

# Adverse effects of cigarette smoking on exhaled breath carbon monoxide, blood carboxyhemoglobin, and hematological parameters amongst Sri Lankan adult tobacco smokers: A descriptive study

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## KEYWORDS

tobacco smoking, Brinkman index, exhaled breath carbon monoxide (eCO), carboxyhemoglobin (COHb%), hemoglobin (Hb)

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## ABSTRACT

**INTRODUCTION** Tobacco smoking is the single most preventable cause of death worldwide and a major risk factor for several non-communicable diseases. Tobacco smoking has both acute and chronic effects on hematological parameters. The study aims to assess the effects of smoking intensity on exhaled breath carbon monoxide (eCO), carboxyhemoglobin (COHb%) and hematological parameters.

**METHODS** Adult male daily smokers (n=360) and matched non-smoking males (n=180) from Colombo district, Sri Lanka, were selected. Sociodemographic data, smoking habits and anthropometric data were recorded. An automated Smokerlyser (Smokerlyser®, Bedfont) was used to estimate eCO and COHb% in exhaled breath and Brinkman index was used to quantify the level of smoking exposure. A venous blood sample was analyzed for a full blood count. Smokers were compared with the non-smoking group.

**RESULTS** Smokers had significantly higher values of eCO, COHb%, Hemoglobin (Hb), Hematocrit (HCT), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), total White Blood Cell total count (WBC), Lymphocyte count, Monocyte count, and Granulocyte count. The number of cigarettes per day, duration of smoking, and Brinkman index were positively correlated with eCO and COHb%. MCV and MCH were positively correlated with the number of cigarettes smoked per day, smoking duration, and Brinkman index.

**CONCLUSIONS** The severity of smoking can be quantified by the exhaled breath CO and blood COHb% levels as these parameters correlate with the severity of smoking. Hematological parameters of smokers were affected with continued long-term low-intensity smoking.

## INTRODUCTION

Smoking is a leading preventable cause of death and illness worldwide<sup>1,2</sup>. Smoking has a detrimental effect on the smoker's life expectancy and has a major economic impact on the family<sup>3,4</sup>. Annual mortality totals 8 million people, with 7 million of these fatalities directly attributable to tobacco usage<sup>5,6</sup>. Over 80% of the 1.3 billion tobacco smokers worldwide live in low- and middle-income countries<sup>7,8</sup> and

tobacco smoking is a critical health issue in Sri Lanka, claiming over 20000 lives each year<sup>9</sup>. According to WHO statistics, 29.4% of Sri Lankan males are smoking tobacco<sup>10,11</sup>, and amongst them 19.5% smoke daily<sup>12</sup>. Smoking is a well-established risk factor for the development of a range of diseases<sup>13,14</sup> including major cardiovascular diseases (CVD)<sup>15,16</sup>, chronic obstructive pulmonary disease (COPD)<sup>17,18</sup>, and some cancers<sup>19,20</sup>. Tobacco smoke contains a variety

of chemicals known to be harmful to human health. Free radicals, nicotine, and carbon monoxide (CO) are believed to be the most important for pharmacological actions<sup>21</sup>.

Smoking increases the level of CO in the blood, which may lead to several cardiovascular diseases (CVD). CO displaces oxygen in the red blood cell to form COHb%<sup>22</sup>. Measurement of CO in exhaled breath (eCO ppm) and carboxyhemoglobin (COHb%) is a non-invasive, objective measure to assess smoking status and has been successfully used in several studies<sup>16,22-24</sup>. Studies have reported that smoking increases the level of hematologic parameters such as hemoglobin (HB), red blood cells (RBCs), neutrophils, eosinophils, monocytes, and platelets while smoking cessation was associated with a decrease in these values among smokers<sup>13,22,25,26</sup>. All blood cells are produced in the bone marrow and they mature in the peripheral blood tissue. These haemopoietic mechanisms can be affected when exposed to the harmful substances in cigarette smoke, and tobacco contains more than four thousand chemicals that may affect haemopoiesis<sup>21</sup>.

However, the information regarding the effect of smoking on blood COHb% and hematological parameters is scarce<sup>21</sup>. According to the best of the authors' knowledge, the relationship of smoking with eCO, COHb%, red cell parameters, and white cell parameters have not been studied in a South Asian population, according to the available literature. Accordingly, the study investigates the duration of smoking and effects of smoking severity on eCO, COHb%, and hematological parameters. Thus, it provides new data for a South Asian population that does not smoke as heavily as the Far-Eastern Asian populations<sup>12</sup>.

