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Conflict, Brain, Thyroid Cancer, and Lyfas: A Step Towards Understanding the Psycho-Oncology with Cardiovascular Optical Biomarkers

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Abstract

Background and objective: Psycho-oncology research envisages the role of psychology (study of the mind) on oncology (study of cancer) and vice versa. It is hypothesized that conflicts influence the brain which causes cancers by causing Autonomic Stress (AS). Lyfas is an m-Health application. It captures AS by examining the optical biomarkers that can bridge conflict and cancers, here, Thyroid Cancers (TCA).

Method: A cross-sectional study involving 33 confirmed TCA cases (16 have a history of conflicts and 17 do not have) took the Lyfas test in the hospital OPD. Among them, 16 had TCA and had a positive history of conflict, while 17 had TCA but no positive history of conflict. Clinical observations are statistically correlated and mapped.

Results: Significant statistical correlations are found between the positive history of conflicts (p-values in males and females are 0.01 and 0.03, respectively), Lyfas biomarkers, e.g., (i) Negative Energy (p-values in males and females are 0.03 and 0.048, respectively), (ii) Stress (p-values in males and females are 0.01 and 0.03, respectively), and (iii) LF/HF in females (p-value 0.04). The study also observes that chance of vasculopathy (high ASI scores by Lyfas) and positive family history, although not statistically significant, have TCA associations.

Conclusions: A high Negative Energy, Stress, LF/HF, along with a positive history of conflict may increase the vulnerability of TCA in the population.

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Introduction

The global incidence rate of *Thyroid Cancer (TCA)* is 10.1 and 3.1 per 100,000 women and men [1]. In India, the incidence of TCA in women and men is 3.9 and 1.3 per 100,000 population, showing a 62% and 48% relative increase [2]. The most type of TCA is papillary or follicular cell CA (60%) in the population [3] and approximately 10% runs in the family due to the mutation of chromosomes 19 and 1 [4].

Conflicts are on the rise, be it societal, financial, political, communal, legal, or so forth globally and India is not an exception. Conflicts cause significant threats, called stress, or one being triggered. Often, it is manifested by repetitive negative self-talking. Negative self-talking combusts higher energy in the brain causing inflammation, which in turn, develops Oxidative Stress (OS) at the mitochondrial level to supply more energy as the demand increases. It results in a neurohormonal imbalance in the encoded signaling and its chemical decoding and vice versa, which leads to mental dysregulations (MD). The brain, as a result, goes into a catabolic state. The Limbic System (LS) in the brain where a tiny structure of emotional processing known as the Amygdala (AG) stays, takes the initial jolt and produces a 'Fight' or 'Flight' or 'Freeze' (FFF) response based on the state of conflict or transfers the signal to the pre-frontal cortex (PFC) for reasoning before responding. Some conflicts are quite dangerous and hijacking AG. In these cases, PFC remains dormant as no signal is transmitted to it from AG. As a result, no sufficient analysis could take place before responding to the conflict-led threat. AG hijacking is therefore a potential stimulus to the sympathetic division of the Autonomic Nervous System (ANS) resulting in flooding of epinephrine in the body. As a result, Heart Rate (HR), Respiratory Rate (RR), Blood Pressure (BP), and glucose production (due to the release of cortisol from the suprarenal glands) are increased to supply the extra energy required for increased catabolism. It leads to Autonomic Stress (AS). Prolonged AS leads to Insulin Resistance (IR)-led MS, mental disorders, sleep problems, etc., which eventually lead to OS at the cellular level, if left untreated, increasing the risk of CA, i.e., unmanageably excessive cytogenesis (cell production) of various sizes and shapes in the tissue, causing tissue growth, called tumor due to loss of programmed cell death mechanism, known as apoptosis.

