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Screening of plasma IL-6 and IL-17 in Bangladeshi lung cancer patients

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ABSTRACT

Lung cancer is responsible for causing one of the highest numbers of cancer deaths. In Bangladesh, both men and women are affected by lung cancer, and environmental contaminants are believed to be one of the main risk factors apart from smoking. The diagnosis of lung cancer is difficult due to the delicate structure and complexity of the lungs. Diagnosis in later stages results in a poor prognosis of the disease. Tissue biopsy is the most reliable way of identifying lung cancer, but it is invasive and requires identification of the primary neoplasm within the lungs. As inflammation is involved in carcinogenesis, circulating levels of cytokines might be elevated in patients during the early stages of cancer. Increased IL-6 levels have been associated with the promotion of tumor growth, and IL-17 is believed to aid metastasis of lung cancer. In this study, the use of IL-6 and IL-17 was investigated as diagnostic markers for lung cancer. IL-6 and IL-17 levels were compared between 35 lung cancer patients and 19 healthy individuals. IL-6 levels were markedly elevated (7.417 pg/mL) in lung cancer cases compared to the controls (0.970 pg/mL), indicating a positive correlation ($p < 0.05$). IL-17 levels were only slightly higher in lung cancer patients (9.400 pg/mL) compared to healthy individuals (8.922 pg/mL). Both IL-6 and IL-17 levels were higher in patients with adenocarcinoma compared with other subtypes of lung cancer. Treatment with chemotherapy and radiotherapy did not significantly affect IL-6 levels. However, IL-17 levels were reduced due to cancer treatment. Further studies with larger sample sizes assessing the IL-6 and IL-17 in lung cancer patients are needed to establish the diagnostic role of the two cytokines.

1. Introduction

Cancer is one of the leading causes of death worldwide, responsible for millions of lives lost annually. There were approximately 19 million new cases and more than 10 million deaths due to cancer in 2020, and this is expected to increase [1]. Lung cancer is the second most common type of cancer, responsible for a significant number of deaths [2]. Although cigarette smoking is the major risk factor, exposure to environmental contaminants and unhealthy lifestyle factors might also increase the probability of lung cancer. In a

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developing country like Bangladesh, the risk of lung cancer is higher due to the prevalence of environmental pollution [3]. In 2020, there were more than 100 thousand deaths due to lung cancer alone, among which approximately 60% were male [4]. In most cases of deaths due to lung cancer, one common cause is the tumor burden which ultimately leads to bronchial obstruction [5]. Therefore, a timely diagnosis of the disease might increase the likelihood of survival.

Lung cancer can be broadly categorized into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), which can be further classified histopathologically as squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell carcinoma [6]. Initially, lung cancer might manifest as a primary tumor with mild symptoms like coughing or an altered chronic cough pattern [7]. The primary tumor might eventually increase in size leading to lesions in surrounding tissues and preventing efficient airflow. In the later stages of the disease, the tumor metastasizes and spreads to local and distant tissues causing systemic complications [8]. Therefore, lung cancer patients have one of the lowest survival rates due to the complexity of the disease and its rapid progression. Approximately 15% of the patients with adenocarcinomas might show a 5-year survival rate [9]. The diagnosis of lung cancer in an early stage is difficult as most patients show signs and symptoms when the disease has progressed significantly.

Like most cancers, the development of primary lung cancer is influenced by both environmental and genetic factors. Smoking is the main cause of lung cancer, as the cells in the lungs are consistently signaled to adapt in the presence of toxic compounds [10]. Non-smokers with a genetic predisposition are also at risk. Squamous cell carcinoma was the most common form of NSCLC; however, with changes in smoking patterns, adenocarcinomas are more prevalent lately [11]. Apart from the influences of genetic and environmental factors, the immune microenvironment might play a key role in lung cancer.

Inflammation is an inherent mechanism that functions to protect the body from invading pathogens or harmful agents. However, chronic effects of inflammatory mediators can elicit injury to cells which might contribute to the evolution and advancement of cancer [12]. A cancer cell might originate from regions that suffer an infection or serious chemical damage, as one of the hallmarks of cancer is the infiltration and abundance of inflammatory cells in the tumor microenvironment [13]. Initially, the inflammatory component of the immune system prevents the inception of neoplastic growth by eliminating abnormal cells. However, these inflammatory components might play a crucial role in the initiation and progression of the cancer. One of the reasons behind the negative role of the inflammatory components could be due to the release of actively mutagenic chemicals into the surrounding tissues [14]. Therefore, targeting inflammation might become a possible treatment strategy against cancer.

