar to PCOS.

2.3 Study

A retrospective double-blind control trial has been conducted for six months (October 2021 to February 2022) on a mixed population (mean age 23.81 years, mean BMI 26.59, mean BP 128/76 mm Hg) of PCOS (N=218) and healthy (N=153) subjects who participated in the study are divided into two groups-a) 'Forward miners or FM' (N=210: PCOS 135, healthy 75), where Lyfas has been used for the first time to mine the 'significant' HRVBs using Spearman's rank correlation scores and their respective p-values (CI 95%), and b) 'Reverse mappers or RM' (N=161 which is a mixture of PCOS and healthy cases), where Lyfas decisions are made on a case whether it qualifies for PCOS or not, based on the mapping of the 'significant' HRVBs and the decisions are matched against the diagnosis made by a panel of gynecologists to compute the classification metric (recall, specificity, accuracy, precision, and j-statistics) to note how close are Lyfas diagnoses with that of the experts. Lyfas tests are taken thrice a day (7 am, 2 pm, and 10 pm) daily for six months in the home comfort in a much-personalized manner (using personal smartphones) and the average of the HRVBs are recorded for the analysis. It is important to note that subjects with hypothyroidism are excluded from the study as hypothyroid women, apart from obesity, HTN, and DM, develop hair in the unusual parts of their bodies and suffer from menstrual abnormalities and infertility as well as mood irregularities [19]. Also, smokers and alcoholics, one under psychiatric medications, oral contraceptive pills, and metformin or ovulation-inducing drugs are discarded from the study.

2.4 Lyfas HRVBs

HRV is a biomarker of Cardiac autonomic modulation (CAM) to maintain the physiological homeostasis (i.e., the sympathovagal balance) of the body. It is the variation of the interval between two consecutive R (also called N) waves. The variation

is controlled by the autonomic nervous system (ANS) having sympathetic and parasympathetic supplies to the heart and rest of the body. A low HRV is due to sympathetic dominance and vice versa. Good health is suggested by a high HRV score. HRV and its associated biomarkers provide the tale-tell signs of overall health condition [20]. Table 1 presents the HRVBs in this work, their normal range, and the rationale behind choosing them.

Table 1: HRVBs

Sl. No.	HRVB	Desired value	Biomarker type	The rationale for PCOS
1	**HRVScore**	>80 ms	Mood/emotion [21]	Mood fluctuation [19]
2	**SDNN**	>40 ms	Good health [22]	Compromised health
3	**RMSSD**	54 – 70	-do- [22]	-do-
4	**pNN50**	>16	-do- [22]	-do-
5	**SD1/SD2**	1 – 2.5	Sympathovagal balance [23] anxiety biomarker	Anxiety disorders [24]
6	**LF/HF**	<2	Sympathovagal balance [22] anger biomarker	Anger traits [25]

2.5 Working principle of Lyfas

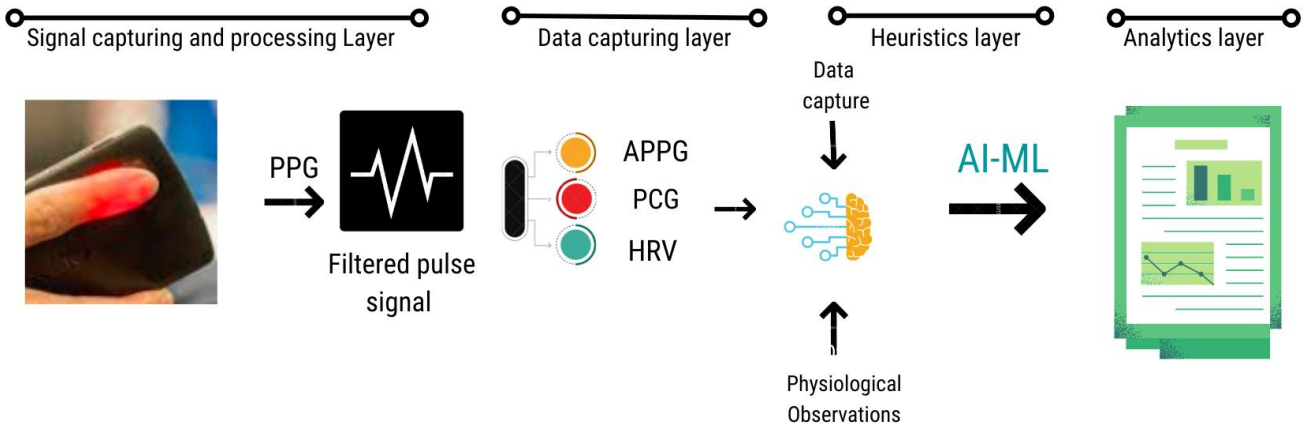

Figure 1: Working principle of Lyfas

Lyfas converts a smartphone into a personalized health device when installed. Fig. 1. describes the working principle of Lyfas in layers. It uses the phone's camera sensor and torchlight to capture the pulse rate variability (a synonymous term with HRV) from the index finger capillary using the technique of photoplethysmography (PPG). The signal is then filtered using signal processing methods. These happen in the 'Signal capturing and processing layer'. From the waveforms, it captures the pulse rate variability (PRV) that surrogates for the HRV and its correlated biomarkers, i.e., the HRVBs. Using photochromatography (PCG) Lyfas captures the solutes and cellular components of the blood simultaneously. These occur in the 'Data capturing layer', which helps in making the physiological observation of the body. The data, thus captured, are then churned in the 'Heuristics layer', and using its proprietary AI-ML algorithm, Lyfas maps the HRVBs to the psychophysiological homeostatic states of the body, and its 'Analytics layer' finally provides a comprehensive report in just 3 minutes (see Fig. 6).

