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Original Article

Internal Medicine Section

Quantitative Definition of Fever Needs a Change: A Longitudinal Study from the Hospital Workers and their Family Members

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ABSTRACT

Introduction: The age-old definition of fever was derived using cross-sectional population surveying utilising old techniques without considering symptomatology. However, the diagnosis of fever must be made only in the presence of associated symptoms that can distinguish it, from the mere asymptomatic physiologic rise of temperature.

Aim: Analysis of symptoms to redefine the cut-off of fever based on symptomatology.

Materials and Methods: A longitudinal study on the healthy population of Uttarakhand, India was conducted and the population was followed-up from July 2019 to September 2020. Healthy staff and students of All India Institute of Medical Sciences (AIIMS), and their family members between 4-100 years of age were chosen. Participants were advised to self-monitor oral temperature with a standard digital thermometer in either left or right sublingual pocket and record it in the thermometry diary. The study was considered complete, if the participant had all the three phases of the study (i.e., prefebrile, febrile, and postfebrile phases) or completed the duration of the study. The febrile phase was defined when the participants subjectively 'felt feverish'. Associated symptoms like fatigue, warmth, headache, and feeling malaise were also recorded.

Results: Mean age of the participants was 24.24±5.92 years, and 52.1% (75) were males. Per protocol analysis was done for febrile participants (n=144, temperature recordings=6544). The mean febrile phase temperature was 100.25±1.44°F. A temperature of 99.1°F had maximum diagnostic accuracy for feeling feverish (98.2%), along with 1 (98.3%) or 2 (99%) associated symptoms. Summer and spring months showed higher temperatures (100.38±1.44 vs 99.80±1.49, p-value <0.001), whereas no significant temperature difference could be noted amongst the genders.

Conclusion: Based on the findings of the present study, the revised temperature cut-off to define fever should be 99.1°F along with one or two associated symptoms.

Keywords: Pyrexia, Symptomatology, Temperature variability, Thermometry

INTRODUCTION

"Humanity has but three great enemies: fever, famine, and war, and of these by far the greatest, by far the most terrible, is fever." This statement by William Osler describes the paramount importance of fever since ancient medicine. The temperature has been one of the most important vital signs and recordings; it has been a critical component of good patient management. The core human body temperature depends on the appropriate functioning of the body [1]. Maintaining it within an optimal range, is necessary for human life. It undergoes a regular circadian fluctuation of 0.5-0.7°C, with the lowest in the early morning and highest in the evening. Similar temperature variation is also seen in the females during their menstrual cycle. The temperature may rise 0.6°C or more through the menstrual cycle [2]. Furthermore, the balance between heat production and heat loss determines the body temperature. Once this balance is lost, the temperature is raised in the body, known as fever. Hence, technically fever is a sign of some underlying pathology.

Wunderlich (1868) had defined the normal body temperature as 37°C (98.6°F). However, his methods were outdated. Mackowiak PA et al., set out to question this time-honoured Wunderlich's dictum. They did a cross-sectional study on young adults (younger than 40 years) using a standardised thermometer and concluded that, 36.8°C (98.2°F) rather than 37.0°C (98.6°F) was the mean oral temperature of their participants; 37.7°C (99.9°F) rather than 38.0°C (100.4°F) was the upper limit of the normal temperature range [3]. Protsiv M et al., hypothesised that the normal oral temperature of adults is lower than the established 37°C of the 19th century and concluded that body temperature has decreased over time in the United States of America (USA) using measurements [4]. Recent studies suggest that normal temperature has invariably decreased by 0.03°C per birth decade, probably due to lowered metabolic rate and infections, henceforth drifting down the normal morning body temperature to less than <98.6°F over the last two centuries [4-8]. The influence of age, time of day, gender, and economic development preclude an updated definition of fever [9].

All studies till now, were cross-sectional resulting in a complete bias of the measured temperature whether in prefebrile, febrile, or postfebrile phase. Temperature rise above normal (known as fever) is a sign that should be studied longitudinally. The change over time provides important physiologic clues to alterations in human health. Considering 98.6°F as normal body temperature in the light of newly available evidence would have untoward consequences, and it has been riddling since the inception of modern medicine and needs to be relooked into a new dimension preferably through a developing society. This can be done by prospectively studying body temperature of a healthy population when they are afebrile, have fever, and in the postfebrile phase.