For lung cancer treatment to be successful, one of the most important factors is the time of diagnosis and the identification of tumor morphology. The primary diagnostic techniques to confirm the presence of lung cancer might involve radiographic findings, sputum cytology analysis, and bronchoscopy, which are almost always followed by a biopsy [8]. Tissue biopsy is the most reliable diagnostic technique for the identification of cancer. However, in lung cancer, a biopsy is only possible after recognizing the location of the tumor within the lungs, and this is generally possible when the tumor size has increased significantly [15]. Also, a single biopsy might not be sufficient to establish the nature of the tumor due to its heterogeneity, making diagnosis more difficult [16]. Therefore, alternative diagnostic techniques might prove to be beneficial.

Interleukins (IL) are cytokines that play a crucial role in mediating immune response. As tumor development is intertwined with immune response, the circulating interleukin levels might be affected by carcinogenesis [17]. In a study involving lung cancer patients, the coevolution of malignant cells with immune responses was demonstrated [18]. The role of interleukin-1 (IL-1) in inflammatory carcinogenesis has been widely evidenced in several kinds of cancer [19]. Although IL-1 might play an important role in inflammatory carcinogenesis, other interleukins might be significantly involved. The critical role of interleukin-6 (IL-6) in lung cancer was demonstrated by a group of researchers where IL-6 was involved with the promotion of tumor growth by using K-Ras protein [20]. Also, IL-6 was found to work synergistically with IL-1 in the development of multiple myeloma [21]. The pro-inflammatory cytokine interleukin-17 (IL-17) has been found to participate in the promotion and progression of lung cancer [22]. IL-17 has also been involved in the promotion of CXCR-2-dependent angiogenic activity and the growth of NSCLC [23]. As interleukins are inflammatory regulators in carcinogenesis, identifying the circulating levels of specific interleukins might signal the development and progression of lung cancer. Therefore, this cross-sectional study aims to assess the level of IL-6 and IL-17 in a group of lung cancer patients from Bangladesh.

2. Methods

This study was carried out in 2019 and samples from lung cancer patients were collected from Ahsania Mission Cancer and General Hospital (AMCGH), Dhaka, Bangladesh, after taking written informed consent.

The information related to patient demographics and their previous history of malignancies was collected through a short questionnaire and from their medical records. The clinical and histopathological data of the patients were obtained from their medical and pathological reports. Patients above 18 years of age with a confirmed diagnosis of lung cancer were included in the experimental group of the study. For the control group, healthy community controls without a previous history of cancer were chosen.

2.1. Sample collection

For assessing plasma IL-6 and IL-17 levels, 5 mL of peripheral blood were drawn from each participant. The blood samples were placed in BD Vacutainer tubes containing 6% ethylenediaminetetraacetic acid (EDTA). The whole blood was centrifuged at 700×*g* for 10 min and the separated plasma was again centrifuged at 2000×*g* for 10 min at 4 °C. The sample aliquots were stored at minus 80 °C.

2.2. Plasma IL-6 assay

The assay for plasma IL-6 was carried out in IL-6 ELISA Kit (ab46027) from Abcam according to the standard instructions. The reagents were prepared and equilibrated at room temperature. The standard solutions and experimental samples were added to the microplate wells, followed by the addition of 50 μl biotinylated anti-IL-6 antibody solution. After incubation of the plate for 1 h at room temperature, the wells were washed three times using the 1× wash buffer. Streptavidin-HRP solution was added to the wells and incubated for 30 min again at room temperature. After washing the well again three times, TMB chromogen substrate solution was added to each well, and the plate was incubated in the dark for 20 min 100 μl of stop reagent were added to each well, and absorbance was measured spectroscopically at 450 nm [24].

2.3. Plasma IL-17 assay

The assay for plasma IL-17 was carried out in IL-17 ELISA Kit (ab119535) from Abcam. Standard guidelines were followed. After preparing and equilibrating the reagents at room temperature, the microplate wells were washed with 400 μl of wash buffer twice. In each well, standard dilutions (100 μl) were added followed by 50 μl of sample diluents and 50 μl of biotin-conjugated anti-IL-17 antibody solution. The well plate was incubated for 2 h at room temperature. After incubation, the wells were washed four times. Streptavidin-HRP solution was added to each well and the well plate was incubated for 1 h at room temperature. Again, the wells were washed four times with the wash buffer and TMB chromogen substrate solution was added. Color development was allowed for 15 min in the dark at room temperature and lastly, the reaction was stopped by the addition of the stop solution (100 μl), and the absorbance was recorded at 450 nm [24].

