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A CONTROLLED CLINICAL STUDY TO EVALUATE A PROPRIETARY NON-INVASIVE SMARTPHONE BASED DIGITAL BIOMARKER TOOL LYFAS® IN ENABLING EARLY DETECTION OF COVID-19 INFECTION AMONG ASYMPTOMATIC INDIVIDUALS

Healthcare

Mr. Rupam Das* Acculi labs Pvt limited, Bengaluru, India.*Corresponding Author

Dr. Shushila Kataria Medanta Medicity Hospital, Gurgaon, India.

Dr. Pooja Sharma Medanta Medicity Hospital, Gurgaon, India.

Dr. Kannan Janakiraman Acculi labs Pvt limited, Bengaluru, India.

Dr. Madhur Shrivastava Acculi labs Pvt limited, Bengaluru, India.

Dr. Geetha H Mahadevappa Managing Director - Probity Pvt Ltd, Saraswathipuram.

ABSTRACT

Coronavirus disease 2019 (COVID-19), is a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). With the increasing number of individuals infected with COVID-19, there is a growing need for easy, dependable, accurate, scalable, and cost-effective tools. These tools should serve the purpose of population screening/surveillance, diagnosis, and prognosis. Unlike the other pandemics in the past, the current viral infection presents itself with long incubation period up to 14days. This situation is challenging because it results in an extremely high proportion of asymptomatic individuals (up to 80% and more). These individuals in turn contribute to high risk of transmission among the vulnerable population with coexisting diseases and the aged. Currently, the real time PCR test and serology is being largely employed only in symptomatic individuals. Therefore, there is a need for a dependable additional test to identify the asymptomatic individuals, to qualify them for the confirmatory rtPCR and/or serology tests.

To meet these the above requirement, we decided to repurpose and test our proprietary non-invasive smartphone-based health screening mobile application Lyfas. The validated parameters captured from Lyfas were found to be inherent indicators of several cardiorespiratory, cardiovascular, autonomic nervous system, hematology and biochemistry anomalies. Apparently, these anomalies were also found and reported as early indicators of COVID-19 infection. Therefore, by means of rationale selection of these parameters, we derived a unique LYFAS_COVID_SCORE to enable detection and prioritize confirmatory testing for asymptomatic individuals.

A controlled clinical study was conducted in 25(n=25) subjects to prove the hypothesis and establish the difference in LYFAS_COVID_SCORE between an infected and non-infected group of individuals. The LYFAS_COVID_SCORE derived out of this clinical study was found to be different between the two groups. The positive infected test group had a significantly high(p=.00012) median score of 19.8(range 9.9 to 22.1) compared to 6.9(range 2.2 to 7.8) that of the healthy uninfected control group. The accuracy, sensitivity and the specificity of the study was found to be 92%, 93.2% and 90% respectively. The result of this study is therefore an evidence to use Lyfas as a potential tool in the identification, screening, and surveillance of asymptomatic individuals. The findings from the study deserves to be extended to a large population confirmatory clinical study to add proof and value to the tool.

KEYWORDS

INTRODUCTION:

At present, the real time polymerise chain reaction (rtPCR) and antibody-based serology testing are the approved and accepted by most global healthcare systems in COVID-19 management. However, both techniques carry their inherent shortcomings. As the crisis unfolds, there is an increasing need for alternative means of testing and screening for the deadly disease.

Shortcomings in the currently employed confirmatory test settings are contributed by laborious sample collection, need for qualified personnel, need for high end protective gear and high risk for infection among healthcare providers.

The antibody test on the other hand does not tell who is infected, instead tells us what proportion of the population has been exposed to the virus. The antibodies are generated post exposure requires a week or two, to reach a detectable level. By then there is a likelihood of the virus getting cleared from the system (1-4).

The conventional clinical laboratory tests like the hematology and clinical biochemistry also carry with them inherent low specificity. Therefore, they can only be employed currently to appraise the clinical condition of an individual or a patient. As a result, they can only be indicative for the purpose of confirmatory testing with rtPCR/serology and radiological studies.