Thereby, a longitudinal study was done on healthy participants using a standardised electronic thermometer in the left or right posterior sublingual pocket and analysing the associated symptomatology, to derive a new symptom-associated definition of fever.

MATERIALS AND METHODS

The longitudinal study was conducted at All India Institute of Medical Sciences Rishikesh (AIIMS), a tertiary healthcare centre in

Uttarakhand, India. It was conducted from July 2019 to September 2020, after approval from Institute Ethical Committee (IEC) (No. 235/IEC/PGM/2019).

Lists of employees and students of AIIMS Rishikesh were obtained from the Human Resource Department and Registrar's office. Information of participating family members was obtained from consenting employees and students. Participants were selected via a simple random sampling method using the computer. If the participant did not consent to the study, then the next person on the list was selected. Taking the standard deviation according to a study done by Mackowiak PA et al., as 0.7 and employing T-distribution to estimate sample size, a sample size of 192 with 95% confidence and a precision of 0.1 was estimated [3].

The participants were recruited based on the following inclusion and exclusion criteria, after taking informed consent.

Inclusion criteria: Healthy staff and students of AIIMS and their accompanying family members between 4-100 years working/studying at AIIMS during the study duration.

Exclusion criteria: Any individuals with any diagnosed or suspected disease (any acute infectious or non infectious illness (including trauma) within last one month and postpartum period upto eight weeks; any known case of or past history of chronic illness-infective (e.g. tuberculosis, Kala azar, brucellosis, infective endocarditis, Human Immunodeficiency Virus (HIV), hepatitis B/C/D etc.), rheumatological (e.g. rheumatoid arthritis, systemic lupus erythematosus, vasculitis etc.), chronic liver disease, chronic kidney disease, cardiovascular disease (e.g. systemic hypertension, coronary artery disease, valvular heart disease, pulmonary arterial hypertension, peripheral vascular disease etc.), chronic lung disease (e.g. any obstructive or restrictive airway diseases), endocrinopathy (e.g. diabetes mellitus, diabetes insipidus, hypo/hyperthyroidism etc.), gastrointestinal disease (e.g. dyspepsia, inflammatory bowel disease, malabsorption syndromes etc.), neurologic disorders (e.g. epilepsy, stroke, dementia, movement disorder, degenerative disorder, cerebral palsy etc.), psychiatric disorder (e.g. mood disorders, psychosis, dependence syndrome (s) etc.), dermatological diseases (e.g. bullous disorders, psoriasis, tinea etc.), any malignancy (treated or otherwise), recent history of vaccination in last six months, and ankyloglossia were all excluded from the study.

Study Procedure

Detailed clinical evaluation (history and examination) was done. Basic investigations (which were done within the last one year; as per Institute recruitment policy): ECG, chest X-ray, viral markers (anti-HIV-1 and 2, HBsAg, anti-HCV), urine routine, complete blood count, fasting blood glucose, liver and kidney function tests were collected from medical record section. If any abnormality was detected, they were excluded without sharing details.

The study was done in three phases:

- The first phase (non febrile phase)
- The second phase (febrile phase)
- The third phase (postfebrile phase).

The participant's subjective sensation of feeling 'feverish' was taken to define the febrile phase's onset with change in baseline temperature. One clinical thermometry diary, a ball pen, and a standard electronic thermometer [Dr. Morepen Digiflexi Flexi Tip Thermometer® (MT222) with error 0.05°F] were provided to all the participants. They washed their hands and ensured no physical exertion in the preceding 30 minutes. The thermometer was placed in the oral left or right posterior sublingual pocket. The participants recorded the temperature on the Fahrenheit scale and the time in the thermometry diary. Three readings were taken, once after waking up (AM), once in the afternoon (AN; 12-3 PM), and once before sleeping (PM). They also recorded any symptoms from the checklist simultaneously. There were three days of more frequent temperature charting (every 2nd hour, except sleeping time) during the non febrile phase and two days of frequent temperature charting during postfebrile phase, and for all the days during the febrile phase.

The investigator verified the first reading. Participants were followed-up fortnightly physically and reminded weekly telephonically for recording temperatures. Self-recording of data was done in the provided clinical thermometry diary, and the same was assessed fortnightly by the investigator (s) for troubleshooting and to see the status of the recording.

