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ORIGINAL RESEARCH

Clinical Analysis and Risk Factors of Bronchiolitis Obliterans After Mycoplasma Pneumoniae Pneumonia

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Purpose: Severe mycoplasma pneumoniae (MP) pneumonia can cause bronchiolitis obliterans (BO). In order to improve the prognosis of BO, it is necessary to grasp the clinical characteristics and risk factors of BO after severe MP pneumonia and intervene as soon as possible.

Patients and Methods: This study retrospectively analyzed the clinical data of 110 patients with severe MP pneumonia, and divided them into BO group (22 cases) and non-BO group (88 cases). The clinical characteristics of BO group were analyzed, and the clinical data of two groups were compared to identify the risk factors of BO.

Results: At the time of diagnosis, all BO patients had symptoms of cough and wheezing, and 10 (45.45%) had decreased exercise intolerance. Lung function showed moderate to severe obstructive ventilatory dysfunction, high-resolution computed tomography (HRCT) showed mosaic perfusion patterns. Multivariate binomial regression analysis showed that higher levels of serum lactate dehydrogenase (LDH) and hypoxemia were independent risk factors for BO after severe MP pneumonia.

Conclusion: Higher levels of serum LDH and hypoxemia were independent risk factors for BO after severe MP pneumonia. For patients with risk factors, clinicians should regular follow-up for early diagnosis and intervention of BO.

Keywords: children, bronchiolitis obliterans, mycoplasma pneumoniae pneumonia, post-infectious bronchiolitis obliterans, risk factors

Introduction

Mycoplasma pneumoniae (MP) is a common pathogen of community-acquired pneumonia in patients and MP pneumonia accounts for about 10–40% of community-acquired pneumonia.[1,2] MP infections are usually mild or self-limited, but in recent years, the incidence of MP pneumonia has been increasing. In addition, cases of severe MP pneumonia and macrolide-resistant MP (MRMP) pneumonia also are increasing, which can be life-threatening in severe cases.[3–5] Severe MP pneumonia and MRMP pneumonia can present with serious complications, including acute respiratory distress syndrome, bronchiolitis obliterans (BO) and so on.[6]

Post-infectious bronchitis obliterans (PIBO) is a chronic obstructive pulmonary disease secondary to a severe lower respiratory tract infection in childhood, which is characterized by inflammation and fibrotic narrowing of bronchioles.[7] MP is a common pathogen of PIBO. However, there were few reports on the clinical characteristics and risk factors of BO after severe MP pneumonia. In order to improve the understanding of BO after severe MP pneumonia, the primary aim of the study was to summarize the clinical characteristics of BO after severe MP pneumonia and explore the potential risk factors, so as to provide a theoretical basis for early recognition and intervention of BO after severe MP pneumonia.

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Materials and Methods

Study Population and Ethical Statement

A total of 22 patients with severe MP pneumonia who developed into PIBO were hospitalized in the Pediatric Respiratory Department of the First Hospital of Jilin University from 2014 to 2021. The control group was randomly selected, with a ratio of 4:1, and the year of severe MP pneumonia was matched. Follow-up for at least 1 year confirmed that there was no possibility of PIBO, and 88 patients with severe MP pneumonia were selected as the control group. The study was approved by the research ethics committees of First Hospital of Jilin University (Approval Number No.2021-747).

Inclusion and Exclusion Criteria

Inclusion Criteria: a. Patients were younger than 14 years old; b. All the Patients met the diagnostic criteria for severe pneumonia in guidelines for the Management of Community-acquired Pneumonia in children (2013);[8] c. Single serum MP-IgM titer ≥1:160.

Exclusion Criteria: a. Patients with bone marrow transplantation or organ transplantation; b. Patients with connective tissue diseases; c. Patients who contracted severe pneumonia again due to infection with other pathogens after the first diagnosis; d. Patients with incomplete clinical data.

PIBO diagnostic criteria:[9,10] a. Persistent or recurrent cough, wheezing, tachypnea, and decreased exercise intolerance for at least 6 weeks after acute severe MP pneumonia; b. There are extensive wheezing and moist crackles in both lungs; c. High-resolution computed tomography (HRCT) showed mosaic perfusion patterns, bronchiectasis or thickening of bronchial wall; d. Lung function showed irreversible or fixed air obstruction; e. Exclude other diseases that cause chronic wheezing, such as bronchial asthma, cystic fibrosis, immune deficiency, bronchopulmonary dysplasia.