At the moment, Sri Lanka does not have baseline values for the above-measured variables in its smoking population. These baseline values and correlations will be critically important when policymakers develop studies on smoking cessation. On the other hand, Sri Lanka has the second-lowest prevalence of daily smoking in South Asia, trailing only India<sup>12</sup>. Bangladesh, Maldives, Myanmar, Nepal, and Thailand, all have a greater smoking prevalence than Sri Lanka<sup>12</sup>. Personal cigarette usage in Sri Lanka is also lower than in other Asian countries<sup>27</sup>. As a result, additional research into the physiological response to this low intensity of tobacco smoking is needed. We also wanted to check existing values with South Asian populations where studies are scarce. Thus, the current study is one of the first studies conducted in Sri Lanka to investigate the above parameters with an objective measure of the severity of smoking using eCO levels<sup>27</sup>.

## METHODS

### Study design and setting

A descriptive cross-sectional study was conducted in selected peri-urban MOH (Medical officer of Health area) divisions named Piliyandala, Homagama, Boralesgamuwa, and Ratmalana, in the Colombo district of Sri Lanka.

### Participants and sample size

A descriptive study was conducted on adult male daily tobacco smokers (n=360) aged 21–60 years with a smoking history of at least five years. They were randomly selected from peri-urban areas of Colombo district, Sri Lanka. A comparison group of 180 non-smokers was randomly chosen from the same location and matched for age, height, and weight. Non-smokers were defined as respondents who stated at the time of enrolment that they had never smoked or had not smoked in the previous five years, as well as had not smoked more than 100 cigarettes in their lifetime<sup>28,29</sup>.

Female smoking frequency is very low in Sri Lanka. It is about 0.2%<sup>12</sup> as smoking among females is considered a cultural taboo in Sri Lanka. Due to the fact that female smoking prevalence is so low in comparison to male smoking prevalence, we excluded female smokers and thus studied only male subjects to represent the smoking community. Thus, this study was conducted on male smokers.

Smokers and non-smokers with a history of myocardial infarction within the previous 4 weeks, diagnosis of alcohol dependence in the previous six months, or drinking six or more drinks on six or more days a week were excluded. Smokers with psychiatric disorders were also excluded, as smoking prevalence is known to be higher in those with psychiatric illnesses than in the general population<sup>30,31</sup>.

All participants providing informed written consent and fulfilling the recruitment criteria were included. Confidentiality of all information and identities of participants were strictly maintained and were not disclosed. The sample was randomly selected from the electoral registers of each Grama Niladhari (GN) Office. The electoral register for the year 2016 was used for this purpose.

### Data collection

An interviewer-administered questionnaire was used to obtain information on participants' baseline data, such as occupation, age, number of years of smoking, frequency, and type of tobacco smoking. Information sheets and consent forms were translated to the local languages of Sinhala and Tamil to ensure that it was accessible, easily understood, and available to all members. The participation was voluntary and the subject had the right to withdraw from participation at any time. The anthropometric measurements of height and weight were obtained using standardized measurement techniques using a stadiometer (KT-GFO6A-Kindcare- China) and a portable electronic bathroom scale (Omron HN-283-Japan). All equipment used were calibrated daily and periodically assessed for accuracy.

COHb% and eCO levels were measured using a calibrated portable Bedfont Micro+™ Smokerlyzer® (Bedfont Scientific, UK). The measuring concentration range of the device is 0–500 ppm (parts per million). Measurement of eCO was performed after a minimum time interval of 30 minutes after the last cigarette, as recommended by the manufacturer. Participants were asked to exhale completely,

inhale completely, hold for 15 seconds, and then exhale with a disposable mouthpiece. The Smokerlyser (Bedfont®) measures exhaled breath carbon monoxide level (eCO) based on the conversion of CO to carbon dioxide (CO<sub>2</sub>) over a catalytically active electrode. COHb% levels were automatically calculated based on eCO levels by the device. The smoking severity was estimated based on the Brinkman index, which is calculated by multiplying the duration of smoking (in years) by the number of cigarettes smoked per day<sup>32-34</sup>.

An aseptically collected sample of venous blood was analyzed to determine the full blood count (FBC) on randomly selected 180 smokers and 180 non-smokers. The 180 smokers were systematically selected based on the smoking severity: mild smokers (n=60) <2 cigarettes/day, moderate smokers (n=60) >2 and <10 cigarettes/day, and severe smokers (n=60) >10 cigarettes/day, based on the available literature<sup>35,36</sup>. Assessment of full blood count was done by an automated Coulter blood cell counter (Beckmann Coulter Inc. US). Participants identified with abnormal test results were referred to the university medical clinic for further management. The consent form, datasheet, and other data were securely stored.