While the testing numbers across the globe have climbed to more than 200,000 tests per day in countries like the US, it is increasingly apparent even this is not nearly enough to allow for sufficient surveillance.

Now, in a country like India, its vital that testing, whether it's PCR or antibodies needs to be ramped up as much as possible to screen the general population on a large scale. The enormity of this exercise makes it nearly impossible for the public healthcare systems to meet the cost and scalability of rtPCR/serology. For instance, even if we scale up to 100000 tests per day, we require 35years to complete 1.3 billion population.

Another concern is that these tests cannot be used beyond healthcare settings because they cannot be self-administered by the general population and patients. Currently there are no such self-administered or point of care tests available for the general population. Such tests are essential to ascertain the need for confirmatory tests like PCR for susceptible and asymptomatic infected individuals. Further, in positive cases, there is also need for such point of care tests to monitor the illness, treatment response and recovery, by the care providers remotely.

Researchers and companies across the world are also striving to develop rapid tests to accommodate a variety of samples like urine, blood, saliva, sweat, serum, and other fluids to increase the speed and convenience of sample collection, aiming to overcome one of the challenges in rapidly scaling up testing. (5-10)

The next major concern is that evidence is building up towards increasing percentage of asymptomatic cases of COVID-19 positive

individuals. These individuals pose an enormous threat as super carriers and go unnoticed until they are symptomatic but continue spreading the virus to other susceptible and vulnerable individuals (11-12).

In the backdrop of all these problems and challenges, we realised the need for developing an alternative screening tool and test which meets the following criteria: -

1. Capture markers specific to COVID-19 and serve as a diagnostic tool to identify asymptomatic cases.
2. Non-invasive, Cost effective, scalable and useful in remote point of care settings.
3. A prognostic tool to monitor the progression of the symptoms and treatment effects in such remote and home care settings

Therefor we repurposed our Non-invasive digital biomarker tool Lyfas which was originally developed for capturing cardiovascular, cardiometabolic, cerebrovascular, neuroendocrine, neuroimmunological functional biomarkers. These functional biomarkers are indicative of physiological, pathological and psychological state of an individual useful in predicting and monitoring health and disease status.

Lyfas tool is based on the principles of photo-plethysmography (PPG) and photochromatography (PCG). PPG measure blood volume changes in the microvasculature and PCG measures the reflected light of various blood components. This is carried out from an optical sensor (camera and the flashlight of a smartphone) acting as an input layer. A signal processing layer, our proprietary mathematical modelling and an algorithm, converts the input signal into actionable metrics which constitute the functional biomarker parameters. These parameters were then validated in clinical settings to reflect cardiovascular mechanics, hemodynamics, hemorheology, heart rate variability (HRV), indicative hematology and biochemistry in an individual.

The validated parameters captured from Lyfas were found to be inherent indicators of several cardiorespiratory, cardiovascular, autonomic nervous system, hematology and biochemistry anomalies commonly found and reported recently in early stages of COVID-19 infection. (13- 20).

Therefore, by means of rationale selection of those parameters, we derived an unique LYFAS_COVID_SCORE to enable detection and prioritize confirmatory testing for the asymptomatic individuals.

METHODOLOGY

OBJECTIVE

The objective of this observational study was to develop a smartphone-based screening tool to detect possibility of a COVID-19 infection in asymptomatic individuals and obtain accuracy, sensitivity, and specificity by comparing the results against the standard test RT-PCR based test.

INCLUSION CRITERIA

- Male and Female individuals above the age of 18.

EXCLUSION CRITERIA

- Any patients with acute or chronic illness of any kind requiring hospitalization and critical care.
- Individuals below the age of 18.

Study Participants

In total, 29 subjects were recruited into the study. Then, they were divided into two groups, test Group and control Group. Test group consisted of confirmed cases of COVID-19 by standard RT-PCR test. Control group consisted of n=11(7 males and 4 females) home-based general population in the lockdown period. Test group consisted of n=18(9 male and 9 females). Positive subjects represented general COVID ward patients under observation in Medanta Medicity Hospital, Gurgaon, India.