Data Source

Clinical data of patients with severe MP pneumonia were retrospectively collected, including gender, age, history of preterm birth, history of allergy, history of wheezing, allergic diseases, clinical manifestations, laboratory and imaging findings, main treatments, response to therapy.

Adenovirus, respiratory syncytial virus, parainfluenza virus and influenza A/B virus antigen were determined by nasopharyngeal secretion immunofluorescence tests.

All patients with PIBO underwent HRCT (SOMATOM Sensation Cardiac 64 CT scanner, Siemens AG, Forchheim, Germany) and lung function testing (Master Screen Paed, Jaeger Company, Wurzburg, Germany) at the time of diagnosis. All patients carried out tidal breathing pulmonary function testing, because most of the patients were less than 3 years old and could not cooperate with forced breathing. Time to peak tidal expiratory flow as a proportion of expiratory time (TPTEF/TE) and volume to peak expiratory flow as a proportion of exhaled volume (VPEF/VE) were used to reflect airway obstruction. Airway obstruction was defined as TPTEF/TE and VPEF/VE <28%, and which were classified according to different levels of obstruction, namely mild obstruction (28–23%), moderate obstruction (22–15%), and severe obstruction (<15%).[11]

Statistical Analysis

SPSS 23.0 and R 3.5.3 software were used for statistical analysis. Measurement data were expressed as the mean ± standard deviation, and comparison between the two groups was performed by independent sample t-test. Non-normally distributed data were described by median and interquartile ranges, and comparison between groups were made by Mann–Whitney U-test. Categorical data were described as numbers and percentages (%). Categorical variables were compared using the chi-Square test. This study applied univariable binomial regression analysis to investigate factors associated with the development of BO after severe MP pneumonia, and significant values were included in multiple binomial regression model. $P < 0.05$ was considered to be of significance for all aforementioned statistical tests.

Results

Clinical Characteristics of BO Group

A total of 22 patients with severe MP pneumonia who developed BO were enrolled, including 12 males (54.55%) and 10 females (45.45%). The mean age at diagnosis of PIBO was 28.72 months (11 months to 81 months), and the mean age difference from diagnosis of severe MP pneumonia was 5.04 months. Among all PIBO patients, 3 (13.64%) had a history of preterm birth, 6 (27.27%) had a history of allergy, 6 (27.27%) had a history of wheezing, and 1 (4.55%) had tracheomalacia. Four (18.18%) were complicated with adenovirus infection, and two (9.09%) were complicated with influenza A virus infection.