**Statistical analysis**

Statistical analysis was performed with SPSS version 23.0

(SPSS Inc.). The normal distribution and the similarity of the variances were tested with the Kolmogorov-Smirnov test before statistical analysis. Groups were compared by Student’s t-test for normally distributed data and Mann-Whitney U test for skewed distributions. The correlations between the normally distributed parameters were analyzed using the Pearson correlation coefficient and Spearman’s rank-order correlation test was used for skewed data. Data are expressed as means with standard deviation (SD) and medians with interquartile range. The level of significance was set at p<0.05.

**RESULTS**

**Baseline characteristics of smokers and non-smokers**

There was no statistically significant difference between age and anthropometric measurements of height, weight, and BMI (kg/m<sup>2</sup>) between smokers and non-smokers (p>0.05). Smokers’ mean (±SD) value of daily cigarette consumption was 5.73±4.88 sticks/day, smoking duration was 22±12.63 years, and smoking-initiation age was 18.7±4.47 years. The median (±IQR) value of the Brinkman index was 80.0±132.0 (Table 1).

**COHb% and eCO levels of smokers and non-smokers**

Statistically significant high levels of eCO (ppm) (p<0.001) and COHb% were observed among smokers compared to non-smokers (p<0.001) (Table 2). This indicates that the

**Table 1. Baseline characteristics of smokers and non-smokers**

| Characteristics                | Smokers (n=360) |        | Non-smokers (n=180) |       | p     |
|--------------------------------|-----------------|--------|---------------------|-------|-------|
|                                | Mean            | SD     | Mean                | SD    |       |
| Age (years)                    | 41.00           | 11.77  | 42.10               | 12.63 | 0.263 |
| Weight (kg)                    | 65.35           | 12.84  | 65.20               | 11.29 | 0.897 |
| Height (cm)                    | 166.18          | 6.62   | 166.68              | 7.91  | 0.492 |
| BMI (kg/m <sup>2</sup> )       | 23.70           | 4.43   | 23.71               | 3.86  | 0.973 |
| Cigarettes/day                 | 5.73            | 4.88   | -                   | -     | -     |
| Smoking duration (years)       | 22.00           | 12.63  | -                   | -     | -     |
| Smoking-initiation age (years) | 18.70           | 4.47   | -                   | -     | -     |
| Brinkman index, median (IQR)   | 80.00           | 132.00 |                     |       |       |

Student’s t test, p<0.05.

**Table 2. COHb% and eCO levels of smokers and non-smokers**

| Variable                          | Smokers (n=360) |      | Non-smokers (n=180) |      | p*     |
|-----------------------------------|-----------------|------|---------------------|------|--------|
|                                   | Median          | IQR  | Median              | IQR  |        |
| Exhaled carbon monoxide (eCO ppm) | 7.00            | 8.00 | 3.00                | 1.00 | <0.001 |
| Carboxyhaemoglobin% (COHb%)       | 1.75            | 1.28 | 0.95                | 0.16 | <0.001 |

\*Mann-Whitney U test, p<0.001.

**Table 3. Comparison of hematological parameters between smokers and non-smokers**

| Hematological parameters         | Smokers (n=360) |       | Non-smokers (n=180) |       | p        |
|----------------------------------|-----------------|-------|---------------------|-------|----------|
|                                  | Median          | IQR   | Median              | IQR   |          |
| RBC ( $\times 10^{12}/L$ )       | 5.22            | 0.77  | 5.32                | 0.94  | 0.160    |
| HGB (g/dL)                       | 14.70           | 2.00  | 14.10               | 2.53  | <0.001** |
| HCT%                             | 45.50           | 7.20  | 44.50               | 7.50  | 0.004*   |
| MCV (fL)                         | 87.00           | 6.30  | 84.20               | 7.55  | <0.001** |
| MCH (pg)                         | 28.40           | 1.80  | 27.40               | 2.75  | <0.001** |
| MCHC (g/dL)                      | 32.50           | 1.80  | 32.00               | 2.10  | 0.001*   |
| WBC ( $\times 10^9/L$ )          | 7.70            | 2.00  | 7.00                | 1.70  | <0.001** |
| PLT ( $\times 10^9/L$ )          | 239.00          | 59.00 | 250.00              | 76.25 | 0.205    |
| Lymphocytes ( $\times 10^9/L$ )  | 2.90            | 1.00  | 2.60                | 0.83  | 0.023*   |
| Monocytes ( $\times 10^9/L$ )    | 0.60            | 0.20  | 0.50                | 0.20  | <0.001** |
| Granulocytes ( $\times 10^9/L$ ) | 3.90            | 1.50  | 3.60                | 1.70  | <0.001** |

Mann-Whitney U test; \*\*p<0.001, \*p<0.05.

CO arising from the smoke was efficiently bound to the hemoglobin in red blood cells.