Inflammation and OS are found as the principal biomolecular mechanisms at the backdrop of AS, which eventually causes IR-led MS and MD. OS is defined as the dominance of prooxidants over antioxidants in the body, where the earlier one is harmful and the latter one is protective [5]. Reactive Oxygen Species (ROS), e.g., Superoxide radical (O^-), Hydroxyl radical (OH^-), Hydrogen Peroxide (HP), hypochlorous acid, etc., and Reactive Nitrogen Species (RNS), such as peroxynitrite, nitrosoperoxycarbonate, which are important prooxidants [6]. Nitric Oxide radicals (NO) cause vasodilatation and maintain homeostasis in endothelial cells of the blood vessels are the RNS antioxidant. ROS maintains cellular homeostasis by controlling the redox-sensitive pathways [7]. Among these, (O^-) and (OH^-) are dangerous as both have a single impaired electron in the external orbit and therefore, are highly reactive chemically. Dual oxidases are critical enzymes for both HP and Thyroid Peroxidase (TPO) [5]. The latter plays an important role in thyroid hormone synthesis in the follicular cells, where thyroid hormones are produced and stored [8]. Hence, OS plays a significant role in hypo and hyperthyroidism and also TCA. Mitochondrial dysfunction due to OS contributes to IR-led MS, causing Cardiovascular Diseases (CVD), Polycystic Ovary Disease (PCOD), early-onset hypertension, atherogenesis, Type-2 Diabetes (T2D), and so on, which are manifested by a metabolic overload due to the overburden of macronutrients in the endoplasmic reticulum. Thyroid hormones maintain the Basal Metabolic Rate (BMR) of the body and there is a risen demand for them in the IR states. Therefore, IR could be linked to OS-induced thyroid disorders and TCA. TCA also produces dysautonomia [5].

Lyfas is a novel biomedical application of one of the medical device startups in India. It is a clinically validated application [9,10], and when installed into an Android smartphone, converts the phone into a healthcare instrument [11]. It uses the phone's hardware to capture Pulse Rate Variability (PRV) from the index finger capillary with the help of arterial photoplethysmography, camera sensors of the phone, and its light source efficiently. From PRV, it captures short (120 sec) Heart Rate Variability (HRV) and its associated Cardiac Optical Biomarkers (CObs) that surrogate the Cardiac Autonomic Modulation (CAM) due to IR-led MS and mental dysregulations due to conflict, which are encountered in AS. In other words, Lyfas captures and analyses the type and extent of AS as the Cardiac Autonomic Neuropathy (CAN). Hence, Lyfas CObs can be useful to understand TCA.

Aim and hypothesis

The paper *aims* to examine the possible correlation between 'retrospective or continued conflicts' and 'TCA' with the help of Lyfas CObs, although chances of cancers in other organs can also be a possibility. The study focuses on TCA and hypothesizes that long-term conflicts may cause TCA.

The expected *impacts* of the study are:

- Aware people to avoid conflicts as much as possible, especially not to live with them for a long time
- Regular monitoring of the Lyfas CObs since the conflict starts in someone's life to note their behavior of causing cancer in the future.

Methods

The study

Type: A case-control study.

Duration: one month (1st October – 1st November)

Recruitment of subjects: A total of 33 subjects, out of which 16 diagnosed TCA patients (mean age 43.5 years, minimum age 15 years, maximum age 65 years, 4 males (M) and 12 females (F)) and 17 not diagnosed as TCA have been considered in the study after written consent from them and their caregivers. The history of conflict of any kind, as mentioned above, and family history of TCA are examined (see Table 1).

Inclusion criteria: Diagnosed TCA and received treatment for 6 months.

Exclusion criteria: Emergent cardiovascular embarrassment.

Data collection: Data has been collected from the department of nuclear medicine of a renowned hospital in southern India under the supervision of nuclear medicine specialists and endocrinologists and after taking the written consent of the subjects and their caregivers. History of conflicts (type and duration) has been collected in each case. Data sources, patients, and doctors are kept anonymous throughout the study to com-

ply with the ethical guidelines of the Helsinki Declaration.

Lyfas tests are taken once in the OPD setup when the patients came for treatment.