2.6 Statistical analysis

This section discusses use of statistical techniques step-by-step as follows:

2.6.1 Data fidelity or internal consistency test

At first, the data fidelity has been tested by computing the Cronbach's alpha (α) [26]. Its value of close to 1.0 indicates that the data is reliable for analysis [27].

2.6.2 Data distribution test

Q-Q plot has been performed to examine whether the data is normally distributed. Adherence of data to a 45-degree slope indicates that the data is normally distributed.

2.6.3 Descriptive statistics

It provides the data spread both longitudinally (mean and median) referring to the central tendency and horizontally (standard deviations or stdev and skewness) denoting the extent of data dispersion.

2.6.4 Correlation test

Pearson's or Spearman's correlation (ρ) and the respective statistical significance (p-values <0.05; CI 95%) between each of the HRVBs and PCOS cases are finally computed according to the data distribution. The correlation values are either positive (close to 1.0) or negative (close to -1.0) or non-correlated (close to 0). Based on these values (ρ and p-values), each of the significant HRVBs is identified [28].

2.6.5 Classification metric

HRVBs are ranked as the representative of PCOS during the FM. Later, these HRVBs are used for PCOS prediction with Lyfas in the RM group and then validated against the diagnosis of the gynecologists, and the recall, specificity, accuracy, precision, f-score, and Youden's index are measured. Fig. 2 shows the schematic diagram of the methodology/study design.

2.6.6 Bland Altman's reliability test (BART)

It is the reliability assessment of the measure of a novel instrument (Lyfas biomarker application in this case) to that of a champion instrument (here, the expert gynecologists) statistically. The reliability score is calculated based on the proportional bias (i.e., the bias in mean difference of two measures) it generates when compared [29]. It is worth noting that the bias and reliability are inversely proportional. Thus, for a reliable instrument, less bias is expected.

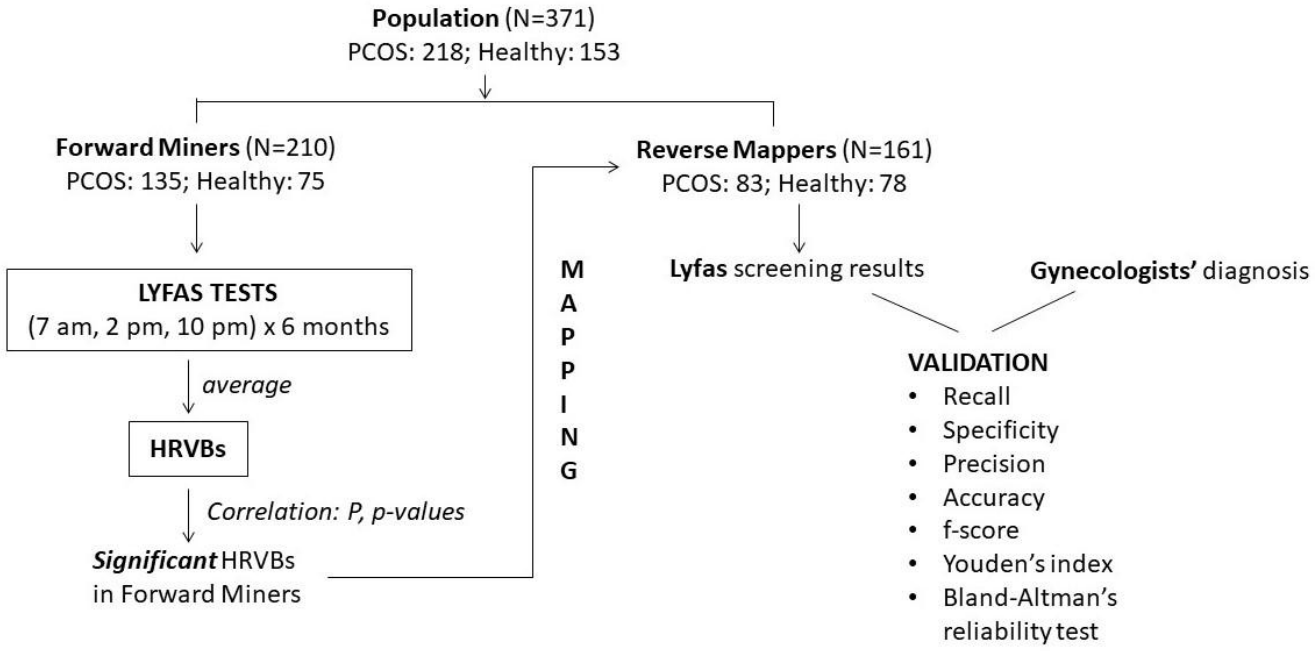

Figure 2: The study design

3. Results

3.1 Internal consistency check

The Cronbach's α for the population is 0.87, which means that the data is of good quality [27] and therefore, reliable for undergoing statistical analysis.