At the time of diagnosis, 22 patients with PIBO had recurrent cough and wheezing, and 10 patients (45.45%) had decreased exercise intolerance. Wheezing and moist crackles could be heard in the both lungs. Mosaic perfusion patterns were observed in all patients, bronchiectasis was observed in 3 patients (16.67%) and thickening of bronchial wall was observed in 5 patients (27.78%). Lung function of all patients at the time of PIBO diagnosis showed moderate to severe obstructive, TPTEF/TE and VPEF/VE were 12.81±2.92 and 18.23±2.70. After the diagnosis, all patients were given oral glucocorticoid (1–2mg/kg/d, gradually reduced for 3–6 months), azithromycin (5mg/kg/d, 3 consecutive days per week, 3–6 months) and continuous inhalation of budesonide (1mL, twice a day). After 1 year of follow-up, 15 patients (68.18%) had almost no cough or wheezing, but still had decreased exercise intolerance. The TPTEF/TE and VPEF/VE were 15.76±3.04 and 20.18±3.01. The mosaic perfusion patterns on HRCT of all patients did not change significantly. Up to now, 8 patients were lost to follow-up, and 13 patients (92.86%) showed obvious improvement in symptoms, occasionally coughing and wheezing after vigorous exercise or acute infection. Only one patient (7.14%) had no Mosaic perfusion patterns on HRCT (Figure 1), 5 patients (35.71%) had fewer mosaic perfusion patterns than before, and 8 patients (57.14%) had no significant changes.
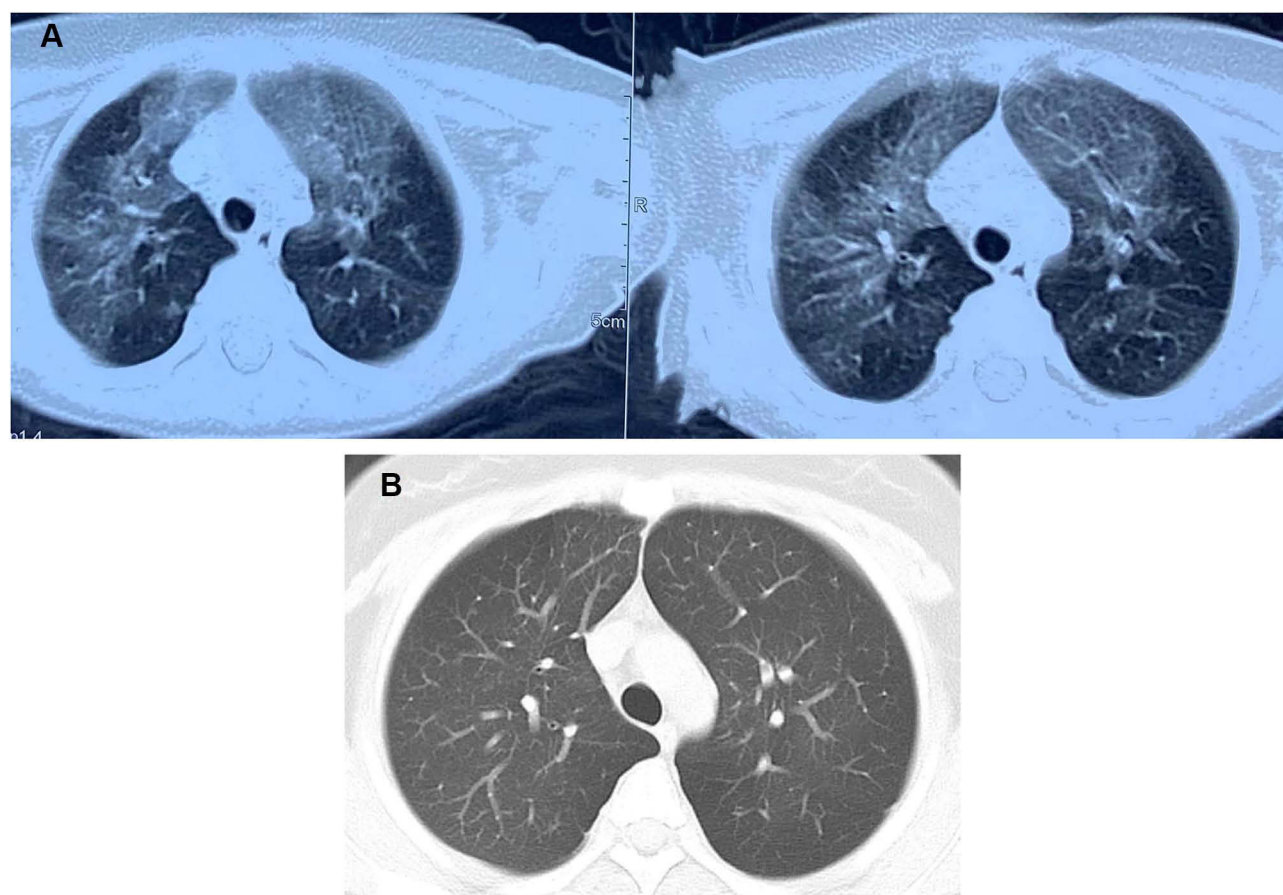

Figure 1 The HRCT of a girl with PIBO. (**A**) HRCT at diagnosis of PIBO. (**B**) Mosaic perfusion patterns disappeared after 6 years.