A. ***Lyfas CObs*, captured from the 120 seconds HRV, and considered in this study are:**

a) HRVScore is the optical biomarker for mood, desired value >75) [12].

b) LF/HF is the ratio of low and high-frequency waves, respectively and its score is a metabolic (IR) biomarker, having the desired value of <1.8) [13].

c) Energy is another metabolic biomarker, derived from the HRV data with the desired value of 35 - 70 mJ/Kg^2, below 35 (low Energy) is found in depression, 70-100 refers to positive Energy, above 100 is a marker of negative Energy) [12].

d) Arterial stiffness index or ASI (vascular health biomarker, the desired range is -0.2 to 0.5, and any score below and above the range needs vascular investigation) [14].

e) VO_2Max (METs) is the maximum amount of O_2 in ml that is utilized during endurance exercise and hence is a potential cardiopulmonary health biomarker. Its values vary between M and F and age-wise. In Lyfas, the desired value of non-exercise VO_2Max is calculated as follows [15]:

Calculation of VO_2Max_{male} : (ml/Kg/min): 67.350 - [0.381*Age in years]-(0.754*BMI)+(1.951*physical activity rating). The normal range as mean±standard deviation is computed as 50.42±8.37, scores below which are considered abnormal.

Calculation of VO_2Max_{female} : (ml/Kg/min): 56.363 - [0.381*Age in years]-(0.754*BMI)+(1.951*physical activity rating). The normal range calculated as before is 36.80±5.59, scores below which are considered abnormal.

f) Stress is a potential biomarker of the hypothalamus-pituitary-adrenal axis, which is disrupted due to AS and its desired value is 12-32%, whereas values over 50% refer to adrenaline fatigue) [12], and

g) SD1/SD2, which is an anxiety biomarker with the desired value of <3) [13].

B. **Following *conflict parameters/threats* are considered as binary parameters (1: positive, 0: negative)**

a) Cheated, b) Got cheated, c) Guilt, d) Greed, e) Jealousy, f) Aggression, g) Got abused, h) Prolonged-bereavement, i) Legal suits, and i) Financial loss.

The above conflict parameters put threats to the brain, which is the key 'facilitator', the authors are proposing in this paper as *conflict-threat-brain circuitry*. Figure 1. Presents a proposed *conflict-threat-brain circuitry* to understand the threat-based conflict pathology (the ellipse in the figure) in the brain. Threats perceived from the environment transmit to the brain, which in turn responds as 'Negative emotions'. It then goes to the hippocampus as the encoded signals and stored. A further challenge with the similar type of external stimuli, the hippocampus decodes the earlier signals and sends them to the brain for responding to the repeated stimuli. 'Negative emotion response' happens in either of two ways – (i) 'conditional' when the brain is prepared based on the learning of the similar stimuli, encountered earlier (known as coping) or (ii) 'unconditional' when that coping mechanism is unavailable because the stimuli are abrupt, unprepared, and unexpected. The latter coupled with a continuous supply of similar types of stimuli by the hippocampus, causes' apprehension and suspicion', which when goes into a recursive loop, leads to stimulation of ANS through sympathetic overdrive that causes inflammation of the brain if continues for a prolonged period. In this work, the researchers delved into the types of 'Negative emotions' that the subjects have perceived continuously or at some part of their lives and found that the threats have lowered their 'self-esteem' (100%) [16] and increased the 'pathological jealousy' (100%) [17], which are two constant emotions that the study population has suffered or still suffering. In this paper, that's why the researchers have hypothesized that long-term conflicts may play a crucial role in brain inflammation, AS, and finally cancers.

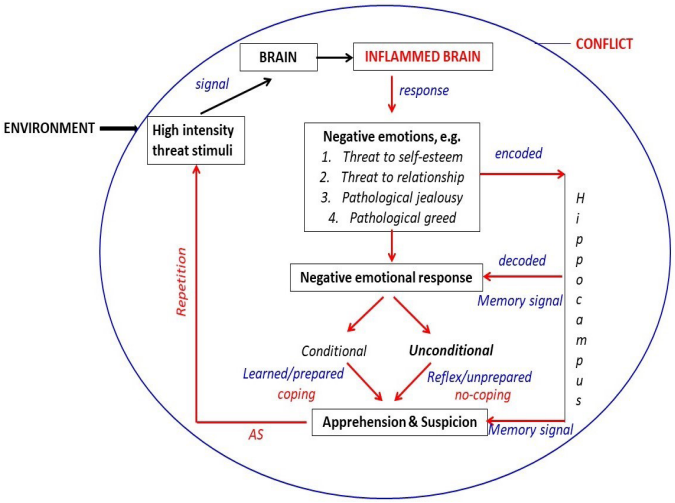

Figure 1: Conflict-threat circuitry of the brain.