Table 1
Demographic data of the study participants.

	Patients (n = 35)		Control (n = 19)	
	Number	%	Number	%
Sex				
Male	31	88.6	16	84.2
Female	4	11.4	3	15.8
Age				
21–40	4	11.4	19	100
41–60	14	40	–	–
61 and above	17	48.6	–	–
Occupation				
Business	4	11.4	–	–
Farmer	7	20	–	–
Homemaker	4	11.4	–	–
Retired	4	11.4	–	–
Self Employed	4	11.4	–	–
Service	9	25.7	6	31.6
Student	–	–	12	63.2
Unemployed	3	8.6	1	5.3
Family history of cancer				
Yes	9	25.7	4	21.1
No	26	74.3	15	78.9
Stress level				
Low	8	22.8	4	21.1
Medium	22	62.9	10	52.6
High	5	14.3	5	26.3
Smoking habit*				
Non-smoker	4	11.4	10	52.6
Light smoker	5	14.3	9	47.4
Medium smoker	14	40	–	–
Heavy smoker	12	34.3	–	–
Exposure to secondhand cigarette smoke				
Yes	28	80	12	63.2
No	7	20	7	36.8
Place of living				
Rural	16	45.7	1	5.3
Urban	18	51.4	18	94.7
Unknown	1	2.9	–	–

* The non-smokers smoked no cigarettes. The light smokers had 1-10 cigarettes per day, the medium smokers had 11-30 cigarettes per day, and the heavy smokers had more than 30 cigarettes per day.

2.4. Data analysis

Data entry and analysis were carried out in Microsoft Excel. The tables and charts were created in Excel as well.

3. Results and discussion

3.1. Demographic data

Plasma samples were collected from 35 lung cancer patients and 19 healthy individuals to assess the levels of IL-6 and IL-17. The demographic data of the study participants are detailed in Table 1.

Among the 35 lung cancer patients, there were 31 males and 4 females. In the control group, there were 16 males and 3 females. The number of female participants was low in both groups. Almost half of the patients (48.6%) were aged above 60, and 40% of the patients were aged between 41 and 60 years. All participants in the control group were aged between 21 and 40 years, whereas only four lung cancer patients were aged 40 and below. In the study group, around one-fourth of the patients were in service, 20% were farmers, and 8.6% were unemployed. All the females were homemakers, and an equal percentage of participants were either retired, had businesses, or were self-employed. In the control group, the majority were students (63.2%), 31.6% were in service, and the rest were unemployed.

25.7% of the patients and 21.1% of the control group participants had a family history of cancer. Therefore, some of the study participants might have a genetic predisposition to cancer. Most of the cases and controls faced medium levels of stress in everyday life. A significant proportion of the lung cancer patients were medium (40%) to heavy (34.3%) smokers. Around half of the control group were light smokers (47.4%), and the other half were non-smokers (52.6%). All the females were non-smokers; however, most of them had been exposed to secondhand cigarette smoke. 80% of the cases and 63.2% of the controls had high levels of exposure to secondhand smoke. An approximately equal proportion of the lung cancer patients were either living in rural (45.7%) or urban (51.4%) areas. Most of the control group participants were living in urban areas (94.7%).

3.2. Lung cancer type

The majority of the 35 lung cancer patients had adenocarcinoma (45.7%) or squamous cell carcinoma (31.4%), and this is consistent with patterns from other studies with a high frequency of patients with adenocarcinoma [25] (Table 2). 5.7% of the patients had small cell carcinoma, and 17.1% had lung cancer that was uncategorized due to poorly differentiated cells.

3.3. Plasma IL-6 levels

Increased IL-6 levels have been associated with tumor progression and metastasis [26]. The plasma IL-6 levels were compared between the lung cancer cases and the control group participants.