There was no comparator except among three phases of temperature recordings. Participants with the febrile phase were further divided into four subgroups based on seasonal months: November-January (represented coldest months of the year); February-April (representing spring months); May-July (representing hottest months); August-October (representing autumn months). A maximum of 45 days of data was taken immediately before the febrile phase, during the non febrile phase of per protocol analysis. A maximum of 10 days of data was taken immediately after the febrile phase during the postfebrile phase, and complete data of the febrile phase was taken for analysis. The frequent temperature readings (i.e. two hourly temperature records) were taken for analysis for all three phases, especially to see variations.

STATISTICAL ANALYSIS

The data was entered in the excel sheet, and primary outcomes were analysed as per protocol analysis (for those participants who had all the three phases in the study) using Statistical Package for Social Sciences (SPSS) version 23.0. Categorical variables were presented as number and percentage (%) and continuous variables as mean±Standard Deviation (SD). The Kolmogorov-Smirnov test tested the normality of data, and if rejected, a non parametric test was used. Quantitative variables were compared using the independent t-test/Wilcoxon's Mann Whitney test (when the data sets were not normally distributed) between two groups and the Kruskal's Wallis test between three and more groups. The continuous variables, those that were not normally distributed, were analysed using Shapiro-Wilk Test. To define fever cut-offs with respect to symptoms, Receiver Operating Characteristic (ROC) curve analysis was done, and the cut-off was taken as the point with maximum diagnostic accuracy. Taking confidence level as 95%, a p-value <0.05 was taken as statistically significant.

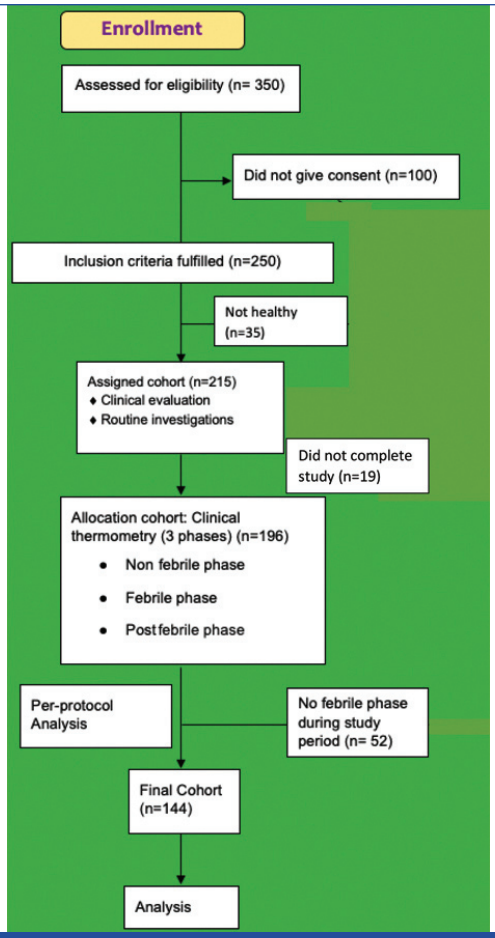
RESULTS

Three hundred fifty (350) participants were screened, 250 consented to be a part of the study, and 215 were found to be clinically healthy, 144 were included in the per protocol analysis [Table/Fig-1]. The participants included healthy subjects with a mean age of 24.24±5.92 years (8-58 years); 72.2% (104) belonged to the age group 20-40 years; 52.1% (75) were males [Table/Fig-2]. The normal temperature variation was measured [Table/Fig-3] along with associated symptoms. According to the per protocol analysis for the 144 participants, 6544 readings were taken for analysis.

The temperature cut-offs for feeling feverish were determined based on ROC analysis with diurnal, seasonal, and gender variations [Table/Fig-4,5a,b]. The temperature values were highest in the months of spring (100.38±1.44°F) and summer (100.26±1.40°F) months as compared to winter (100.13±1.42°F) and autumn (99.80±1.49°F) (p-value <0.001).