**Comparison of hematological parameters between smokers and non-smokers**

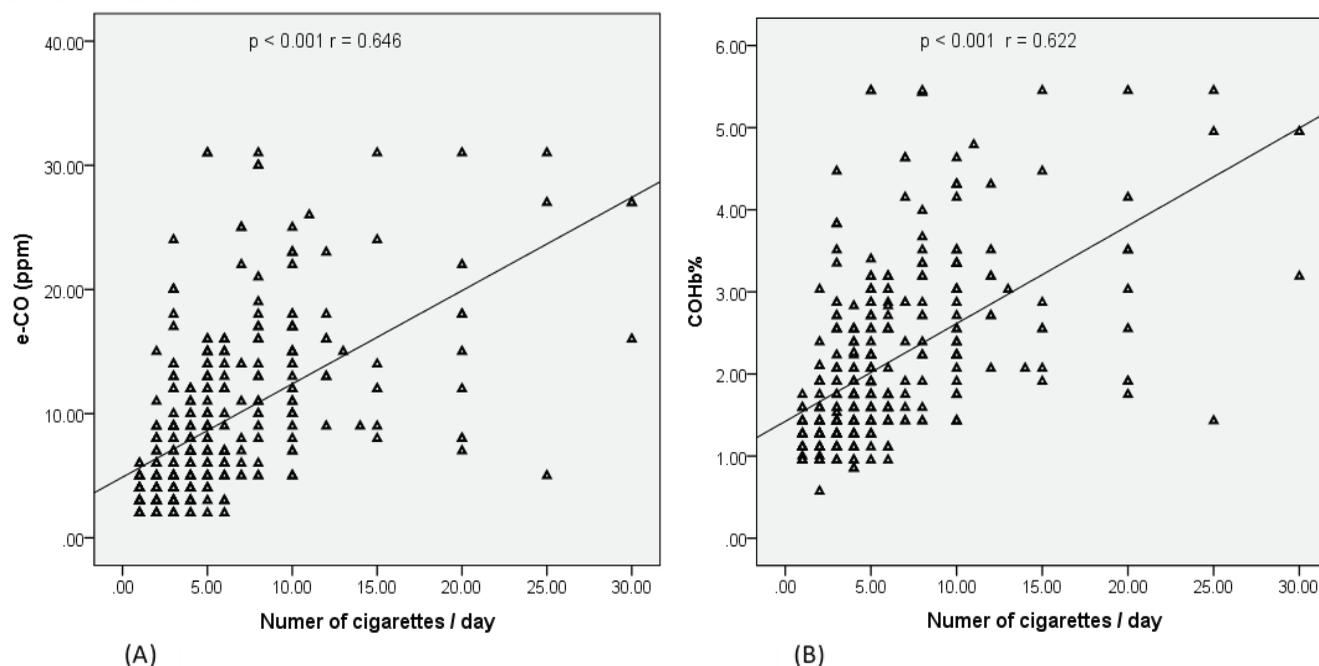
The smokers had significantly higher Hb, HCT, MCV, MCH, and MCHC, WBC counts, lymphocyte count, monocytes count, and granulocytes count, compared to the non-smokers (Table 3). This would be mostly stimulated by the hypoxia caused by the CO bound Hb being unable to transport O2 to tissues

efficiently, thus a rise in erythropoietin would result in the increase in hematological parameters.

**Correlation of smoking variables with eCO and COHb% levels**

There was a strong, positive correlation between the number of cigarettes smoked per day with eCO and the COHb% levels (p<0.001) (Figure 1). The duration of smoking (p<0.001) (Figure 2) and Brinkman index (p<0.001) (Figure 3) were also strongly positively correlated with eCO and the COHb%

**Figure 1. Correlation between the number of cigarettes smoked per day with (A) eCO levels, and (B) COHb% levels of smokers**



levels ( $p < 0.001$ ). There was a strong negative correlation between the time gap from the last smoked episode with eCO and COHb% levels ( $p < 0.001$ ) (Figure 4).

### Correlation between the number of cigarettes smoked per day and hematological parameters

A Spearman's rank-order correlation test was used to establish the relationship between smoking-related variables and hematological parameters. There was a significant,

positive correlation between the number of cigarettes smoked per day and the MCV ( $r = 0.148, p = 0.046$ ), and the MCH ( $r = 0.184, p = 0.013$ ).