The mean IL-6 level in the control group participants was 0.970 pg per milliliter (pg/mL), whereas in lung cancer cases, the level was 7.417 pg/mL. The mean IL-6 level was higher by 6.447 pg/mL in cancer patients and this was statistically significant as $p < 0.05$ (Fig. 1A). This is consistent with previous evidence supporting increased levels of IL-6 in lung cancer patients [27]. Though not statistically significant, in both controls and cases, the female subjects had higher levels of IL-6. In lung cancer, the mean IL-6 level in males was 6.928 pg/mL, whereas, in females, it was 12.471 pg/mL. In the control group, the mean IL-6 level in males was 0.928 pg/mL and 1.177 pg/mL in females (Fig. 1B). As the number of female participants was very low in both the disease and control groups, the high level of IL-6 might have been by chance. However, as circulating levels of certain hormones affect the cytokine levels, this might have influenced the IL-6 levels in the female participants [28]. The majority of the lung cancer cases were either adenocarcinoma or squamous cell carcinoma. The patients with adenocarcinoma had a mean IL-6 of 8.453 pg/mL, and the patients with squamous cell carcinoma had 6.510 pg/mL (Fig. 1C). The mean IL-6 level in patients with adenocarcinoma was higher by 1.943 pg/mL compared to patients with squamous cell carcinoma. This difference is too small to suggest any significance. However, with a higher number of patients, a correlation between adenocarcinoma and increased IL-6 levels could be established. As IL-6-based cancer treatment strategies are being developed, patients with adenocarcinoma might benefit more from the other cancer subtypes if a large-scale study corroborates similar results [29]. The IL-6 levels were compared among patients who had taken no treatment during the study, patients who had been given chemotherapy, and patients who received both chemotherapy and radiotherapy previously. The IL-6 levels were

Table 2
Lung cancer subtypes of the study participants.

	Patients (n = 35)	
	Number	%
Lung Cancer Type		
Adenocarcinoma	16	45.7
Squamous cell carcinoma	11	31.4
Small cell carcinoma	2	5.7
Lung cancer poorly differentiated	6	17.1