DISCUSSION

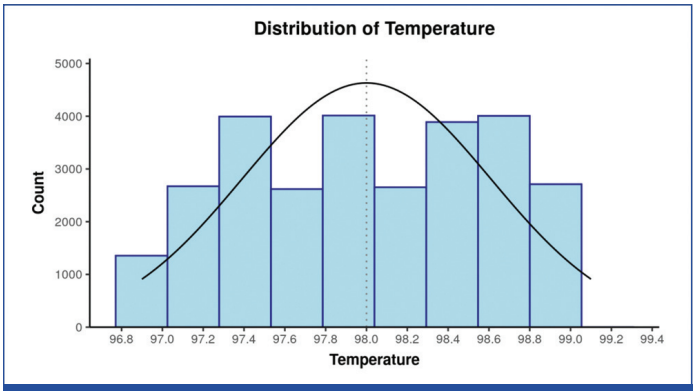
Analysis of 6544 temperature readings of the 144 healthy participants was done longitudinally over one year. This longitudinal study of a healthy population, mainly in the adult age group, demonstrated that a temperature of 99.1°F had the highest diagnostic accuracy in predicting fever (98.2%), which increased



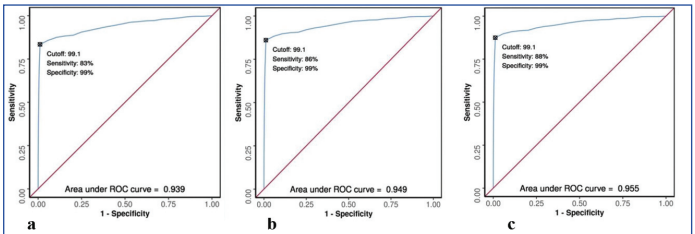
[Table/Fig-1]: The study protocol.

Age (Class Interval-Years)	n (%)
<20	37 (25.7)
20-40	104 (72.2)
>40	3 (2.1)
Sex	**n (%)**
Male	75 (52.1)
Female	69 (47.9)

[Table/Fig-2]: Age and gender distribution.



[Table/Fig-3]: Temperature variability in the afebrile phase of the cohort.



[Table/Fig-4]: ROC curve analysis showing diagnostic performance of (a) temperature in predicting feeling feverish; (b) temperature +1 more symptom in predicting feeling feverish; (c) temperature +2 more symptoms in predicting feeling feverish.

Group	Temperature cut-off (°F)	Sensitivity	Specificity	Diagnostic accuracy
Feeling feverish	98.5	91%	75%	75.4%
	98.8	89%	88%	88%
	99.1	83%	99%	98.2%
	99.3	79%	99%	97.6%
	99.5	78%	99%	97.5%
Feeling feverish and one more associated symptom	98.5	94.7%	70%	70%
	98.8	93%	84%	84%
	99.1	86%	99%	98.3%
	99.3	82%	98.5%	97%
	99.5	81%	98.8%	97.8%
Feeling feverish and two more associated symptoms	98.5	99.9%	70%	71%
	98.8	96%	84%	84%
	99.1	88%	99%	99%
	99.3	87%	99%	98.9%
	99.5	85%	99%	98.8%

[Table/Fig-5a]: Sensitivity, specificity, and diagnostic accuracy of various temperature cut-offs for determination of fever.

further when associated with 1 (98.3%) or 2 (99%) additional symptoms. The diagnostic accuracy of temperature measurement and the associated symptomatology for fever prediction was highest in the morning compared to the afternoon or evening. The predictive ability was maximum in the summer months (May-July) compared with spring, winter, and autumn [Table/Fig-4a,b,c,5a,b]. The criteria demonstrated, higher sensitivity amongst the females than the males. Accuracy increased with the increase in the number of associated symptoms.

An AM temperature of >37.2°C (>98.9°F) or a PM temperature of >37.7°C (>99.9°F) defines fever [10]. American College of Critical Care Medicine, the International Statistical Classification of Diseases, and the Infectious Diseases Society of America define fever as a core temperature of 38.3°C (100.9°F) or higher, just above the upper limit of normal human temperature, irrespective of the cause [11]. This quantitative diagnostic study considers the associated symptomatology to determine the temperature cut-off for fever and is the first to be reported. As mentioned before, all previous studies on the definition of fever were cross-sectional, and no study took into account the symptomatology along with the quantification of fever. The present study defines fever accurately, because of the longitudinal instead of cross-sectional design. Accordingly, when the person has the associated symptoms, fever sets in as mere temperature rise can be physiological also. Usually, the body temperature rises as the day passes [12]. This formed the basis of the old fever definition having a lower threshold for the morning temperature than the evening.