Data Collection

Each subject was given a Vivo Mobile Smartphone (Vivo S1), pre-installed with Lyfas (Version 9.81) mobile application.

Online hands-on training of standard operating procedure of the application (as per figure 1) was provided to all the subjects. Following this demonstration, every subject was requested to take at least three sample tests to get them familiar with the execution of the test. These tests were excluded from the actual study test results. Following the sample tests, all subjects were made to qualify for the study.

As per the pre-determined criteria for testing, each subject was instructed to execute the Lyfas test two times a day before food (once in the morning and once in the evening).

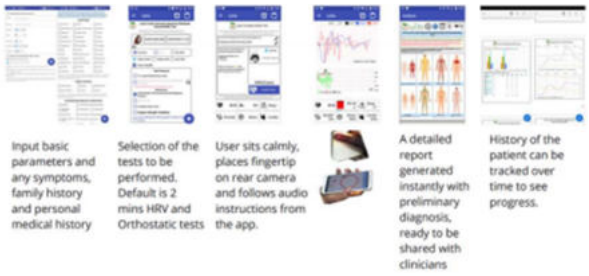


Figure 1: Standard Operating Procedure of Lyfas

Extracted signals are further processed through our proprietary algorithms to extract body Organ system-wide vitals. Changes in these vitals from one session to another session is observed and a detailed risk score is developed. The block-diagram of the system is as shown in figure2.

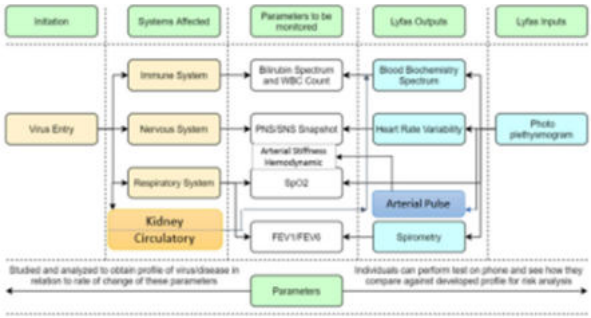


Figure 2: Schematic representation of the proposed hypothesis in repurposing Lyfas COVID 19 testing

LYFAS_COVID_SCORE was derived from a non-linear correlation analysis of quantitative and qualitative parameters captured from the test. The parameters captured includes Heart Rate Variability metrices, Arterial Pulse, an estimate of the functional blood biochemistry reflected in photo chromatographic spectrum(13-20).

Following this, an average daily score was tabulated for minimum three days in every subject.

The score ranges from 0-100 and a threshold of 9.4 was calculated based on Linear Regression with Multiple-R method(cl=99%). The threshold was selected as a differentiating factor between a possible infection (test subject) from non-infection (control subject).

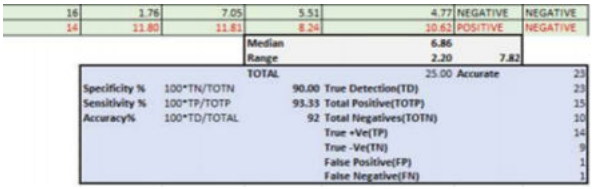
STATISTICALANALYSIS

All the variables were presented as median and range. We used the Man-Whitney U test to compare differences between the two groups (Control and Test groups). A level of 0.01($p<.01$) was considered.