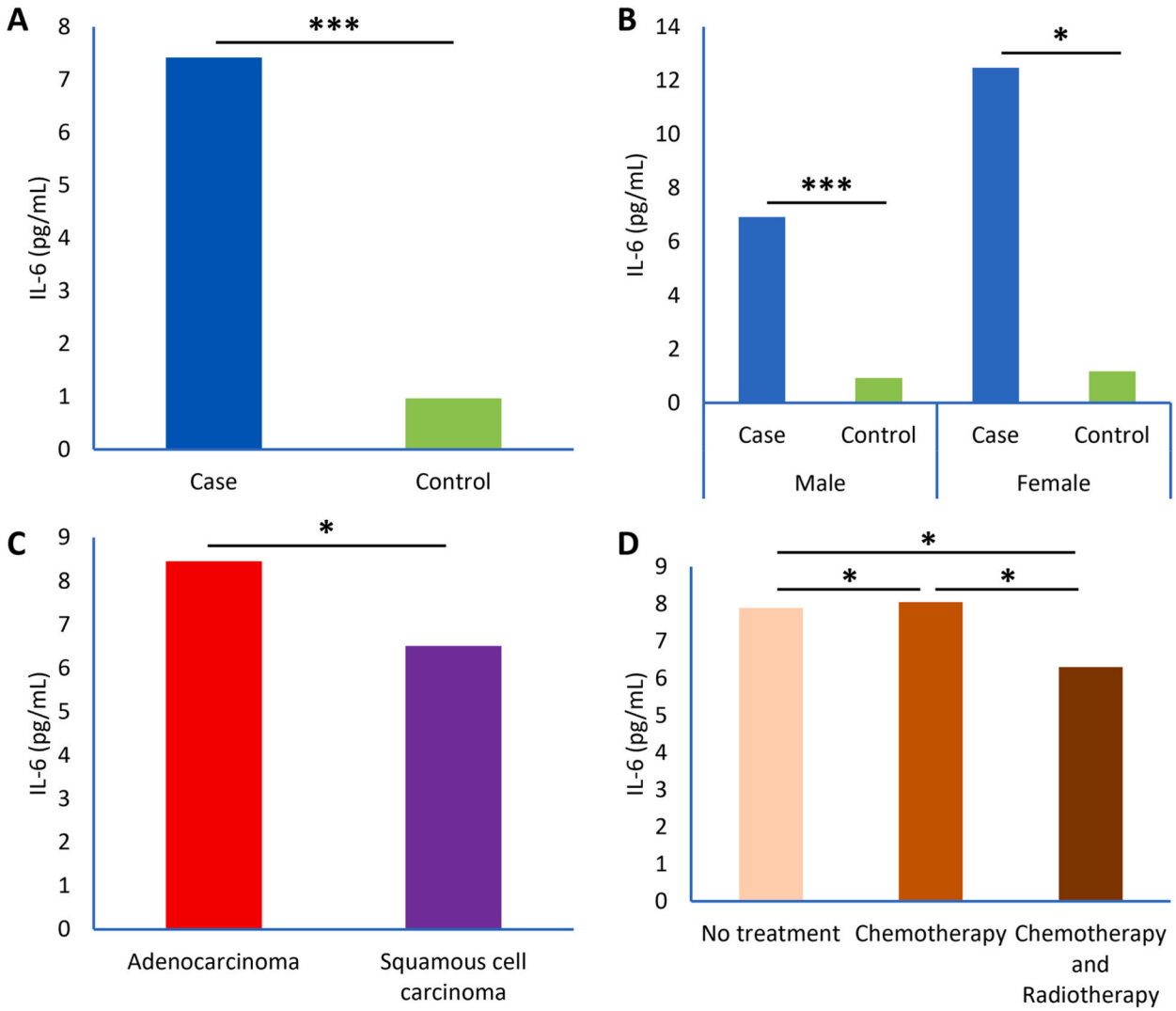

Fig. 1. The plasma IL-6 levels in lung cancer cases and controls in picogram per milliliters. The data are expressed as mean. *** Indicates $p < 0.05$ and * indicates $p > 0.05$, determined by using two-sample *t*-test assuming unequal variances. **(A)** Plasma IL-6 levels in lung cancer patients and healthy participants, **(B)** difference in IL-6 between males and females, **(C)** IL-6 levels in patients with adenocarcinoma and squamous cell carcinoma, **(D)** IL-6 level in patients who have taken no treatment, chemotherapy and both chemotherapy and radiotherapy *(Reference Table S1)*.

similar in patients who had not taken any treatment (7.898 pg/mL) and those who had chemotherapy (8.051 pg/mL). However, patients who had both chemotherapy and radiotherapy had a slightly lower level of IL-6 (6.302 pg/mL) (Fig. 1D).

3.4. Plasma IL-17 levels

The pro-inflammatory cytokine IL-17 has been evidenced to be increased in lung cancer patients [23]. In this study, the overall IL-17 levels were identified. The plasma IL-17 levels were compared between the lung cancer cases and the control group participants.

The mean IL-17 in the control group participants was 8.922 pg/mL, and in the lung cancer patients was 9.400 pg/mL (Fig. 2A). Both groups had only a difference of 0.478 pg/mL. Unlike the difference found in IL-6 levels (6.447 pg/mL) between lung cancer patients and control group participants, IL-17 was only slightly higher in lung cancer patients. This could have been due to the small sample size of the study. Although an increase in IL-6 positively influences IL-17 levels in cancer, the results of this study could also indicate that IL-6 levels played a superior role in cancer development in certain categories of patients [30]. No significant difference was observed in IL-17 levels in males and females. The mean IL-17 level in all the males with lung cancer was 10.317 pg/mL, and in all the males of the control group was 10.422 pg/mL. Overall, the IL-17 levels were lower in females, with the control group mean (2.423 pg/mL) being slightly higher than the mean in lung cancer patients (1.150 pg/mL) (Fig. 2B). Again, this could be attributed to the small percentage of female subjects in the study. As seen with IL-6, the IL-17 levels were slightly higher in patients with adenocarcinoma (8.642 pg/mL)