3.2 Data distribution check

Quantile-Quantile plot (Q-Q plot) for the normality test shows (refer to Fig. 3) the probability distribution of the data along a 45-degree straight line, which refers to the mean value. Data well-wrapped around the mean value is normally distributed, otherwise, it is not a normal distribution [30].

In this study, the population is not normally distributed.

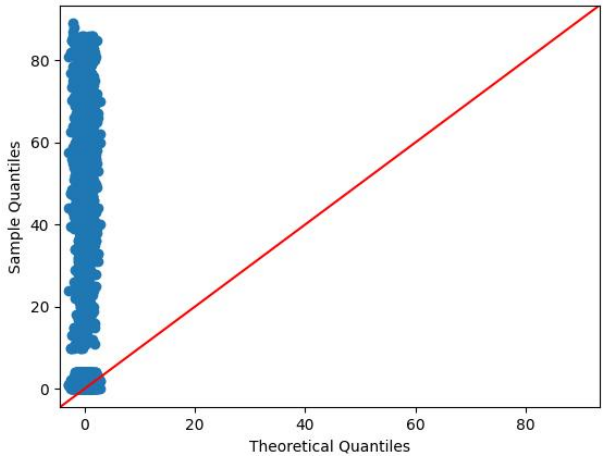

Figure 3: Q-Q plot of the study population

3.3 Central tendency and data dispersion check

Descriptive statistics of the PCOS and healthy subjects can be viewed in Table 2.

Table 2: Descriptive statistics of PCOS and healthy groups

HRVBs	Mean		Median		Stdev		Skewness	
	PCOS	Healthy	PCOS	Healthy	PCOS	Healthy	PCOS	Healthy
HRVScore	66.38	66.34	66	66	9.67	9.51	0.08	0.07
SDNN	47.13	47.15	47	47	8.15	8.22	-0.10	-0.10
RMSSD	65.66	65.32	66	66	12.15	12.22	-0.08	-0.08
pNN50	35.02	35.12	35	35	14.83	14.67	0.07	0.05
SD1/SD2	1.99	2	2	2	0.79	0.78	0.008	-0.01
LF/HF	**2.54**	**2.56**	**3.6**	**3.4**	1.11	1.10	-0.02	-0.03

Descriptive statistics do not show any appreciable differences in the HRVB values between the PCOS and healthy groups. It is important to mention here that higher LF/HF scores are seen in both PCOS and healthy groups, however, PCOS cases have corroborating symptoms, laboratory reports (e.g., high testosterone), and pelvic ultrasound showing multiple cystic changes in the ovaries.

3.4 Correlation check

Spearman's rank correlation test has been conducted as the data is not normally distributed (refer to Fig. 3) and is large-sized. The strength of correlation (positive and negative) and the respective p-values are calculated to rank the significant HRVBs. Fig. 4 shows the heatmap for visualizing the correlation results on FM. Significant HRVBs are then mapped on RM to screen PCOS by Lyfas, which is later validated by the gynecologists.