C. Family history of TCA (1: positive, 0: negative).

Data analysis:

The tool used:

i) MS Excel (Office Professional Plus 2019), and

ii) Python 3.8 on Windows 10 Pro having Intel(R) Core(TM) i5-3360M CPU @ 2.80GHz 2.80 GHz.

Step-1: The data is sampled group-wise in the form of a contingency table to get a clear picture of gender-wise distribution.

Table 1: The contingency table (group-wise).

Group	Present		Absent		Subtotal		Total
	M	F	M	F	M	F	
Conflict	3 (18.75%)	13 (81.25%)	3	14	6	27	33
Family history	3 (18.75%)	8 (50%)	5	17	8	25	
TCA	4 (25%)	12 (75%)	6	11	10	23	

It is important to note here that 100% of M give a history of 'lack of self-esteem' with guilt (34%) repentance for over a decade as they cheated on their friends or family members at some point in time. On the other hand, F gives a prolonged (over a decade) history of 'jealousy' (100%) alongside the 'greed' (20%) [18] due to the compare-and-complaining nature of themselves or their mothers or mothers-in-law, as obtained from the history. The remaining parameters of conflict are not found significant in the study population.

Step-2: Descriptive statistics

It shows the data distribution as minimum value, maximum value, mean, median, and standard deviation, parameter-wise.

Table 2 shows the descriptive data.

Step-3: Normality check

A Quantile-Quantile plot or Q-Q plot is a type of data scatter plot on a 45-degree diagonal straight line. For normally distributed data, the scatter plot is aligned to that diagonal line. Fig. 2 shows the Q-Q plot.

Step-4: Mann-Whitney U-test (U-statistics) to note the median difference between the following groups:

a) Male vs. Female as the independent parameters and TCA is the dependent parameter,

b) Positive history of conflict vs. No history of the conflict as the independent parameters and TCA as the dependent parameter, and

c) Positive family history vs. Negative family history as the independent parameters and TCA as the dependent parameter

The null hypothesis is that the samples are derived from the same source and there are no median differences (p-value >0.05; CI 95%), which the alternative hypothesis refutes (p-value <0.05).

Step-5: Spearman's correlation test to note the correlation of Lyfas CObs with (i) family history, (ii) positive history of conflict, (iii) positive history of both (i) and (ii), and finally with (iii) TCA. The 'ρ' values are the correlation values between any two parameters and the 'p-values' are to note how statistically significant is the correlation. Positive, negative, and close to '0' 'ρ' values indicate positive, negative, and non-correlations. In this study, 'ρ' values on both the positive and negative sides (within -1.0 to -1.0 scale, i.e., 100% to -100%) are considered important alongside the p-values (statistical significance of such correlations). Table 3 shows the correlation-based ranks of the parameters and their respective p-values.

Results

Table 2: The descriptive statistics.

	Minimum value	Maximum value	Mean	Median	Standard dev
Age (years)	18	65	43.5	43	14.18
Family history	0	1	0.45	0	0.50
Conflict	0	1	0.63	1	0.48
HRVScore	69	90	81.33	81	5.15
LF/HF	0.4	1.9	1.16	1.1	0.42
Energy	20	490	113.33	77	113.37
ASI	0.4	1.9	1.01	1	0.42
VO2Max	42	103	80.81	82.45	15.23
Stress	0	68	28.09	28	15.96
SD1/SD2	0.5	2	1.43	1.55	0.41
TCA	0	1	0.48	0	0.5

Descriptive statistics show the average (i) Energy is >100 mJ/Kg^2, which means that most have negative energy, and (ii) ASI score is >0.5, which means they might have vasculopathy and need investigations. These are two important observations to ponder. Table 3 shows the statistical validity of these observations.

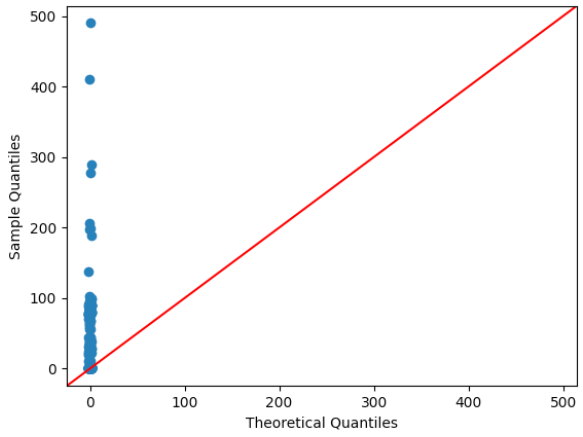

Figure 2: The Q-Q plot.