### Correlation of Brinkman index and hematological parameters

A Spearman's rank-order correlation test was used to determine the relationship between the Brinkman index and hematological parameters. There was a significant

Figure 2. Correlation between the duration of smoking with (A) eCO levels, and (B) COHb% levels of smokers

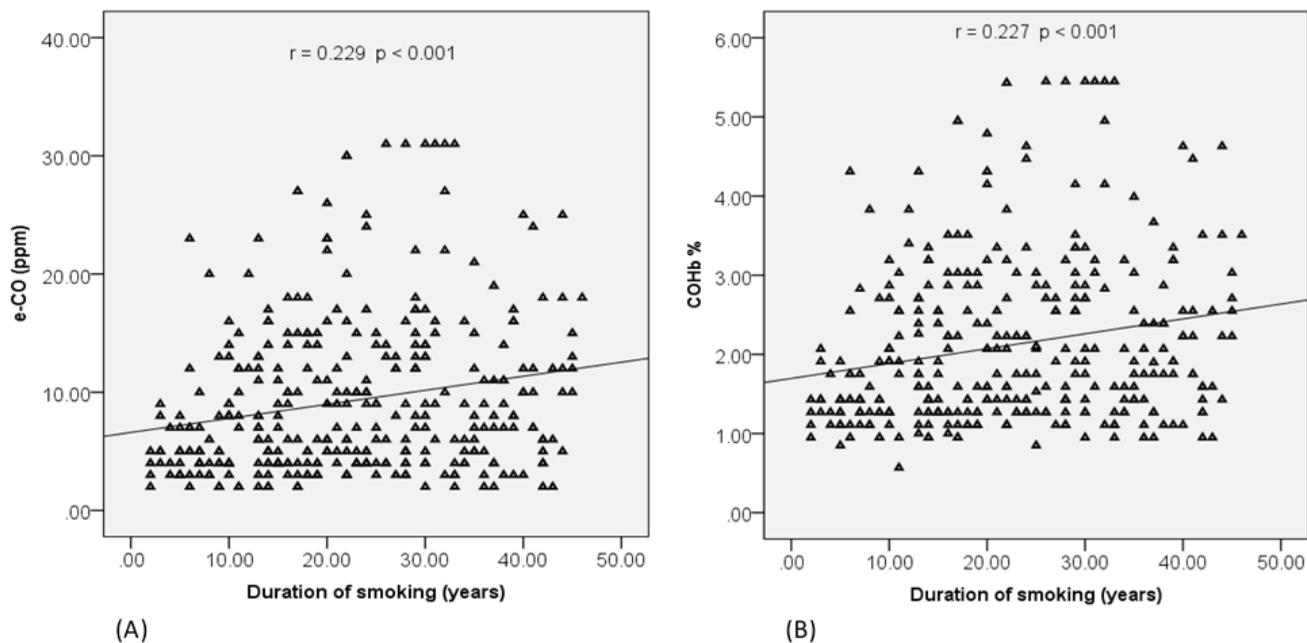
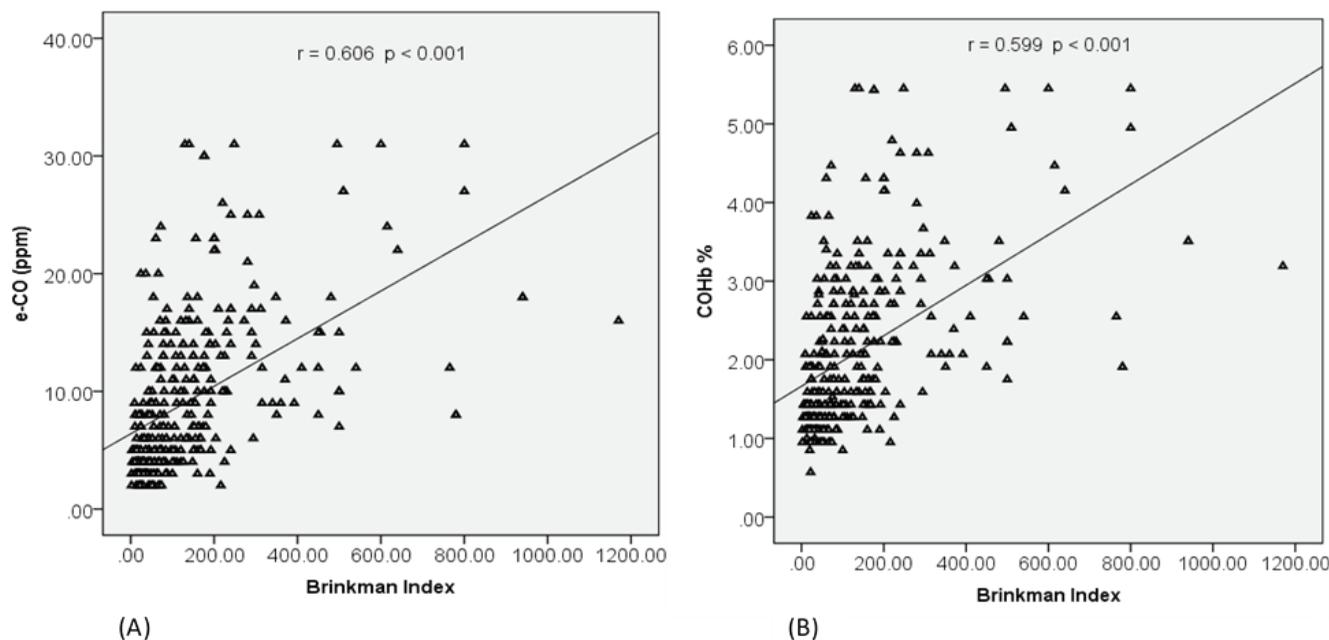
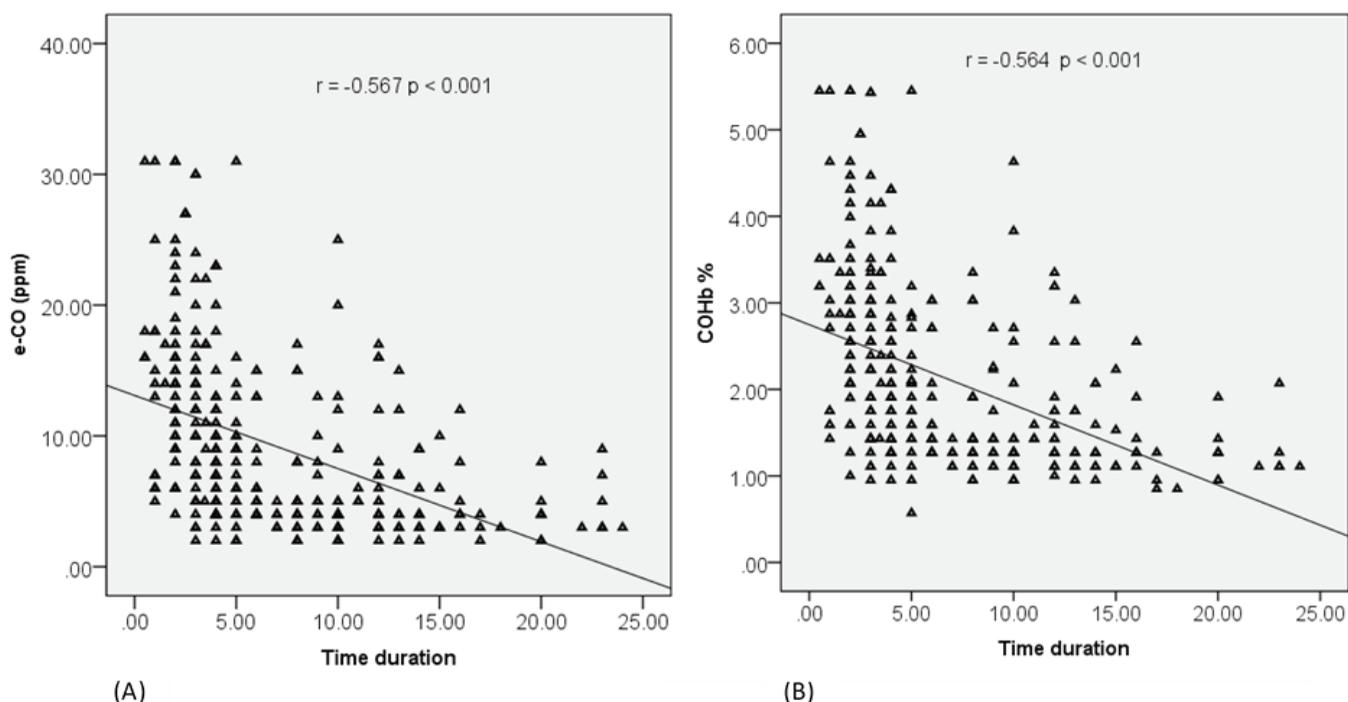