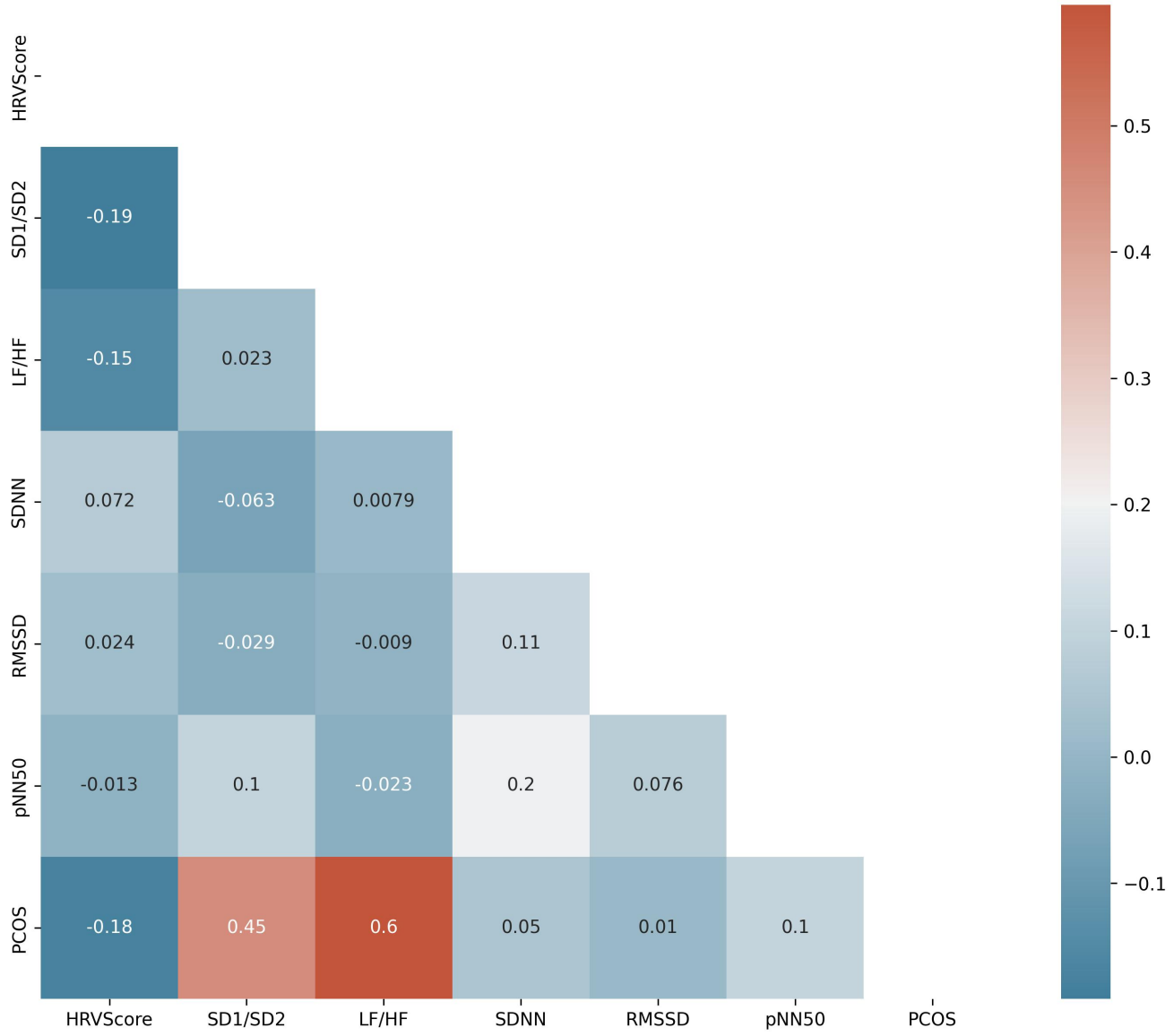

Figure 4: Spearman's correlation plots

The plot showcases high positive correlations between SD1/SD2 (ρ = 0.45) and LF/HF (ρ = 0.60) each with PCOS and are statistically significant (p-values 0.02 and 0.009, respectively). Based on these HRVBs, PCOS prediction is then performed on the RM group, which is then validated by the gynecologists (refer to Table 3).

3.5 Classification metric

Table 3: Lyfas prediction (PCOS_L) based on significant HRVBs validated by gynecologists (PCOS_G)
Color code: High Values , TP TN , FP , FN

No.	HRVScore	SD1/SD2	LF/HF	SDNN	RMSSD	pNN50	PCOS_L	PCOS_G
1	67	2	2	60	51	54	0	1
2	64	2	4	42	51	40	1	1
3	55	3	1	48	67	55	1	0
4	67	2	4	54	78	30	1	0

5	70	2	1	41	62	12	0	0
6	64	2	3	57	54	39	1	0
7	51	1	3	59	62	53	1	1
8	66	2	1	39	52	14	0	0
9	56	2	3	58	76	13	1	1
10	62	1	3	35	62	12	1	1
11	65	3	4	36	75	51	1	1
12	58	3	4	52	60	55	1	1
13	58	3	4	56	80	52	1	1
14	55	3	3	60	61	57	1	1
15	74	3	2	37	50	54	1	1
16	75	1	1	59	64	17	0	1
17	67	2	2	38	51	20	0	1
18	79	1	4	57	51	16	1	1
19	72	3	3	35	78	34	1	1
20	50	3	4	42	47	48	1	0
21	77	1	4	37	53	30	1	0
22	82	2	2	59	71	45	0	0
23	55	1	3	47	85	27	0	0
24	60	2	1	46	79	37	0	0
25	64	3	4	46	49	37	1	1
26	59	2	1	38	50	42	0	1
27	66	2	2	40	65	50	0	1
28	70	2	4	57	80	19	1	1
29	57	2	4	57	46	45	1	1
30	52	3	3	54	58	26	1	1
31	73	2	1	44	75	11	0	0
32	72	2	1	50	50	39	0	0
33	62	1	4	46	74	21	1	0
34	55	2	3	55	80	15	1	0
35	54	3	1	44	77	21	1	1
36	52	2	1	44	61	37	0	1
37	50	3	1	46	62	57	1	1
38	56	3	2	49	45	32	1	1
39	68	2	4	51	76	52	1	1
40	73	3	2	42	60	23	1	1
41	79	2	2	46	45	34	0	1
42	80	2	2	47	66	37	1	1
43	51	2	4	48	57	28	1	1
44	78	2	4	46	59	56	1	0
45	65	3	4	59	84	32	1	0
46	55	2	3	40	84	33	1	1
47	63	2	4	56	84	25	1	1
48	78	3	2	36	76	60	1	1

