

# Determinants of Community-Acquired Pneumonia Among Adults Patients Attending Debre Berhan University Hakim Gizaw Hospital, Northeast Ethiopia: A Case–Control Study

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**Background:** Community-acquired pneumonia among adults remains an important cause of morbidity and mortality in both industrialized and developing countries, including Ethiopia. Moreover, despite the availability of the best clinical standards, morbidity and mortality from community-acquired pneumonia have not improved over the last few decades. Therefore, prompt assessment and correction of modifiable risk factors are crucial to reduce morbidity and mortality. However, there are limited data on the determinants of community-acquired pneumonia among adults in the current study area.

**Purpose:** This study aimed to identify the determinants of community-acquired pneumonia among adult patients visiting Debre Berhan University Hospital, Ethiopia, May 2023.

**Methods:** A hospital-based unmatched case–control study design was conducted to select 113 cases and 113 controls using a consecutive sampling technique. Using the SPSS version 25 software bi-variable and multivariable logistic regression analyses were performed to identify the determinants of community-acquired pneumonia. Adjusted odds ratios with 95% confidence intervals and p-values < 0.05 were used to assess the level of significance.

**Results:** In this study, recent history of common cold [AOR: 4.35, 95% CI: (2.22, 8.51)], recent history of toothache [AOR: 2.51, 95% CI: (1.18, 5.33)], and not brushing teeth regularly [AOR, 2.79; 95% CI: (1.32, 5.88)] were significantly associated with community-acquired pneumonia.

**Conclusion:** In this study, common cold, recent history of toothache, and lack of regular oral hygiene were significantly associated with community acquired pneumonia in adults. Therefore, health promotion of oral hygiene and the common cold is recommended to decrease the risk of pneumonia.

**Keywords:** community acquired pneumonia, determinants, case control, oral hygiene

## Background

Community-acquired pneumonia (CAP) is an acute disease caused by infection of the lung parenchyma acquired outside the hospital setting.<sup>1,2</sup> Globally, CAP remains an important cause of morbidity and mortality in both industrialized and developing countries. In adult population, the annual incidence of CAP ranges between 1.6 and 13.4 cases per 1000 inhabitants, 22–51% of whom require inpatient care, with a lethality of 3–24%. The mortality rate varies between 0.1 and 0.7 per 1000 persons each year.<sup>3</sup> According to the World Health Organization (WHO) data, pneumonia accounts for 6.1% of deaths that are responsible globally for 3 million deaths annually.<sup>4</sup> In Africa, CAP is associated with an in-hospital mortality of 6–15% among adults, as reported from hospital-based studies.<sup>5</sup> In sub-Saharan Africa, approximately 4 million cases of pneumonia occur annually, resulting in approximately 200,000 deaths.<sup>6</sup> In Ethiopia, the estimated

incidence of CAP varies among studies, but a study conducted in the Tigray region revealed that the magnitude of CAP in adults is as high as 16%.<sup>7</sup> Furthermore, when considering the overall burden of the disease, CAP is the second leading cause of death in Ethiopia.<sup>8</sup> Overall, in low-income countries such as Ethiopia, epidemiological data on pneumonia at the population-based level are scarce and are mainly based on hospital registries, with pneumonia being one of the most common reasons for hospitalization in adults.

Unfortunately, CAP is a neglected but common medical event, and the lack of a sense of emergency within the general public, little economic investment at a public and private level, and absence of advocacy and disease awareness are worrisome.<sup>3,9</sup> Therefore, recognizing and managing risk factors for CAP could be a way to prevent the disease and reduce complications, especially since mortality from CAP has not improved during the last decades despite the availability of the best clinical standards.<sup>3</sup> Even though recognizing and managing risk factors could be a way to prevent the disease and reduce complications, information on determinants of CAP in primary care is scarce.<sup>10</sup> In addition, robust national studies on determinants of CAP among adults are largely missing in Ethiopia.<sup>7,11</sup> Therefore, this study was conducted at Debre Berhan University Hospital, northeast Ethiopia.

The outcomes of the present study have the potential to benefit various stakeholders, including policymakers, organizations working on pneumonia and its risk factors, and future researchers. This information can be used as additional evidence for planning and implementing intervention strategies to prevent CAP and reduce the burden on the community. These findings can inspire new approaches to foster activities concerning the main determinants of CAP. Furthermore, this study can provide an initial idea for planning further prospective and experimental studies to explore this topic in greater depth.