Comparison of Clinical Features Between BO Group and Non-BO Group

A total of 110 patients with severe MP pneumonia were enrolled, including 22 in BO group and 88 in non-BO group. The PIBO group was significantly younger (P = 0.011, Table 1), had a higher rate of preterm birth rate (P = 0.007, Table 1), and had a higher rate of history of wheezing (P = 0.001, Table 1). In clinical manifestations, the BO group had significantly longer hospital stays and duration of fever (P < 0.001, Table 1), and was more likely to experience wheezing, tachypnoea, hypoxemia and respiratory failure than those in the non-BO group (P < 0.001, Table 1). In terms of treatment, the BO group was likely to require the invasive mechanical ventilation, glucocorticoids and immunoglobulin (P < 0.05, Table 1). Laboratory findings revealed that the levels of aspertate aminotransferase (AST), creatine kinase-MB (CK-MB) and lactic dehydrogenase (LDH) levels in BO group were higher than those in non-BO group (P < 0.05, Table 2). The number of patients with pleural effusion in non-BO group was significantly more than that in BO group (P = 0.018, Table 2). There were no significant differences between the two groups in gender, previous allergic history and allergic diseases, IgM titer level, complicated adenovirus infection, duration of invasive mechanical ventilation and the use of Continuous Positive Airway Pressure (CPAP) (P > 0.05, Tables 1 and 2). For details, see Tables 1 and 2.

Risk Factors for BO in Patients with Severe MP Pneumonia

Table 3 shows the potential risk factors for the development of BO in the univariate analyses. In patients with BO after severe MP pneumonia, the younger at first diagnosis of severe MP pneumonia, the longer the fever lasts, experienced wheezing, tachypnoea, hypoxemia, respiratory failure, the higher levels of LDH, CK - MB and AST, and the need of invasive mechanical ventilation, glucocorticoids and immunoglobulin, the greater the risk of PIBO occur. Multivariable binomial regression analysis showed that higher levels of serum LDH (OR, 10.857; 95% CI, 2.713–72.949) and hypoxemia (OR, 48.899; 95% CI, 9.611–476.364) were the strongest independent risk factor for BO after severe MP pneumonia. See Table 4 for details.

Table 1 Comparisons of Clinical Characteristics and Treatment Between BO and Non-BO

	BO	Non-BO	*P*-value
Number of patients (n)	n=22	n=88	
Male, n (%)	12 (54.55)	48 (54.55)	>0.999
Age (months)	20 (13.00, 30.50)	33.00 (15.50, 64.50)	0.011
Premature birth, n (%)	3 (13.64)	0 (0.0)	0.007
A history of allergic, n (%)	6 (27.27)	12 (13.64)	0.221
Allergic disease, n (%)	0 (0.0)	2 (2.27)	>0.999
A history of wheezing, n (%)	6 (27.27)	3 (3.41)	0.001
Clinical manifestations			
Length of hospital stay	20.50 (16.75, 32.50)	14.00 (12.00, 19.00)	<0.001
Duration of fever	13.00 (4.75, 14.50)	8.00 (2.00, 11.00)	0.018
Peak temperature, °C	39.50±0.579	39.38±0.807	0.136
Wheezing, n (%)	22 (100.0)	36 (40.91)	<0.001
Tachypnoea, n (%)	16 (72.73)	26 (29.55)	<0.001
Hypoxemia, n (%)	18 (81.82)	18 (20.45)	<0.001
Respiratory failure, n (%)	13 (59.09)	15 (17.05)	<0.001
Treatment			
Invasive mechanical ventilation, n (%)	10 (45.45)	7 (7.95)	<0.001
Length of mechanical ventilation, d	8.60±3.78	6.29±2.81	0.392
CPAP, n (%)	5 (22.72)	7 (7.95)	0.108
Use of glucocorticoids, n (%)	19 (86.36)	51 (57.95)	0.013
Use of immunoglobulin, n (%)	14 (63.64)	17 (19.32)	<0.001