49	76	2	2	44	84	25	0	0
50	50	2	1	48	53	43	0	0
51	58	3	1	57	48	14	1	1
52	73	2	3	45	49	16	0	0
53	52	1	1	49	61	58	0	0
54	69	2	3	37	71	32	0	0
55	69	2	4	43	56	42	1	0
56	74	1	3	45	62	31	0	0
57	61	1	3	59	54	36	0	0
58	74	1	3	43	68	55	0	0
59	81	1	3	56	83	38	0	0
60	58	1	2	54	80	27	0	0
61	74	2	4	49	73	23	1	1
62	72	2	4	39	75	57	1	1
63	71	1	4	49	73	23	1	1
64	75	3	2	42	48	17	1	1
65	61	2	1	38	69	54	0	0
66	71	2	4	54	81	26	1	1
67	67	3	1	50	73	44	1	1
68	71	3	2	37	75	44	1	1
69	82	2	2	60	67	29	0	0
70	72	1	4	43	61	60	1	1
71	50	3	3	39	45	42	1	1
72	80	1	2	56	50	50	0	0
73	68	1	1	47	57	28	0	0
74	58	1	2	58	66	30	0	0
75	64	3	4	52	57	41	1	1
76	72	1	2	52	52	41	0	0
77	78	3	3	41	79	56	1	1
78	56	3	1	50	66	46	1	1
79	59	2	1	53	82	36	0	0
80	67	3	1	34	62	29	1	1
81	55	2	3	60	65	31	1	0
82	68	1	4	42	68	58	1	1
83	73	1	3	44	51	31	0	0
84	68	1	3	60	72	52	0	0
85	70	2	4	37	45	58	1	1
86	50	3	1	59	46	48	0	0
87	66	3	3	44	86	45	1	1
88	66	2	2	35	45	30	0	0
89	62	3	1	57	61	44	0	0
90	53	1	3	60	65	59	0	0
91	57	3	2	36	59	60	1	1
92	63	2	3	35	74	38	1	1

93	60	2	3	33	71	17	1	1
94	58	3	4	40	85	44	1	1
95	68	3	2	37	59	31	1	1
96	76	1	4	38	61	53	0	0
97	54	1	4	55	65	34	0	0
98	65	2	3	35	79	53	1	1
99	55	2	2	47	49	15	0	0
100	78	2	4	56	65	26	1	1
101	60	2	2	55	48	29	0	1
102	74	2	1	57	45	60	0	0
103	71	3	4	41	61	37	1	0
104	69	3	1	56	81	51	1	1
105	74	1	1	49	48	57	0	0
106	82	2	2	54	56	36	0	0
107	51	1	3	35	74	12	0	0
108	53	2	2	59	81	19	0	0
109	73	3	2	33	72	52	1	1
110	53	2	3	46	51	60	1	1
111	61	2	2	54	46	21	0	0
112	52	3	4	58	81	31	1	1
113	63	3	2	50	45	38	1	1
114	58	2	3	38	61	37	1	1
115	58	3	4	44	57	24	1	1
116	68	1	2	52	58	28	0	1
117	75	3	2	52	51	20	1	1
118	65	3	1	38	70	36	0	1
119	60	2	4	52	86	55	1	1
120	79	1	1	47	54	35	0	0
121	69	1	4	56	79	35	0	0
122	51	3	3	49	48	32	0	0
123	56	1	4	58	83	12	0	0
124	51	1	1	49	64	46	0	0
125	63	1	2	56	48	18	0	0
126	81	2	4	36	64	37	1	1
127	60	2	3	39	45	43	1	1
128	79	2	1	39	79	43	0	0
129	62	1	3	55	68	24	0	0
130	65	2	2	51	77	57	0	0
131	50	2	3	37	61	48	1	1
132	68	1	4	59	81	12	0	0
133	52	2	4	35	86	50	1	1
134	65	1	1	49	67	23	0	0
135	73	1	4	47	60	25	1	1
136	50	2	2	39	67	49	0	0

137	59	1	2	55	86	42	0	0
138	61	1	2	47	84	58	0	0
139	80	1	4	57	46	43	0	0
140	50	1	3	60	69	47	0	0
141	76	3	4	46	68	19	1	1
142	82	2	3	51	60	55	0	0
143	66	1	2	60	64	16	0	0
144	61	3	3	59	62	41	1	1
145	59	2	2	46	53	32	0	0
146	74	2	2	39	69	20	0	0
147	57	1	2	49	83	24	0	0
148	80	3	3	56	65	11	1	1
149	69	1	2	32	57	28	0	1
150	82	2	3	32	71	35	1	1
151	81	3	2	41	60	16	1	1
152	58	1	4	54	75	15	0	0
153	56	1	4	36	70	43	0	0
154	81	3	4	50	62	25	1	1
155	59	3	1	36	71	31	0	0
156	65	3	4	56	57	28	1	1
157	72	3	1	39	85	58	0	1
158	65	1	1	55	49	38	0	1
159	66	1	3	33	44	31	0	1
160	67	3	1	53	70	33	0	1
161	64	3.2	2	50	67	32	1	1

In the RM group, from Table 3, it can be noted that there are high values of anxiety and anger biomarkers, i.e., SD1/SD2 and LF/HF, which are found in 30.6% and 53.12% of the cohort respectively. As per the correlation studies, LF/HF ranks first, closely followed by SD1/SD2, and hence, in cases where both SD1/SD2 and LF/HF are high, Lyfas predicts that there are high chances of PCOS (column PCOS_L in Table 3 and marked by '1'). On the other hand, gynecologists have used their clinical experience and International PCOS guidelines (2018) [31] for arriving at the diagnosis (column PCOS_G in Table 3 and marked by '1'). Below, Table 4 shows the classification metric i.e., recall I, specificity (Sp), precision (P), accuracy (A), fscore (f), and Youden's index (Y) of Lyfas when compared to the diagnosis made by the gynecologists are mentioned. True positive (TP), True negative (TN), False positive (FP), and False negative (FN) are calculated for validation [32]