RESULTS

Table 1: Overall Tabulation of all the Subjects

Testing Days	DAY1	DAY2	DAY3	Threshold=9.4		
SUBJECT NO.				Average	Detection	Actual
1	17.74	10.54	4.11	10.80	POSITIVE	POSITIVE
2	14.05	14.88	17.23	15.39	POSITIVE	POSITIVE
3	8.04	11.00	10.74	9.93	POSITIVE	POSITIVE
4	12.41	21.90	23.52	19.27	POSITIVE	POSITIVE
5	30.70	12.71	17.26	20.22	POSITIVE	POSITIVE
6	15.24	18.07	15.94	16.42	POSITIVE	POSITIVE
7	28.59	33.75	18.69	27.01	POSITIVE	POSITIVE
8	19.88	12.05	11.72	14.55	POSITIVE	POSITIVE
9	18.14	20.52	24.35	21.00	POSITIVE	POSITIVE
10	21.99	24.00	20.51	22.16	POSITIVE	POSITIVE
11	25.11	24.95	26.77	25.61	POSITIVE	POSITIVE
12	22.55	24.98	25.16	24.23	POSITIVE	POSITIVE
13	11.62	19.68	21.71	17.67	POSITIVE	POSITIVE
14	16.54	26.62	22.15	21.77	POSITIVE	POSITIVE
15	7.54	11.75	2.93	7.41	NEGATIVE	POSITIVE
			Median	19.75		
			Range	9.93	22.07	
16	4.98	2.85	6.90	4.91	NEGATIVE	NEGATIVE
17	1.84	1.85	2.91	2.20	NEGATIVE	NEGATIVE
18	7.69	6.92	8.14	7.58	NEGATIVE	NEGATIVE
19	2.68	4.75	7.25	4.89	NEGATIVE	NEGATIVE
20	11.54	6.42	5.50	7.82	NEGATIVE	NEGATIVE
21	10.90	15.27	0.00	8.72	NEGATIVE	NEGATIVE
22	7.42	9.53	10.89	9.28	NEGATIVE	NEGATIVE
15	6.85	5.90	7.82	6.86	NEGATIVE	NEGATIVE



16	1.76	7.05	5.51	4.77	NEGATIVE	NEGATIVE
14	11.80	11.81	8.24	10.62	POSITIVE	NEGATIVE

Median		6.86	
Range		2.20	7.82
TOTAL		25.00	Accurate

Specificity %	100*TN/TOTN	90.00	True Detection(TD)	23
Sensitivity %	100*TP/TOTP	93.33	Total Positive(TOTP)	15
Accuracy%	100*TD/TOTAL	92	Total Negatives(TOTN)	10
			True +Ve(TP)	14
			True -Ve(TN)	9
			False Positive(FP)	1
			False Negative(FN)	1

We also managed to capture the LYFAS_COVID_SCORE beyond three days, until the day of discharge (when they were found RT-PCR negative). In our future studies, we would consider this preliminary finding to be included in the protocol to derive a longitudinal Analysis. The results of which assist in the prognosis of the illness.

25 out of the 29 subjects complied to the protocol and completed the study. At the end of the study, 4 subjects were excluded from the final analysis because they failed to meet the pre-determined criteria of minimum two tests a day for three continuous days. 3 of the belonged to the test group and 1 belonged to the control group.

As tabulated in the table 1, 14 out of 15 positive subjects were accurately classified as POSITIVE based on their LYFAS COVID SCORE. 9 out of 10 Control subjects were correctly classified as normal. Overall Accuracy was 92%, Sensitivity of 93.2%, Specificity of 90%.

The average LYFAS_COVID_SCORE in test subjects (positive cases) was significantly (P value is 0.00012) higher than the control group (negative subjects).

DISCUSSION AND CONCLUSION

Our study and findings clearly provide a way and means to identify, differentiate, and prioritize confirmatory testing for the asymptomatic infected individuals using the rtPCR and/or serology. This strategy will certainly help in community level screening and surveillance of the infection. On one hand it will help us to identify high risk asymptomatic individuals, on the other hand reduce the burden on subjecting healthy uninfected individuals to the expensive confirmatory rtPCR testing in an already resource constraint settings.

Using our technology Lyfas and the LYFAS_COVID_SCORE derived out of it, we could for the first time differentiate infected asymptomatic individuals from the healthy. This is a significant breakthrough in providing an effective strategy to prioritize the overburdened testing environment.

In future, a longitudinal study of the score and subsequent analysis can extend its use to monitor the patient's disease progression and treatment response. This can also enable the physicians to assist and monitor mild and moderate cases in a remote care setting using telemedicine platforms (21). Such an initiative can further add value towards reducing unwanted hospital admissions. This preliminary finding deserves extension into a larger population study in similar settings, paving the way for its use in general population.

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