## Methods

### Study Design and Setting

An institution-based unmatched case–control study was conducted at Debre Berhan University Hospital from March 1/2023 to May 30, 2023. The hospital is located 130 km northeast of the country's capital, Addis Ababa, in Debre Berhan Town, North Shewa District of the Amhara Region, Ethiopia. The hospital provides specialized services to patients from different departments. It has more than 200 beds and serves approximately 3 million people in the surrounding area.

### Population and Eligibility Criteria

The source population included all adults visiting Debre Berhan University Hospital during the study period. A case was defined as an adult with a new CAP diagnosis during the study period. The diagnosis of CAP was determined by the treating physician based on the clinical presentation and confirmed by chest radiography. The control group included adult patients who visited the hospital during the study period for any medical conditions, but did not have CAP. Patients aged <18 years, those with overt aspiration, HAP, or VAP, and those with suspected or confirmed viral or COVID-19 pneumonia were excluded from the study.

### Sample Size and Sampling Procedure

A sample size of 226 (113 cases and 113 controls) was determined using two population proportion formulas by considering power of 80%, 95% confidence interval (95% CI), ratio of 1:1 between cases and controls, taking poor oral hygiene as a main predictor of CAP with the percentage of controls exposed 41%, and Odds Ratio 2.29 from previous study<sup>12</sup> and an estimated non-response rate of 10%. It was calculated using the Epi Info (unmatched case-control), a program developed by the Centers for Disease Control and Prevention.

Consecutive sampling was used to select cases and controls until the required sample size was reached. Participants who had been diagnosed with community acquired pneumonia were included in the case group, regardless of the severity and treatment setting, as well as one control for each case on a daily basis from the same hospital setting. The main inclusion criterion for the control group was the absence of CAP.

## Data Measurement and Tool

Data were obtained through interviews with patients and a review of their medical records through a structured questionnaire. Sociodemographic characteristics, health conditions, and lifestyle habits were recorded. To ensure data quality, training was provided to the data collectors (two medical interns) and a supervisor (one internist). The questionnaire, originally developed in English, was translated into Amharic and back into English to ensure consistency. The interviews were conducted in Amharic's local language. On-spot checks, re-interviewing, and vigilant examination of completed questionnaires and quality of the recordings were performed through daily supervision. Before data processing, information was checked for internal consistency.

## Study Variables

The dependent variable in this study was CAP, and the independent variables were sociodemographic characteristics, general health conditions, lifestyle habits, and oral health status.

## Data Processing and Analysis

Data were cleaned for completeness and consistency, coded, and entered into Epi Info version 7.0, and transported into IBM SPSS Statistics version 20 for further analysis. Descriptive analyses were conducted for the main dependent variables and all covariables considered in the study. A comparison of the factors between cases and controls was performed using the chi-square ( $\chi^2$ ) test. Crude odds ratios (COR) with a 95% confidence interval (CI) were estimated in the bi-variable logistic regression analysis to screen the effect of each independent variable on the outcome variable and to select candidate variables for the multivariable logistic regression analysis. Because of the relatively large number of independent variables considered, it was screened using bi-variable analysis to minimize the chance of multicollinearity in the multi-variable regression. Thus, only the independent variables with a p-value of 0.20 or less in the bi-variable logistic regression were included in the multivariable logistic regression to obtain the adjusted effect of each covariate. Variables that were significant at p-value 0.05, and 95% CI in the multivariable logistic regression analysis were considered to be the determinant factors of CAP.

## Definition of Terms

### Community-Acquired Pneumonia

Community-acquired pneumonia is an acute onset of signs or symptoms suggestive of a lower respiratory tract infection acquired outside the hospital setting (e.g., cough, fever, sputum production, dyspnea, chest pain, and new focal chest signs), and a demonstrable infiltrate by chest radiograph or other imaging technique, with or without supporting microbiological data.<sup>2</sup>

### Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is defined by infection of the pulmonary parenchyma in patients exposed to invasive mechanical ventilation for at least 48 h and is part of ICU-acquired pneumonia.<sup>2</sup>