Figure 3. Correlation between the Brinkman index with (A) eCO levels, and (B) COHb% levels of smokers



**Figure 4. Correlation between the time duration from the last cigarette smoked with (A) eCO levels, and (B) COHb% levels of smokers**



positive correlation with Brinkman index and MCV ( $r=0.227$ ,  $p=0.002$ ), MCH ( $r=0.270$ ,  $p\leq 0.001$ ), and total granulocyte count ( $r=0.153$ ,  $p=0.043$ ).

## DISCUSSION

This study was conducted to assess the effects of tobacco smoking on exhaled breath carbon monoxide (eCO), blood carboxyhemoglobin levels (COHb%), and hematological parameters, amongst Sri Lankan adult male tobacco smokers. Sri Lanka currently lacks baseline values for the aforementioned characteristics in its smoking population. These baseline values and associations will be important in the development of smoking cessation studies; a more in-depth study into the physiological response to low-intensity tobacco smoking is needed.

Smokers' values were compared with weight, height, BMI and age-matched non-smokers ( $p>0.05$ ) to improve the scientific validity of the study. eCO has been used in many studies<sup>14,16,22-24,37,38</sup> to assess the smoking status of tobacco smokers. Combusted cigarettes produce CO which enters the bloodstream by diffusion at the pulmonary capillaries. CO has a high affinity to hemoglobin and binds to hemoglobin in red blood cells and was measured as COHb% in the present study. According to the literature, 85% of CO in the body is attached to hemoglobin in circulating red blood cells, and the majority of the remaining CO is linked with myoglobin in the muscles<sup>39</sup>. The eCO is in dynamic equilibrium with COHb%. The present study is the first study

conducted in Sri Lanka to determine the severity of smoking taking the eCO and COHb% into consideration. CO levels in breath can be influenced by many factors such as diet, exercise, inflammation, and time of the day<sup>23</sup>. It is believed that CO is produced endogenously, mainly through oxidative stress and inflammation of lung diseases such as COPD and asthma. However, a study has observed that there is no significant difference in CO values of smokers with normal lung function compared to smokers with COPD<sup>23</sup>.

In this study, there was a statistically significant higher eCO concentration and COHb% of smokers than non-smokers. The results of the study are in line with other studies<sup>16,24,37</sup>. Further, the present study showed a strong positive correlation between eCO and COHb% with the number of cigarettes smoked per day, duration of smoking<sup>22,24,37</sup> and Brinkman index. Besides, there was a strong negative correlation between eCO levels as well as COHb% with the time from the last cigarette. Therefore, the measurement of smoking through the assessment of eCO can be objectively used to assess the smoking status. In a primary care setup, it is very important to identify current smokers, in order to deliver quitting advice and to promote quitting and adherence to quitting amongst smokers. Further, as the method of testing is easy to conduct, eCO measurement further promotes better monitoring of patients who have still not quit smoking.

Measurement of eCO is more practical and easier to sustain in low-cost healthcare delivery settings such as in Sri

Lanka. It is practically difficult in primary care to determine cotinine levels in the blood and other samples as it is not cost-effective<sup>40</sup>. Further, the cotinine levels are known to vary depending on the ethnic group. A portable exhaled breath CO monitor is a cost-effective calibrated device which is easy to administer in a clinic setting. Further, the results are immediately available to the healthcare provider as well as to the patient, so that eCO level can be easily determined. Therefore, a portable CO monitor is a highly reliable tool to assess smoking severity. Once current smokers are identified with the eCO monitor, it will help to deliver more effective counseling sessions for them<sup>24,41</sup>, as both the counselor and smoker can have an excellent quick assessment of smoking status or the success of quitting attempts.

Robust scientific evidence exists to support the relationship between smoking and cardiovascular illness<sup>42,43</sup>. The exact mechanisms of the onset of disorders due to smoking cigarettes are unknown, but these effects are thought to be caused by changes in blood physiology, infections and inflammation, oxidative stress and antithrombotic effects, and changes in the fibrinolysis system<sup>13</sup>. Smoking causes alterations in various hematological parameters<sup>13,41</sup>. The present study confirmed that smokers had significantly higher levels of total white blood cell (WBC) counts, lymphocyte counts, monocyte counts, and granulocyte count, compared to non-smoker controls. Increasing WBC counts is a simple marker for endothelial injury<sup>43</sup>. Similar to our study, Acik et al.<sup>21</sup> found higher WBC, neutrophil, eosinophil, monocyte, and lymphocyte counts, compared to non-smokers.

Exposure to the irritant chemicals of tobacco smoke causes inflammation of the bronchial mucosa which increases the WBC counts. Further, an increase in WBC count has been described as a risk factor for subclinical atherosclerosis as well as vascular wall thickening<sup>43</sup>. Similar leukocytosis has been observed in other studies<sup>25,26</sup>. Although the exact mechanism of leukocytosis is not fully clarified, and smoking-induced leukocytosis may be due to several factors, and it may be explained in different ways. Leukocytosis may be the result of the nicotine-induced release of catecholamine and steroid hormones from the adrenal gland. It is known that an increase in the level of certain endogenous hormones, such as epinephrine and cortisol, increases the number of circulating leukocytes<sup>27,28</sup>.