Table 2 Comparisons of Auxiliary Examinations Between BO and Non-BO Groups

	BO	Non-BO	P-value
Number of patients (n)	n=22	n=88	
Laboratory findings			
WBC (×10⁹/L)	8.90 (5.88, 16.59)	9.69 (6.66, 14.00)	0.794
HGB, g/L	117.86±13.49	120.93±14.06	0.602
PLT (×10⁹/L)	307.50 (259.00, 471.75)	317.00 (237.00, 400.00)	0.862
CRP, mg/L	1.35 (6.62, 31.70)	11.40 (4.48, 39.21)	0.127
AST, U/L	64 (46.75, 94.43)	37.30 (31.20, 55.10)	<0.001
ALT, U/L	20.6 (14.40, 39.5)	20.00 (13.70, 32.30)	0.705
CK-MB, U/L	33.05 (23.15, 38.73)	23.10 (17.60, 28.83)	0.001
LDH, U/L	685 (401.50, 1081.75)	378.50 (301.25, 553.25)	0.001
Neutrophil proportion, %	0.64±0.18	0.60±0.18	0.925
Lymphocytes, proportion, %	0.29 (0.13, 0.39)	0.25 (0.18, 0.39)	0.862
Levels of MP-IgM antibodies	1:160 (1:160, 1:200)	1:160 (1:160, 1:320)	0.199
Co-infection, n (%)			
Adenoviridae	4 (18.18)	5 (5.68)	0.139
Other viruses	2 (9.09)	4 (4.55)	0.345
Imaging findings, n (%)			
Pulmonary consolidation	22 (100)	81 (92.05)	0.379
Pleural effusion	1 (5.6)	25 (28.04)	0.018
Atelectasis	1 (5.6)	8 (9.09)	0.804

Table 3 Univariate Analysis of Potential Risk Factors for the Development of BO

Variables	P-value	OR (95% CI)
LDH	<0.001	8.209 (2.906–29.763)
Hypoxemia	<0.001	17.500 (5.734–66.600)
CK-MB	0.036	4.755 (1.406–26.265)
AST	0.021	2.193 (1.134–4.434)
Age	0.015	0.201 (0.045–0.618)
Duration of fever	0.009	2.814 (1.334–6.513)
Invasive mechanical ventilation	<0.001	9.643 (3.145–31.561)
Need the glucocorticoids	0.020	4.595 (1.433–20.577)
Need the immunoglobulin	<0.001	7.309 (2.707–21.091)
Tachypnoea	<0.001	6.359 (2.338–19.430)
Respiratory failure	<0.001	7.030 (2.591–20.077)

Table 4 Multivariable Binomial Regression Analysis of Potential Risk Factors for the Development of BO

Variables	P-value	OR (95% CI)
LDH	0.003	10.857 (2.713–72.949)
Hypoxemia	<0.001	48.899 (9.611–476.463)

Discussion

PIBO is a chronic airflow obstruction syndrome caused by severe lower respiratory tract injury, and adenovirus is the most common pathogen of PIBO. Currently, MP is found to be the second major pathogen of PIBO, causing about 20% of PIBO.[6,12] Lee et al[13] found that the prevalence of BO after MP pneumonia was 12%, no less than that BO after severe adenovirus pneumonia. Therefore, attention should be paid to severe MP pneumonia, to identify the risk factors of BO after severe MP

pneumonia at an early stage and reduce the occurrence of PIBO. Grasping the clinical characteristics of BO after severe MP pneumonia, and early intervention to improve the prognosis of patients.

A total of 22 patients with BO after severe MP pneumonia were analyzed in this study. Although lung biopsy is considered as the gold standard for diagnosing PIBO, lung biopsy cannot always be meaningful due to the patchy distribution of lesions and invasive. Therefore, the diagnosis of PIBO in this study was based on clinical manifestations, lung function and typical HRCT findings. All the patients included in this study had recurrent cough and wheezing after acute severe respiratory tract infection, almost half of them had decreased exercise intolerance, moderate to severe obstructive ventilatory dysfunction in lung function, and mosaic perfusion patterns were observed on HRCT. After 1–6 years of follow-up, recurrent cough and wheezing symptoms of most of the patients were relieved, while some patients still had decreased exercise intolerance. Lung function was better than at the time of diagnosis, and the mosaic perfusion patterns on HRCT was reduced in 43.86% of the patients, and the mosaic perfusion patterns disappeared in one patient.

Damage to small airway epithelial cells, persistent inflammatory factors, and abnormal airway repair may contribute to PIBO.[14] This study found that patients in the BO group had a younger onset age, a higher rate of the history of premature birth and wheezing, longer hospital stays and duration of fever, prone to wheezing, tachypnoea, hypoxemia, respiratory failure, higher levels of AST, LDH, CK-MB levels, and more likely to require invasive mechanical ventilation, glucocorticoids and immunoglobulin. The occurrence of PIBO seems to be related to the severity of lung tissue injury during MP pneumonia. The more serious the lung tissue injury is, the more likely PIBO occurs. Yu et al[15] also found that the occurrence of BO after adenovirus pneumonia was related to the severity of adenovirus pneumonia.