### Nursing- and Healthcare-Associated Pneumonia

Nursing- and healthcare-associated pneumonia (NHCAP) includes drug-resistant pneumonia that occurs during advanced medical care, dialysis and immunosuppressant therapy, and pneumonia caused by opportunistic pathogens.<sup>13</sup>

### Aspiration Pneumonia

Aspiration pneumonia is diagnosed following confirmation of inflammatory findings in the lungs and overt aspiration (apparent aspiration), a condition in which aspiration is strongly suspected, or the existence of dysphagia is confirmed.<sup>14</sup>

## Results

### Sociodemographic Characteristics of Participants

A total of 226 participants participated in both groups. Of these participants, 69 (61.1%) cases and 57 (50.4%) controls were male. The mean ( $\pm$ SD) age of the patients was 45.07 ( $\pm$ 18.35) years and 42.51 ( $\pm$ 16.13) years for cases and controls,

respectively. Among study participants, urban residents accounted for 62 (54.9%) of cases and 70 (61.9%) of controls. Most of the participants of case 72 (63.7%) and control 75 (66.4%) were married. Approximately 59 (52.2%) of cases and 43 (38.1%) controls had no formal education. When we looked at the occupation, 45 (39.8%) of case and 33 (29.2%) controls were farmers. Majority of the cases and controls 87 (77.0%) had more than five family members living in the house. Of these cases, 43 (38.1%) and 51 (45.1%) of the controls had a household monthly income of more than 5000 birr (Table 1).

## Medical Conditions of Study Participants

The common comorbidities were heart failure, consisting 14 (12.4%) of cases and 15 (13.3%) of controls; chronic obstructive pulmonary disease and asthma, which consisted 19 (16.8%) of cases, 8 (7.1%) of controls; hypertension accounted 10 (8.8%) both in cases and controls; diabetes mellitus consisted 6 (5.3%) of cases and 13 (11.5%) of controls; 9 (8.0%) of cases and 4 (3.5%) of controls had history of pulmonary tuberculosis. Other identified chronic medical conditions included stroke, cancer, mental disorders, HIV infection, and chronic liver disease. Additionally, 36 (31.9%) of cases and 16 (14.2%) controls reported prior use of proton pump inhibitors (PPI). Again, from the study participants, 31 (27.4%) of the cases and 25 (22.15%) of the controls had a history of CAP in the last two years. Majority of the cases 58 (51.3%) and 21 (18.6%) of the controls had a recent history of common cold in the last two weeks. A recent history of toothache accounts 36 (31.9%) in the cases and 15 (13.3%) in controls (Table 2).

## Behavioral and Lifestyle-Related Conditions of the Participants

Of the study participants, 64 (56.6%) of the cases 44 (38.9%) controls were exposed to cooking fuel smoke, 47 (41.6%) of the cases, and 30 (26.5%) controls had dusty working environment. Thirty-nine (34.5%) of the cases and 25 (22.1%)

**Table 1** Sociodemographic Characteristics of Study Participants, Debre Berhan University Hospital, 2023

Variables	Category	Case (n=123)	Control (n=123)	$\chi^2$	P-value
		N (%)	N (%)		
Sex	Male	69 (61.1)	57 (50.4)	2.58	0.21
	Female	44 (38.9)	56 (49.6)		
AGE>65	≥ 65	24 (21.2)	14 (12.4)	3.16	0.075
	<65	89 (78.8)	99 (87.6)		
Residence	Urban	62 (54.9)	70 (61.9)	1.16	0.28
	Rural	51 (45.1)	43 (38.1)		
Marital status	Single	29 (25.7)	34 (30.1)	4.45	0.21
	Married	72 (63.7)	75 (66.4)		
	Divorced/ widowed	12 (10.6)	4 (3.5)		
Occupation	Government employed	20 (17.7)	27 (23.9)	7.47	0.22
	Farmer	45 (39.8)	33 (29.2)		
	Merchant	17 (15.0)	12 (10.6)		
	Unemployed	17 (15.0)	15 (13.3)		
	Student	14 (12.4)	26 (23.0)		
Education	No formal education	59 (52.2)	43 (38.1)	5.6	0.28
	Primary education	14 (12.4)	17 (15.0)		
	Secondary education	17 (15.0)	17 (15.0)		
	College diploma and above	23 (20.4)	36 (31.9)		
Household income	<2500	33 (29.2)	23 (20.4)	2.51	0.28
	2500–5000	37 (32.7)	39 (34.5)		
	>5000	43 (38.1)	51 (45.1)		
Family size	<5	87 (77.0)	86 (76.1)	0.02	0.87
	>5	26 (23.0)	27 (23.9)		
Children in household	No	47 (41.6)	57 (50.4)	1.7	0.25
	Yes	66 (58.4)	56 (49.6)		