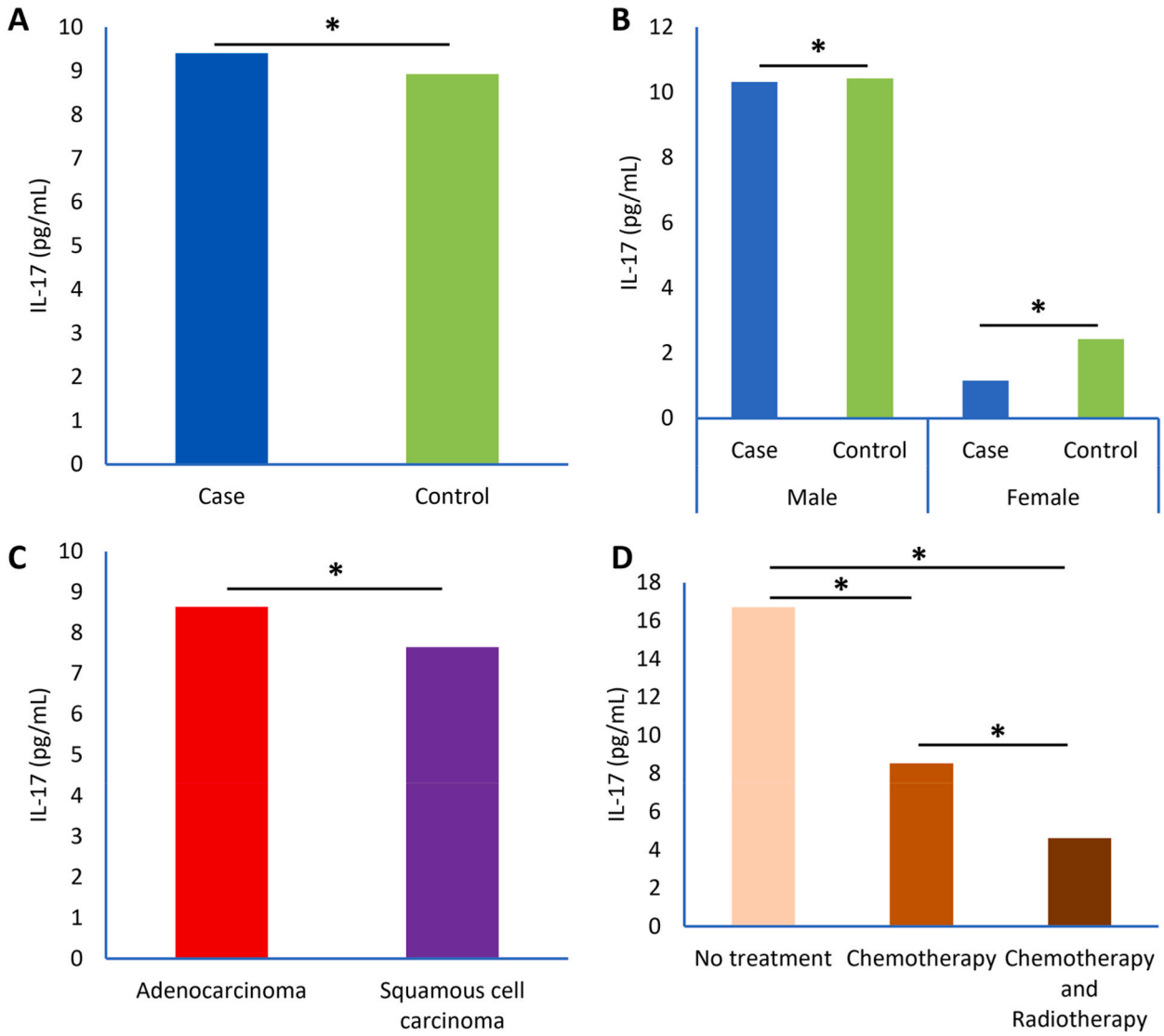

Fig. 2. The plasma IL-17 levels in lung cancer cases and controls in picogram per milliliters. The data are expressed as mean. * Indicates $p > 0.05$, determined by using two-sample *t*-test assuming unequal variances. **(A)** Plasma IL-17 levels in lung cancer patients and healthy participants, **(B)** difference in IL-17 between males and females, **(C)** IL-17 levels in patients with adenocarcinoma and squamous cell carcinoma, **(D)** IL-17 level in patients who have taken no treatment, chemotherapy and both chemotherapy and radiotherapy.

than in patients with squamous cell carcinoma (7.649 pg/mL) (Fig. 2C). The difference is not significant enough to suggest any correlation. However, the results suggest that patients with adenocarcinoma had higher levels of both IL-6 and IL-17. The patients taking no treatment had a mean IL-17 level of 16.694 pg/mL, patients who had taken chemotherapy had a mean IL-17 of 8.526 pg/mL, and the patients who had taken both chemotherapy and radiotherapy had a mean IL-17 of 4.608 pg/mL (Fig. 2D). Due to the small sample size, $p < 0.05$ could not be achieved. However, the results suggest that both chemotherapy and radiotherapy could have had an effect in slowing down cancer progression, thus causing decreased levels of circulating IL-17.