Renbourn ET and Bonsall FF in British India found out that oral temperatures higher than those accepted as usual for temperate climates were recorded during the summer months in North India [13]. This again demonstrates that, the temperature per se is just a quantitative variable that can also undergo fluctuations with the outside seasonal variation, further strengthening present study's importance. A mere rise of temperature value should not be called fever, but this should be termed fever when combined with the associated symptoms. In present study also, the temperature values were highest in the spring (100.38±1.44°F) and summer (100.26±1.40°F) months as compared to winter (100.13±1.42°F) and autumn (99.80±1.49°F) (p-value <0.001). No previous studies have observed these changes. Females are considered to have higher baseline temperatures, although present study could not find any significant temperature difference between the two sexes in present study.

Variation	Group	Subgroup	Temperature cut-off (°F)	Sensitivity	Specificity
Diurnal variation	Feeling feverish	AM	99.1	86%	99%
		AN	99.1	84%	99%
		PM	99.1	81%	99%
	Feeling feverish and one more associated symptom	AM	99.1	88.2%	99.1%
		AN	99.1	86.1%	98.8%
		PM	99.1	83.4%	98.7%
	Feeling feverish and two more associated symptoms	AM	99.1	90.2%	99.1%
		AN	99.1	86.6%	98.7%
		PM	99.1	85.1%	98.7%
Seasonal variation	Feeling feverish	February-April	99.1	85.4%	98.6%
		May-July	99.1	93.3%	99.3%
		August-October	99.1	60%	98.8%
		November-January	99.1	83.6%	98.4%
	Feeling feverish and one more associated symptom	February-April	99.1	89.5%	98.4%
		May-July	99.1	93.3%	99.3%
		August-October	99.1	63.2%	98.8%
		November-January	99.1	83.6%	98.4%
	Feeling feverish and two more associated symptoms	February-April	99.1	90.5%	98.4%
		May-July	99.1	93.3%	99.3%
		August-October	99.1	63.9%	98.7%
		November-January	99.1	83.3%	98.3%
Variation with gender	Feeling feverish	Male	99.1	82.7%	98.9%
		Female	99.1	84.2%	98.9%
	Feeling feverish and one more associated symptom	Male	99.1	85.2%	98.9%
		Female	99.1	86.9%	98.8%
	Feeling feverish and two more associated symptoms	Male	99.1	87.2%	98.8%
		Female	99.1	87.7%	98.8%

[Table/Fig-5b]: Sensitivity and specificity of temperature cut-off 99.1°F in determining fever amongst subgroups.
AM: 12 am-12 Noon; AN: 12 noon-3 pm; PM: 3 pm-12 am

Limitation(s)

The sample was unicentric and difficult to generalise; thus, a more extensive multicentric study is required. The vulnerable group of the population, elderly and children, could not be included in the study desirably. The participants were defined healthy, based on history and predefined biochemical and laboratory parameters; therefore, indolent chronic infections and subclinical non infectious illnesses could not be ruled out. No physical way of checking the adherence to the advised procedure for the temperature measurement was there. The participants were reviewed and followed-up fortnightly. So, strategies to measure directly observed temperature may be required. The oral temperature in the left or right sublingual pocket is close representative of core body temperature but not precisely the core body temperature. The ongoing Coronavirus Disease-2019 (COVID-19) pandemic might have influenced the results. The participants constituted were a high-risk populace for infectious agents and stress. As mentioned, patients were allowed to take antipyretics; hence the temperature values could be lower with drug use. Another major limitation was that the febrile phase's categorisation was solely based on the subject's subjective sensation of feeling feverish. As it is a subjective sensation, it can vary from person to person. Nevertheless, this in itself forms the basis of the present study that fever is a sign that varies from person to person, and it is not merely a numerical cut-off that can be generalised to the whole population.

CONCLUSION(S)

Authors propose an oral temperature cut-off of 99.1°F, along with one or more associated symptoms, to accurately predict fever with a sensitivity of 88% and specificity of 99%. This finding calls for a universal change in the definition of the same in Indians. There is lower value of the evening temperatures in the febrile phase, may be due to more antipyretics intakes at day times. The temperature values were highest in the spring and summer months as compared to winter and autumn.

Declaration

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