**Table 2** Medical Conditions of the Study Participants, Debre Berhan University Hakim Gizaw Hospital, 2023

Variables	Category	Case (n=113)	Control (n=113)	$\chi^2$	P-value
		N (%)	N (%)		
Heart failure	Yes	14 (12.4)	15 (13.3)	0.04	0.84
	No	99 (87.6)	98 (86.7)		
Stroke	Yes	2 (1.8)	5 (4.4)	1.32	0.25
	No	111 (98.2)	108 (95.6)		
Chronic respiratory disease	Yes	19 (16.8)	8 (7.1)	5.09	0.02
	No	94 (83.2)	105 (92.9)		
Diabetes mellitus	Yes	6 (5.3)	13 (11.5)	2.81	0.93
	No	107 (94.7)	100 (88.5)		
Hypertension	Yes	10 (8.8)	10 (8.8)	0.00	1.00
	No	103 (91.2)	103 (91.2)		
Cancer	Yes	2 (1.8)	2 (1.8)	0.00	1.00
	No	111 (98.2)	111 (98.2)		
Previous history of pulmonary tuberculosis	Yes	9 (8.0)	4 (3.5)	2.04	0.35
	No	104 (92.0)	109 (96.5)		
Prior use of PPI	Yes	36 (31.9)	16 (14.2)	9.99	0.002
	No	77 (68.1)	97 (85.8)		
Recent history of CAP	Yes	31 (27.4)	25 (22.1)	0.85	0.35
	No	82 (72.6)	88 (77.9)		
Recent history of common cold	Yes	58 (51.3)	21 (18.6)	26.64	<0.001
	No	55 (48.7)	92 (81.4)		
Recent history of toothache	Yes	36 (31.9)	15 (13.3)	11.16	0.001
	No	77 (68.1)	98 (86.7)		

controls had to regular contact with animals, whereas 20 (17.7%) of the case and 13 (11.5%) controls had regular contact with children. When we look at the oral hygiene behavior, only 20 (17.7%) of cases and 39 (34.5%) controls brushed their teeth on a daily basis. Regarding lifestyle, 35 (31.0%) of the cases and 28 (24.8%) controls drank alcohol, while only two (1.8%) of the cases and four (3.5%) controls had smoked cigarettes (Table 3).

## Risk Factors for Community-Acquired Pneumonia in Adults

A binary logistic regression model was used to determine the association between dependent and independent variables. Eight variables (age, cooking fuel smoke exposure, regular contact with animals, chronic respiratory disease, recent

**Table 3** Behavioral and Lifestyle Conditions of the Study Participants, Debre Berhan University Hakim Gizaw Hospital, 2023

Variables	Category	Case (n=113)	Control (n=113)	$\chi^2$	P-value
		N (%)	N (%)		
Cooking fuel smoke exposure	Yes	64 (56.6)	44 (38.9)	7.09	0.008
	No	49 (43.4)	69 (61.1)		
Regular contact with animals	Yes	39 (34.5)	25 (22.1)	4.27	0.039
	No	74 (65.5)	88 (77.9)		
Regular contact with children	Yes	20 (17.7)	13 (11.5)	1.73	0.23
	No	93 (82.3)	100 (88.5)		
Alcohol consumption	Yes	35 (31.0)	28 (24.8)	1.07	0.29
	No	78 (69.0)	85 (75.2)		
Cigarette smoking	Yes	2 (1.8)	4 (3.5)	0.68	0.40
	No	111 (98.2)	109 (96.5)		
Frequency of brushing	Occasionally	93 (82.3)	74 (65.5)	8.28	0.004
	Daily	20 (17.7)	39 (34.5)		

**Table 4** Summary of Multivariate Analysis of Factors Associated with Community Acquired Pneumonia of Patients Visiting Debre Berhan University Hakim Gizaw Hospital, 2023