Table 4. The classification metric

TP	71		**R**	0.82
FP	12		**Sp**	0.84
TN	63		**P**	0.85
FN	15		**A**	0.83
Total	161		**f**	0.84
			Y	0.66

Hence, Lyfas is found to be 83% accurate and 85% precise in predicting PCOS possibilities using just two HRVBs, i.e., SD1/SD2 and LF/HF in just 3-5 minutes. Youden's index is a reliability test for any novel medical instrument where a value over 50% qualifies it for its usability [22] when compared to a gold-standard instrument [33].

3.6 Agreement check between Lyfas (new measure) and gynecologists (gold standard expert measure)

Bland Altman reliability test measures the reliability in terms of calculating the proportional bias, which is expected to be low for a reliable instrument/model. Fig. 5 shows Bland Altman's reliability plot. Here, the proportional bias (i.e., a bias between the mean differences) of Lyfas is merely -1.27, which means that its agreement is high.

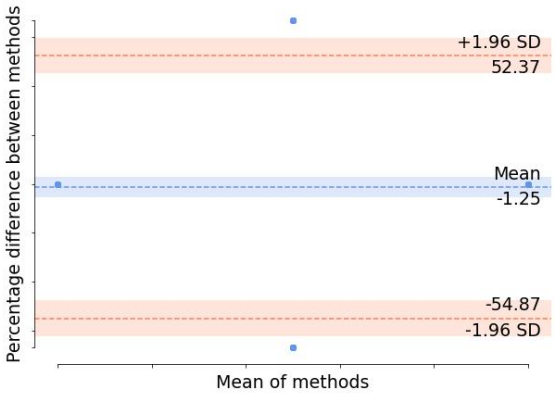

Figure 5: BART plot: Lyfas prediction mapped to the gynecologist's prediction

3.7 A case study

A sample POS case with the Lyfas report, laboratory tests, and USG report can be viewed in Fig. 6. Here, the case is a 35-year-old unmarried woman with the chief complaint of hirsutism, obesity, mood dysregulations, insomnia, and amenorrhea for four months. On the Lyfas test, her LF/HF is >2, and a low pNN50 explains that she is not in a good health state. Her serum testosterone level is high and pelvic USG shows multiple cystic lesions in both ovaries.

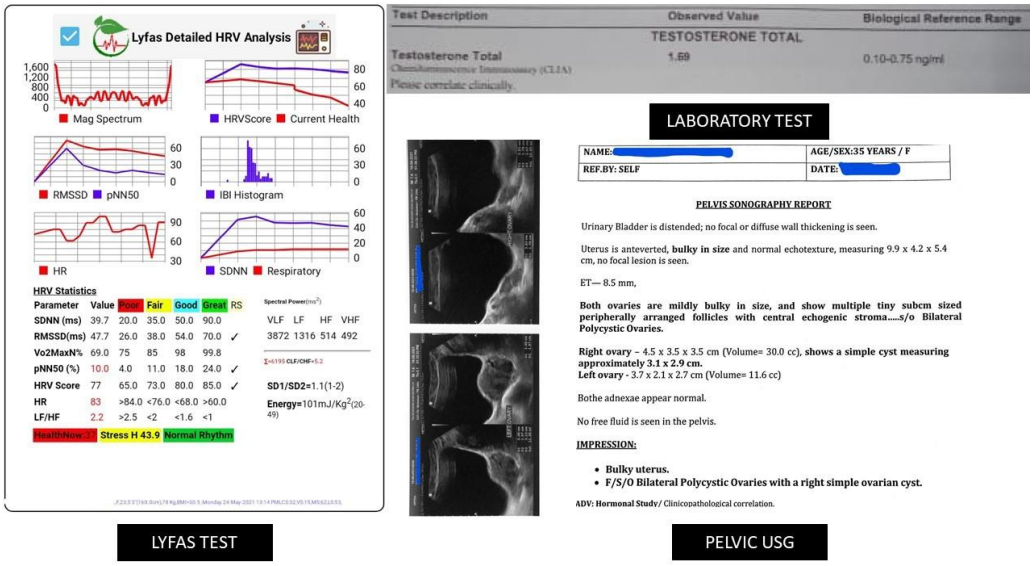

Figure 6: A sample PCOS case with Lyfas, Laboratory, and Pelvic USG report

4. Discussion

Sound reproductive health is the sign of autonomic-endocrine balance in the body. Due to lifestyle changes, it is being affected worse in the global population. Reproductive health has been worst-affected in the COVID-19 pandemic due to immune-endocrine axis dysregulations, sedentary lifestyles, and uncertainties leading to biopsychosocial stress in the population [34]. Present studies have shown that there is a drastic fall in reproductive health, globally [35]. The rate of infertility has gone up [36], and so has early menopause (menopause before the age of 45 years) [37]. In most cases, PCOS is the principal reason, affecting teenagers as well [38].