Table 3: Experimental observations statistically correlated.

Independent parameters	Dependent parameter	Observation		Correlation (ρ)		p		Rank
		M	F	M	F	M	F	
+ve Family history	TCA	18.75%	81.25%	-38%	-24%			
+ve History of conflict		18.75%	50%	99%	31%	0.01	0.03	1
HRVScore		0	6.25%	-73%	-48%			
LF/HF		0	12.5%	84%	15%	0.09	0.04	
Energy (negative)		18.75%	43.75%	81%	14%	0.03	0.048	3
ASI		100%	50%	-68%	-50%			
SD1/SD2		N	N	NC	49%			
VO2Max		12.5%	53.75%	-76%	-39%			
Stress		12.5%	18.75%	54%	58%	0.01	0.03	2

The plot in Figure 2 shows that the data scatter is not aligned to the 45-degree line and hence it is not normally distributed.

Mann-Whitney U-statistics does not bother about the normality of the data and the sample size to note whether the median differences of two independent groups (cause) to the dependent group (outcome) are true or not. In this study, the differences between two independent parameters, such as male and female associated with TCA, positive family history vs. negative family history of TCA, and positive history of conflict vs. negative history of conflict to the development of TCA are tested. Here, TCA is the dependent parameter. The study observes that there is a significant difference in the respective study groups and the p-values are 0.045, 0.001, and 0.033, respectively.

The findings of *Spearman's correlation* study are mentioned in Table 3 to substantiate the strength of observations genderwise.

In this table, Lyfas CObs having low/poor scores are considered to establish the link with TCA. NC is non-correlation and N is not observed. *Positive family history of conflicts, Stress* and *Negative Energy* are the first, second, and third-ranked parameters, which significantly influence the occurrence of TCA in this study group. In the case of F, *LF/HF stands* as another cofounding factor. Ranks are assigned to the parameters, which impact both genders.

Discussions

The study aims to correlate conflicts with the incidence of TCA in the vulnerable population. It is an attempt to map the conflict-threat-brain circuitry, the authors have proposed, at its backdrop. The study has two important analytical parts – the *observational* data and the validation of such observations statistically by computing the strength of *correlations* between any two parameters. Based on the findings, it has attempted to provide a biopsychosocial model of TCA in the vulnerable population.

Key observations of the study are a high (i) negative Energy and (ii) risk of vasculopathy (abnormal ASI scores), a positive (iii) family history, and (iv) history of conflicts are key parameters of TCA in this population.

Key correlations findings are (i) history of conflicts (rank 1), followed by a new parameter called (ii) high stress (rank 2), and (iii) negative energy (rank 3) shows high correlations with the risk of TCA in both the genders. In the case of F (iv), increased LF/HF scores are positively correlated as an additional marker of IR and high sympathetic drive during expressed anger [19].

The biopsychosocial theory of cancer is under the epidemiological scanner for years now. The revolutionary study of Dr. Ryke Geerd Hamer (2008) showed that sudden (unexpected and unprepared) emotional shock, called the Dirk Hamer Syndrome (DHS) in certain areas of the brain is the principal conspirator of cancers or similar dreaded diseases develop in our body [20]. Dr. Hamer envisioned in the German New Medicine that the psychic-brain-organ ratio governs the cancers and similar grave diseases, that originate in the brain, where 'conflicts' and 'stress' (i.e., the psychic part) are the two key drivers of the 'brain'-based 'organ' defects (20). 'Organ' defects are the consequences of 'tissue' defects, which are due to certain changes in the 'cells' [21].

The authors, in this work, have conceived logically the observation of Dr. Hamer and applied it to create a biopsychosocial model of TCA with the help of modern neurobiology and Lyfas optical biomarkers, which are statistically correlated (see Figure 3).