Variables	Category	Case	Control	COR (95% CI)	AOR (95% CI)
		N (%)	N (%)		
Age	≥ 65	24 (21.2)	14 (12.4)	1.90 (0.92, 3.91)	1.51 (0.65, 3.49)
	<65	89 (78.8)	99 (87.6)	1	1
Cooking fuel smoke exposure	Yes	64 (56.6)	44 (38.9)	2.04 (1.20, 3.48)	1.18 (0.56, 2.22)
	No	49 (43.4)	69 (61.1)	1	1
Regular contact with animals	Yes	39 (34.5)	25 (22.1)	1.85 (1.02, 3.30)	1.00 (0.480, 2.09)
	No	74 (65.5)	88 (77.9)	1	1
Chronic respiratory disease	Yes	19 (16.8)	8 (7.1%)	2.65 (1.11, 6.30)	1.95 (0.73, 5.20)
	No	94 (83.2)	105 (92.9)	1	1
Recent history of common cold	Yes	58 (51.3)	21 (18.6)	4.62 (2.53, 8.42)	4.35 (2.22, 8.51)*
	No	55 (48.7)	92 (81.4)	1	1
Prior use of PPI	Yes	36 (31.9)	16 (14.2)	2.83 (1.46, 5.40)	1.81 (0.86, 3.79)
	No	77 (68.1)	97 (85.8)	1	1
Recent history of toothache	Yes	36 (31.9)	15 (13.3)	3.05 (1.56, 5.98)	2.51 (1.18, 5.33)*
	No	77 (68.1)	98 (86.7)	1	1
Frequency of teeth brushing	Occasionally	93 (82.3)	74 (65.5)	2.45 (1.31, 4.553)	2.79 (1.32, 5.88)*
	Daily	20 (17.7)	39 (34.5)	1	1

**Notes:** \*Statistically significant in multivariate analysis,  $p < 0.05$ ; 1, reference.

**Abbreviations:** OR, odds ratio; AOR, adjusted odds ratio.

history of common cold, prior use of PPI, recent history of toothache, and frequency of tooth brushing) were significantly associated with CAP ( $P < 0.2$ ). Multivariable logistic regression analysis was used to identify confounding factors. According to this analysis, only three of the above variables (history of common cold in the last two months, recent history of toothache, and frequency of teeth brushing) had a significant association at the 5% significance level. Therefore, based on multiple logistic regression analysis, study participants with a history of common cold in the last two months were 4.3 times (AOR: 4.35, 95% CI: (2.22, 8.51)) more likely to have CAP than those who had no history of common cold. Participants with a recent history of toothache were about 2.5 times (AOR, 2.51; 95% CI: (1.18, 5.33)) more likely to develop CAP than those who had a recent history of toothache. Regarding oral hygiene, individuals who did not regularly brush their teeth were 2.79 times (AOR, 2.79, 95% CI: (1.32, 5.88)) more likely to have CAP than those who regularly brush their teeth on a daily basis (Table 4).

## Discussion

This study aimed to identify the determinants of CAP among adult patients at DebreBerhan University Hospital by including a number of variables from various categories, such as socio-demographic characteristics, health status, behavioral and lifestyle factors, and oral hygiene parameters. According to the findings of this study, a recent history of a common cold, a recent history of toothache, and not cleaning teeth on a regular basis were all risk factors for community-acquired pneumonia.

The results of the current study indicate that individuals who had a recent common cold within the past two weeks had a four-fold higher likelihood of developing CAP than those who did not have a history of common cold. These findings are in line with those of a study conducted in Spain,<sup>10</sup> Kenya,<sup>5</sup> and Ethiopia,<sup>7,11</sup> that showed an increased risk of CAP due to the recent common cold. Another study from the United Kingdom showed that rhinovirus infection, which is the most common etiology of the common cold, has been followed by a number of other microbiological pneumonias.<sup>15</sup> The pathogenesis of superinfection has been attributed to direct mucosal/epithelial damage caused by the virus and increased bacterial colonization of the upper and lower respiratory tracts, all of which lead to increased susceptibility to secondary bacterial infections. In addition, antiviral immune responses induced by acute respiratory infections are associated with changes in microbial composition and function in the respiratory system, which in turn may alter the

subsequent immune function against secondary bacterial infections or alter the dynamics of intermicrobial interactions, thereby enhancing the proliferation of potentially pathogenic bacterial species.<sup>16</sup>