This study further identified the risk factors for BO after MP pneumonia. This study found that patients with severe MP pneumonia were younger, had longer duration of fever, was more likely to experienced wheezing, hypoxemia, tachypnoea, had higher levels of LDH, AST and CK-MB, and was likely to needed invasive mechanical ventilation, glucocorticoid and immunoglobulin, which were the risk factors for PIBO. At present, it is generally believed that PIBO occurs mostly in infants, and the non-specific and specific immune responses of infants are low. After MP infection, it is easy to cause serious lung tissue damage through multi-pathway and multi-mechanism immune response. However, Colom et al[16] found that age was not a risk factor for PIBO. Considering that not all of the included patients were MP infection-related, further studies are needed to verify our conjecture. Previous studies have found that mechanical ventilation is a risk factor for BO after adenovirus infection,[16,17] this study also found that mechanical ventilation was a risk factor for BO after MP pneumonia. Longer duration of fever, wheezing, hypoxemia, tachypnoea, the use of glucocorticoid and immunoglobulin all reflected the severity of severe MP pneumonia, which reflected the correlation between the occurrence of PIBO and the severity of severe MP pneumonia. Moreover, we believed that the use of mechanical ventilation reflected the severity of the disease and did not increase the risk of PIBO. In the future, we should be alert to the occurrence of PIBO in patients with severe symptoms of MP pneumonia.

In this study, higher levels of serum LDH was an independent risk factor for BO after severe MP pneumonia. Serum LDH level can reflect the severity of organ damage, especially lung tissue. The level of serum LDH is now used as a routine indicator to reflect the severity of lung disease, and has been suggested as a predictive marker of severe or refractory MP pneumonia.[18–20] Moreover, the high level of serum LDH is related to the prognosis of patients. Lee et al[13] also found that higher LDH level was related to the occurrence of BO after MP infection. Therefore, patients with pneumonia whose serum LDH level is significantly higher should be vigilant and treated as early as possible to improve the prognosis. Inamura et al[21] suggested that glucocorticoid therapy should be considered when LDH ≥410IU/L. This study found that hypoxemia was also an independent risk factor for BO after severe MP pneumonia. Wu et al[22] found that hypoxemia was also an independent risk factor for BO after adenovirus infection, and they suggested that hypoxemia was more sensitive than other predictors.

A study had found that the high titer of MP specific IgM antibody in acute stage is the risk factor for PIBO.[13] However, in this study, IgM antibody titer level in the BO group and non-BO group had no significant statistical significance, and was not the risk factor for PIBO, so further research is needed. It was well known that adenovirus infection was a risk factor for the occurrence of PIBO, and some studies have found that adenovirus and MP co-infection increases the risk of PIBO.[13] However, this study found that MP and adenovirus co-infection did not increase the risk of PIBO. Previous studies had found that the atopic was a risk factor for severe MP pneumonia, and asthma was a risk

factor for PIBO after MP pneumonia.[23] However, in this study, the history of allergies and allergic diseases were not statistically different between the BO group and the non-BO group, nor were they risk factors for PIBO. The risk factors reported so far are not exactly the same as those found in this study, and might be related to the inclusion of study subjects, pathogens infected or variables analyzed.

There were several limitations in this study. First, the number of sample size in this study was small, and heterogeneity may exist. Further studies will be carried out in the future. Secondly, this was a single-center study. Large-scale multi-center studies with large samples are needed for further exploration.

Conclusion

At present, there is no specific and unified treatment standard for PIBO, and the prognosis is poor. Therefore, it is important to identify the risk factors for PIBO. In addition, severe MP pneumonia should arouse the attention of clinicians. Especially in severe MP pneumonia with hypoxemia and higher serum LDH, the occurrence of PIBO should be vigilant. For patients with high risk factors, clinicians should pay attention to regular follow-up for early diagnosis and intervention of PIBO patients.

Ethics Approval and Consent to Participate

Verbal informed consent was obtained from all patients or legal guardians. The Ethics Committees of First Hospital of Jilin University approved this consent process. The study complied with the Declaration of Helsinki.

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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 and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; 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.

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