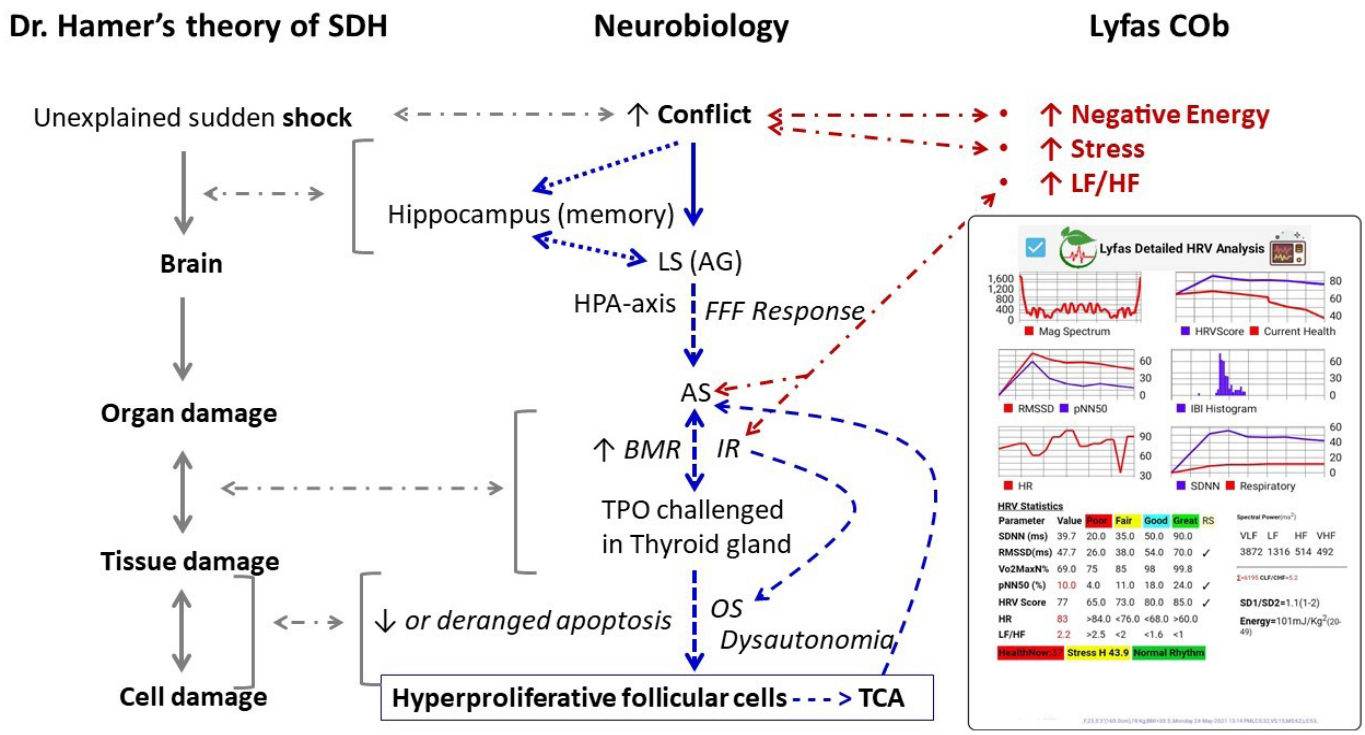

Figure 3: The biopsychosocial model of TCA with Lyfas CObs.

The authors, in Figure 3, explain how Dr. Hamer's theory of SDH is logical and pertinent to explaining the rise of conflicts and TCA in society. As mentioned earlier, conflicts trigger LS and AG in the first instance. The extent of the effect is stored in the hippocampus i.e., the memory center of the brain as any other high-impact information is stored as encoded signals [22]. Each time a similar conflict arises, the hippocampus is stimulated and transfers the encoded signal to LS (AG) and then the PFC, if AG is not hijacked. High impact (unexpected and abrupt) conflicts highjack AG, e.g., pathological jealousy [17,23]. Hence, the signal does not reach the PFC for further reasoning and analysis, as mentioned before. It excites the HPA-axis and the brain goes into an inflammatory state [24]. From the adrenal gland, at first, cortisol isesteem secreted as a protective mechanism to increase the glucose (the energy) in the blood to meet up the high BMR due to inflammation. In case of a prolonged demand, the adrenal gland secretes epinephrine that produces a sympathetic drive in the body and the heart rate and respiratory rate are increased to supply the energy to the affected tissues. The body goes into AS and IR [25]. Thyroid hormones balance the BMR in the body. TPO, found in the follicular cell membrane, is the key enzyme for their synthesis [26]. It helps by adding iodine to a protein called thyroglobulin, a critical step for thyroid hormone production [26]. In the case of IR and AS, TPO may be challenged to produce more thyroxins in the follicular cells, which in turn, undergo into OS, causing differentiated and undifferentiated TCA, where TPO antibody is a potential marker of TCA [27]. Coupled with loss or decreased apoptosis (the body's protective mechanism of programmed cell deaths to maintain the homeostatic balance in the cell growth), and the genetic predispositions, TCA finally occurs in the vulnerable population, as the authors envision.