The paper is an attempt to predict the possibility of PCOS in the suspected population using smartphone technology, Lyfas. Android smartphones have successfully been used to telemonitor the ECG [39]. Lyfas works on both android version 7 and above and iOS OS [15]. It is (i) fast (takes 3-5 minutes from start to analytics-powered reporting), (ii) ubiquitous (user can install it on her mobile phone at the home-comfort), and hence the test can be taken from anywhere at any time, (iii) user-friendly (voice-assisted), (iv) non-invasive (just needs placing the index finger on the rear camera of mobile and no breach of the skin is required), (v) personalized (the report is generated within the smartphone of the user), and (vi) validated through rigorous clinical research.

PCOS is a metabolic syndrome involving the ANS widely [40]. The IR is central to its pathophysiology. IR causes a high amount of circulating insulin in the blood, which has a negative feedback loop with the circulating Sex hormone-binding globulin (SHBG) [41]. Low SHBG causes high free testosterone in the blood, produced majorly from the ovaries than the adrenal gland, as evident by ovarian enlargement [42]. Hypersecretion of luteinizing hormone (LH), high LH-Follicular stimulating hormone (FSH) ratio, and hypothalamic-pituitary-ovarian axis malfunction is blamed for hypersecretion of testosterone by the ovaries [42]. High testosterone hinders folliculogenesis and infertility in PCOS women. It stimulates hair growth like men (hirsutism) and also men-pattern of baldness. Testosterone stimulates amygdala-driven fight or flight mode [43] in the brain. As a result, sympathetic overdrive occurs in most PCOS cases and the sympathovagal balance is compromised often. SD1/SD2 and LF/HF are the sympathovagal ratios, widely acknowledged as the anxiety and anger biomarkers (see table 1), respectively. In both conditions, sympathetic dominance is noted and the ratios are high. Persistent dominance (reflected by higher SD1/SD2 and LF/HF scores) coupled with the symptoms such as mood dysregulations, such as anxiety [44] and anger [45], arterial stiffness [46], and lack of sleep [44] are the signs of PCOS. The authors of this paper suggest that the Lyfas results, later, supported by the laboratory tests, such as a high level of testosterone, HOMA-IR or Belfiore index (IRI) [47], and a positive pelvic ultrasound would suffice in predicting PCOS at a much early stage of the disease. Early intervention, such as lifestyle modifications, regular exercise, and the start of medications, would reduce the risk of infertility due to anovulation, T2DM due to IR, and CVD due to early atherosclerosis and hypertension. A study has also shown that IR alone elevates the testosterone level in PCOS cases [48]. The interlinked pathophysiology of PCOS to HRVBs can be seen in Fig. 7.

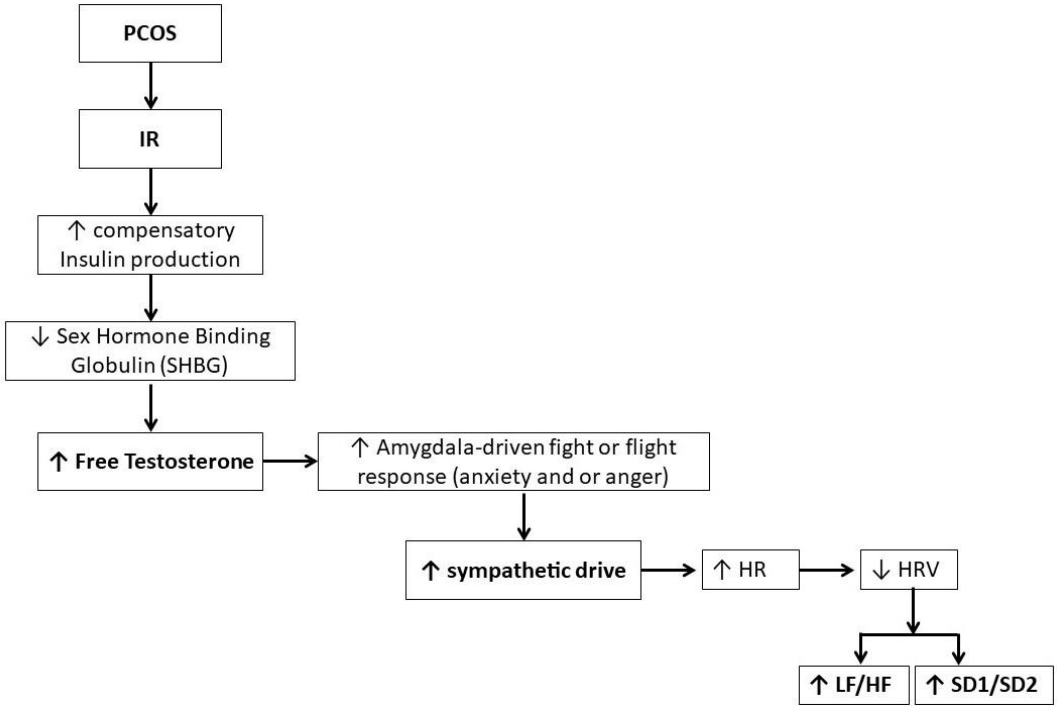

Figure 7: Pathophysiology of PCOS to HRVBs

This study is a novel one where a smartphone application Lyfas has been successfully applied. As mentioned before, mHealth has tremendous potential to cater to a larger population across the wider geopolitical regions in the world in addressing women's health. Its adoption is easy as the number of smartphone users in the world is already quite high and is still increasing. Installation of Lyfas in the phone converts it into a personalized and pervasive healthcare instrument. There is no extra hardware required as it uses the phone's in-built hardware. It has made Lyfas affordable and a greater reach. It provides psychophysiological insight in just 3-5 minutes and thus can be used as a predictive tool in PCOS.