In this study, individuals who did not brush their teeth were 2.8 times more likely to develop CAP than those who brush their teeth regularly on a daily basis. The oral hygiene and the incidence of aspiration pneumonia and nursing and healthcare-associated pneumonia (NHCAP) have been well established.<sup>14</sup> Many studies on geriatric, nursing home, hospitalized, and intensive care unit patients<sup>17–21</sup> have reported an association between oral health and pneumonia. Additionally, Japanese study<sup>22</sup> revealed that infrequent denture cleaning is significantly associated with the incidence of pneumonia. Consistent with this finding, a study from Korea<sup>23,24</sup> showed that frequent tooth brushing significantly decreased CAP. Another study from Spain<sup>17</sup> and Japan<sup>10,22</sup> also revealed that poor dental hygiene increased the risk of developing CAP. This finding is consistent with that of a study conducted in Tigray, Ethiopia.<sup>7,11</sup> This association could indicate that the oral cavity is a reservoir of various respiratory pathogens, and poor oral hygiene is associated with an increased overgrowth of bacteria in the mouth, making it possible to inhale the microbes into the lungs, which is positively related to a higher risk of developing pneumonia. The prevention of plaque accumulation and bacterial colonization, particularly in subjects with dental caries and periodontal disease, is an important practical consequence.

This study also found that participants with a recent toothache were approximately 2.5 times more likely to have CAP than those without a toothache. Toothache can be caused by caries or periodontal disease, which can spread bacteria from an infected tooth or gum, most commonly by aspiration of oropharyngeal secretions, and can cause CAP. This finding was consistent with that of a study conducted in South Korea.<sup>22</sup> The connection between periodontal disease and pneumonia may result from the colonization of pathogenic bacteria present in the dental biofilm, followed by aspiration of the colonized pathogens, which is considered a significant risk factor for pneumonia.

The current study did not show an association between prior use of PPI and developing pneumonia. This might be explained by the frequent use of PPI as an over-the-counter (OTC) medication in the study area. This is also in line with other studies done in the UK<sup>25</sup> that indicate no strong association between the use of PPIs and an increase in the risk of community acquired pneumonia. But this study is inconsistent with studies<sup>26–29</sup> that showed using PPI could increase the risk of CAP.

As a strength, this study used primary data and included only cases of radiologically confirmed pneumonia. One potential limitation of this study is that bacteriological confirmation was not used for the diagnosis of CAP.

## Conclusion

This case–control study revealed that having a common cold in the last two weeks, recent toothache, and not brushing teeth regularly were risk factors for community-acquired pneumonia in adults. Hence, practicing regular tooth brushing and promoting good oral hygiene have a positive effect on health that goes beyond aesthetics. Therefore, I would recommend that dentists and dental care professionals collaborate with other stakeholders to promote oral health to reduce unnecessary morbidity and mortality as well as to reduce healthcare costs associated with CAP. Moreover, it is important to recommend that healthcare providers and public health organizations provide education on basic preventive and treatment measures for the common cold, to further reduce the risk of CAP.

## Abbreviations

AOR, Adjusted Odds Ratio; CAP, Community Acquired Pneumonia; COPD, Chronic Obstructive Pulmonary Disorder; CI, Confidence Interval; HAP, Hospital Acquired Pneumonia; HCAP, Health Care Associate Pneumonia; ICP, ICU, Intensive Care Unit; OR, Odd Ratio; PPI, Proton Pump Inhibitors; VAP, Ventilator Associate Pneumonia.

## Data Sharing Statement

The original contributions presented in this study are included in the article, and further inquiries can be directed to the corresponding author.

## Ethical Approval

Ethical approval was obtained with IRB Protocol number, IRB-113 from the Ethical Clearance Review Board of the Asrat Woldeyes Health Science Campus, Debre Berhan University. The approval was in accordance with the Helsinki Declaration guidelines and regulations. Additionally, permission was obtained from the hospital. Written informed consent was obtained from all study participants after they were informed about the purpose of the study. All necessary data were collected and registered based on the unique codes of the study participants and names were not taken throughout the study. Hence, all the information was kept confidential.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, interpretation, drafting, revising, and critically reviewing the article. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript and approved its submission for publication in Dove Medical Press.

## Disclosure

The authors report no conflicts of interest in this work.

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