Lyfas measures the AS from short HRV data. In this study, high negative Energy and high Stress can be seen in both the genders significantly. In F, LF/HF, which is the IR biomarker is an additional parameter that might be responsible for the increased risk of TCA in them, compared to M. TCA also produces dysautonomia by manipulating brain cell growth [5]. However, the authors mention that these are preliminary but interesting findings and a metanalytical study might be needed to affirm the roles of these biomarkers. Based on the findings of this study, the authors suggest that TCA can be predicted/apprehended/suspected much early if persistent high negative Energy, positive history of conflicts, high autonomic stress, and high IR risks are noted in Lyfas test-takers. In this way, Lyfas can be used for screening and early risk assessment of TCA in the population at risk. This is the contribution of this work.

The societal impacts of this work are as follows:

- Early screening of the vulnerable population
- Based on the risk grade, those can be sent for oncological consultations
- Early management of cancer at its very early stage improves the prognosis of the case and less chance of metastatic dissemination in the body, and
- Lyfas is user-friendly, economic, pervasive, and a non-invasive health instrument

The limitation of the study is the small sample size. However, the authors argue that a small sample, even of a size of <10 or so is normally found in the preliminary studies in biology and healthcare. Trial studies are performed with small samples. The size of the sample does not necessarily tamper with the fundamental principles of science and limits the key observation, which this work corroborates. The small size of the sample could be due to financial constraints, availability of data, rare diseases e.g., certain types of cancers, neuromuscular diseases, immune disorders, and so forth. TCA is quite rare in the population. Therefore, the available data is small in this study. However, the U-statistics among the groups show a significant median difference, and hence, it can be affirmed that the data, although small in size, is scientifically acceptable and not limited to biased observation.

Conclusion

The paper is a three-pronged approach to understanding the psychobiological basis of TCA with the help of (a) Dr. Hamer's SDH model, (b) neurobiology, (c) Lyfas optical biomarker m-health instrument. The study proposes that the brain is the key decider of cancers and other inflammatory and deadly metabolic diseases. Psyche is the manipulator of the brain. The organ-specific insult at the cellular level is a complex phenomenon as it involves the HPA-axis-led AS, IR, and OS. Hence, negative thoughts that are originated out of conflicts (measured as Lyfas Negative Energy, p-value 0.03 and 0.048 in M and F) and AS (measured by Lyfas Stress score, p-value 0.01 and 0.03 in M and F) fall under the psyche, which drives the brain (HPA-axis and FFF-response dysregulation or AS) crazy, which is captured as the LF/HF biomarker scores in Lyfas (p-value for F is 0.04). The study proposes that recurrent threat stimuli inflame the brain, if not coped enough. The inflamed brain, due to prolonged low quality of life [28], in turn, causes TCA in the study population.

The scores of Negative energy, Stress, and LF/HF biomarkers in Lyfas tests could throw light on the risk of TCA in the vulnerable population. According to the result of the study, the presence of the history of the conflict increases the vulnerability.

The authors, based on these preliminary findings, are encouraged to study a larger population for full-proof research.

Ethical considerations: Vagus Institutional Ethics Committee, Bangalore India, 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). The study has been conducted per the declaration of Helsinki. Consents to participate are taken from all participants on the organizational letterhead. The detailed process of the study has been duly explained to them and their caregivers.

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Conflict of interest: There is no conflict of interest.

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