WBC, platelet and red blood cell production in bone marrow increases due to stimulation by erythropoietin as a response to CO-mediated hypoxia<sup>21</sup>. This, in turn, leads to increased hemoglobin levels. According to the present study, we assessed all subgroups of leukocytes, which were also significantly higher in smokers than non-smokers. Furthermore, the average cigarette consumption of our selected population is not high though they had this significantly higher leukocyte level compared to the non-smokers. This is significant evidence to confirm that there is no safe level of smoking for an individual's health.

According to the findings, smokers had significantly higher levels of hemoglobin (Hb) values and this may be due to the CO-mediated stimulation of hypoxia inducing greater production of hemoglobin. Carbon monoxide binds to Hb and forms carboxyhemoglobin, an inactive form of hemoglobin that cannot carry oxygen. Carboxyhemoglobin also alters the Hb degradation curve on the left side, resulting in a decreased ability of Hb to deliver oxygen to tissue. To compensate for the reduced oxygen supply, smokers maintain higher hemoglobin levels than non-smokers<sup>13,21</sup>. The synthesis of erythropoietin in renal capillary tubular cells increases in response to hypoxia. These significant elevations in hemoglobin level are in accordance with previous studies<sup>13,21</sup>. This is known to account for the higher levels of hemoglobin of smokers of the present study.

The present study established significantly larger values of MCV, MCH, and MCHC, amongst smokers compared to non-smokers. Similar increases in the red cell indices have been observed with significantly larger values of MCV and MCH among smokers, while differences in values of MCHC were not significant between smokers and non-smokers<sup>13</sup>. MCV, MCH, and MCHC, are the three main red blood cell indices that help in measuring the average size of red cells and the hemoglobin structure of the red blood cells. MCH is the average weight of hemoglobin that is present inside a single red blood cell whereas MCHC denotes the amount of hemoglobin in a specific volume of 'packed' red corpuscles or cells. Further, a significant, positive correlation between Brinkman index and MCV, MCH, and granulocytes count, was also identified. Thus, this study established a relationship between the Brinkman index and hematological parameters. In addition to that, there was a significant positive correlation between the number of cigarettes smoked per day and MCV and MCH.

This study supports the idea that prolong cigarette smoking has adverse effects on the hematologic parameters<sup>28</sup>. Prolonged smoking exposure seems to have contributed to inducing the above changes of hemoglobin within the red cells. There was no significant difference in RBC count and that finding is compatible with the study conducted by Malenica<sup>13</sup>. However, a study conducted by Sherke et al.<sup>43</sup> found that the RBC count too increased with smoking among adult males. The present study did not find any difference between smokers and non-smokers in terms of platelet count. This finding is consistent with other studies<sup>43</sup>.

### Strengths and limitations

Our research has many strengths. We used a random sampling methodology to choose the sample. The sample size was large, with 540 participants. The fact that we selected age and anthropometric parameters matched non-smokers to match with smokers was our greatest strength. All measurements were taken with calibrated standard equipment. Furthermore, this is the first study

ever conducted in Sri Lanka amongst smokers to estimate the effects of tobacco smoking on exhaled breath carbon monoxide (eCO) levels, blood carboxyhemoglobin levels (COHb%), and hematological parameters, amongst adult male tobacco smokers. Our research has several limitations. We did not do a subgroup analysis because this is cross-sectional research. However, we selected them in a standard manner. Furthermore, their smoking history was approximated based on their verbal response.

## CONCLUSIONS

Cigarette smoking is associated with a significant increase of exhaled breath CO as well as COHb% level and it is positively correlated with the number of cigarettes smoked per day and the Brinkman index. Measurement of eCO using a CO monitor is a quick, non-invasive, cost-effective easy and efficient test to confirm the patient's smoking status. Continued cigarette smoking is associated with alterations of peripheral red cell counts, red cell indices, and white cell counts. These alterations might be associated with a greater risk for developing cardiovascular diseases subsequent to long-term smoking. The present study was rigorously conducted to confirm some of the known effects of cigarette smoking hitherto not estimated in the Sri Lankan population. The purchase of the monitor although expensive to initially purchase is relatively maintenance-free and does not involve costly calibration methods. These simple methods can be used effectively to deliver better healthcare and facilitate the quit smoking efforts of Sri Lankan smokers.

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The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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(ERC application 23/17). Participants were recruited to the study after obtaining written permission from the respective Provincial Director of Health – Western Province, Regional Director of Health.

#### DATA AVAILABILITY

The data supporting this research cannot be made available for privacy reasons.

#### AUTHORS' CONTRIBUTIONS

PH, SW, TA, MF and ST conceived and designed the study. PH performed the study. PH, SW, TA and MF were involved in data interpretation and statistical analysis. PH wrote the first draft of the manuscript. SW, TA, MF and ST critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. All authors are responsible for the academic content of the article.

#### PROVENANCE AND PEER REVIEW

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