3.5. Plasma IL-6 and IL-17 as diagnostic markers

Patients with NSCLC who have high levels of circulating IL-6 have poorer survival rates [31]. Also, patients having higher circulating IL-17 were found to have faster rates of metastasis of NSCLC [32]. This study aimed to identify that plasma IL-6 and IL-17 could potentially be used to diagnose the early stages of lung cancer. The results of the study show IL-6 levels to be markedly higher in patients with lung cancer (6.447 pg/mL higher) compared to the control group participants. However, a similar level of difference was not observed for IL-17 (0.478 pg/mL higher). One of the reasons behind this could be due to some of the control group participants being smokers. Upon comparison of the IL-6 and IL-17 levels between the light smokers and non-smokers in the control group, it was

found that the light smokers had higher IL-17 levels (13.213 pg/mL) than the non-smokers (5.585 pg/mL) (Table S2). On the other hand, the IL-6 levels were slightly lower in light smokers (0.860 pg/mL) than in non-smokers (1.056 pg/mL) (Table S2). This indicates that smoking could have an effect on circulatory IL levels.

Both IL-6 and IL-17 levels were higher in lung cancer patients with adenocarcinoma compared to patients with squamous cell carcinoma. In the case of IL-16, patients who were on chemotherapy and radiotherapy did not show a considerably different cytokine level. However, patients who have had chemotherapy and radiotherapy showed much lower levels of IL-17 than the patients who had taken no therapy at all. Lung cancer patients who have had treatment with radiotherapy had lower levels of both IL-6 and IL-17 than the patients taking no treatment (Fig. 1D and 2D). Overall, based on the results of this study, IL-6 could have a better potential to serve as a diagnostic marker for lung cancer than IL-17.

3.6. Limitations of the study

The main limitation of this study was the small sample size and the difference in the number of participants in both groups. Out of the 35 patients with lung cancer, IL-6 values were identified from 34 cases and 18 controls, and IL-17 values were identified from 30 cases and 17 controls. The small size of the study also resulted in high standard error of mean (Table S1). Also, an unusual IL-17 level value from a control group participant was excluded from the study. While the peripheral blood was collected from the patients, most of them were already receiving cancer treatment which could have affected the levels of the cytokines. For all the participants, the total IL-17 levels were analyzed, and the subtypes of the interleukin were not identified. This was mainly because of the small number of participants in the study, and although IL-17A and IL-17F have been evidenced to be involved in inflammatory carcinogenesis, the roles of the other IL-17 subtypes in inflammation are not well established [33]. Despite the limitations, results from this study might help to understand the relationship between the cytokines IL-6 and IL-17 in lung cancer in patients from Bangladesh.

4. Conclusion

Lung cancer patients have poor prognoses due to difficulties in the diagnosis of the disease in the early stages. Inflammation, an intrinsically protective mechanism, contributes to the development and progression of primary tumors. Therefore, inflammatory cytokines IL-6 and IL-17 levels are believed to be higher in lung cancer patients. Although the results from this study could not significantly establish a positive relationship between lung cancer and the two circulating cytokine levels, a positive outcome was achieved as IL-6 levels were much higher in lung cancer cases. Despite the major limitation of having a small number of study participants, a significantly increased level of IL-6 was identified in lung cancer patients. This indicates that a larger study with a higher number of lung cancer patients might result in a strong correlation between IL-6 and lung cancer which could lead to IL-6 potentially being used as a diagnostic marker. Also, the IL-17 levels were lower in patients who had chemotherapy and radiotherapy. As both the IL-6 and IL-17 levels were higher in patients with adenocarcinoma, this outcome could lead to an opportunity to develop a targeted treatment strategy for patients with a particular subtype of lung cancer.

Ethics statement

This study was approved by the NSU Institutional Review Board/Ethics Review Committee (IRB/ERC, Protocol # 2019/OR-NSU-IRB-No.0507).

Author contribution statement

Manik Chandra Shill, Farhana Afrin Ferdausi, Qamruzzaman Chowdhury: Conceived and designed the experiments.
Sadia Kamal: Analyzed and interpreted the data; Wrote the paper.
Bisshojit Biswas, Moriam Islam, Sharmin Sultana Rima: Performed the experiments.
Hasan Mahmud Reza: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.
Asim Kumar Bepari: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20471.

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