There are other PPG-based health instruments available commercially in the market and most are wearable types. Table 5. Gives a comparative picture.

Table 5: Comparative picture of PPG-based tools and applications

Abbreviations: Dn, Device name; Dt, Device type; HRV, Heart rate variability; T, Time; A, Affordability; AS, Arterial stiffness; AG, Aging; S, Stress; A, Anxiety; D, Depression.

	Dn	Dt	HRV	T	A	AS	ECG	AG	S	A	D
1	Polar H10 sensor [49]	Chest wearable	Yes	5 min	Costly			Yes	Yes		
2	Apple watch [50]	Wrist wearable		24 hrs	Costly		Yes	Yes	Yes		
3	SanketLife [51]	Single gadget		5 min	Economic		Yes		Yes		
4	Elite HRV [52]	Single gadget	Yes		Costly			Yes	Yes		
5	Dozee [53]	Contact-less gadget	Yes	24 hrs	Costly		Yes		Yes		
6	Fibricheck [54]	Finger touch gadget			Economic				Yes		
7	Lyfas [15]	Finger touch app	Yes	120 sec	Economic	Yes		Yes	Yes	Yes	Yes

Contribution

The study has introduced a novel non-invasive m-Health application Lyfas.

Lyfas HRVBs, which are the cardiovascular optical biomarkers of ANS, introduced to explain the pathophysiology of PCOS.

Lyfas HRVBs give psychophysiological insight into PCOS, which helps mental health professionals and the gynecologists work hand-in-hand to treat the patients in a much more holistic way, and

Lyfas can be used as a monitoring tool to assess how well the patients are responding to the treatment.

Limitation

Smaller sample size, and

Chances of accidental sampling bias as the history of COVID-19 infection and vaccination history are not taken. The impact of COVID-19 on reproductive health is already discussed beforehand.

5. Conclusions

Prediction of the possibilities of PCOS in women with the help of a personalized smartphone application Lyfas is the first-ever attempt to the best of the knowledge of the authors. Early prediction and then seamless personalized monitoring of PCOS cases with two important HRVBs (SD1/SD2 and LF/HF) would help gynecologists treat patients effectively. The chances of treatment dropouts would be less. Early treatment would reduce the risk of infertility, CVD, T2DM, mental diseases, and other metabolic illnesses in the vulnerable population. In this paper, the authors encourage the use of Lyfas in clinical practice as a valid and reliable risk screening and health monitoring tool to evaluate the underlying autonomic stress in the affected population, much earlier than the pathology develops.

Future work

Encouraging findings of this study have stimulated the authors to conduct a much larger multicentric research, which has been taken up already by the authors to assess not only the roles of SD1/SD2 and LF/HF but also the plausible widespread roles of other HRVBs, such as pNN50, HRVScore, SDNN, RMSSD, Stress, Energy, and so forth in the much wider population of PCOS.

6. Recommendations

The authors' recommendations are as follows:

1. Choice of candidates: Using Lyfas, early screening of PCOS may be initiated as early as the adolescence period if amenorrhea, hirsutism, and obesity are present. History of infertility abreast these symptoms in adults encourage them to take Lyfas tests too.

2. Lyfas testing: At a rate of thrice daily for 21 days of their menstrual cycle for three consecutive cycles, Lyfas tests can be taken in the suspected population. The last 7 days of the cycle are discarded to exclude premenstrual dysphoria which often influences the biomarker scores.

3. Optical biomarkers: High LF/HF and SD1/SD2 levels could be good non-invasive biomarkers of suspected PCOS.

4. Usability: This method could be useful in the rural or remote areas in the world where USG facilities and high-end blood tests such as hormone assays are not available or there is no gynecologist and mental health professionals, available.

5. Holistic approach: PCOS must be treated both by mental health professionals and gynecologists simultaneously to tackle the psychopathology holistically. The current trend of singleton therapy only by gynecologists might be insufficient.

6. Continuous support: Apart from screening, response to the treatment can also be non-invasively monitored by Lyfas biomarkers. Effective treatment may show normal LF/HF and SD1/SD2 scores alongside the improvement of signs and symptoms. However, it requires more longitudinal studies on a larger population.

7. Value adds to biomedical sciences: Lyfas may be used as a validated assistive biomedical tool for both gynecologists and mental health professionals in the hospital/clinic setup. It would facilitate an evidence-based (Lyfas analytics supported) multidisciplinary therapeutic approach, which is yet to be adopted by medical doctors.

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