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Laryngology

Serum interleukin 1β in patients with acquired laryngotracheal stenosis

Livelli di Interleuchina 1β sierica in pazienti con stenosi laringotracheale acquisita

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SUMMARY

Objectives. To determine the serum levels of interleukin-1beta (IL-1β) in patients with acquired laryngotracheal stenosis (ALTS) and healthy volunteers and compare levels between serum and tissue of the stenotic segment.

Materials and methods. An exploratory cohort study included 20 participants with ALTS and 5 healthy volunteers. ALTS group was categorised into mild and severe according to grade of stenosis and presence of tracheostomy. Comparisons of serum levels of IL-1β between pre- and post-surgical intervention and between blood and tissue samples in the severe ALTS group were made. Correlation of IL-1β levels between blood and tissue was assessed using Spearman's correlation.

Results. Severe ALTS patients showed higher serum levels of IL-1β compared to mild ALTS and healthy volunteers ($p = 0.045$). IL-1β was higher before surgical intervention than after surgical intervention ($p = 0.003$). There was a strong positive correlation of IL-1β between serum and tissue ($r = 0.74$, $p = 0.035$).

Conclusion. Serum levels of IL-1β are higher in ALTS patients than in healthy controls and positively correlate with tissue levels. The decreasing trend of serum IL-1β observed following successful surgical intervention reflects the absence of ongoing inflammation at the stenotic segment.

KEY WORDS: acquired laryngotracheal stenosis, interleukin-1beta, laryngeal stenosis, subglottic stenosis, inflammatory mediators

RIASSUNTO

Obiettivi. *Determinare i livelli sierici di Interleuchina-1beta (IL-1β) in pazienti con stenosi laringotracheale acquisita (ALTS) e volontari sani, confrontarne i livelli nel siero e nel tessuto stenotico.*

Materiali e metodi. *Uno studio di coorte esplorativo ha incluso 20 partecipanti con ALTS e 5 volontari sani. Il grado di ALTS è stato classificato in lieve e grave in base alla stenosi e alla necessità di tracheostomia. È stato effettuato il confronto dei livelli sierici di IL-1β pre e post-chirurgici, e tra campioni di sangue e di tessuto nel gruppo con ALTS grave. I livelli di IIL-1β tra sangue e tessuto sono stati confrontati utilizzando la correlazione di Spearman.*

Risultati. *I pazienti con ALTS grave hanno mostrato livelli sierici di IL-1β più elevati rispetto a ALTS lievi e volontari sani ($p = 0,045$). IL-1β è risultata maggiore prima dell'intervento chirurgico rispetto al post chirurgico ($p = 0,003$). È risultata una forte correlazione positiva di IL-1β tra siero e tessuto ($r = 0,74$, $p = 0,035$).*

Conclusioni. *Il livello sierico di IL-1β è più alto nei pazienti con ALTS rispetto al gruppo sano ed è positivamente correlato al livello di IL-1β dei tessuti. Una tendenza alla riduzione dell'IL-1β sierica, osservata a seguito di un intervento chirurgico con esito positivo, riflette l'assenza di infiammazione in corso nel segmento stenotico.*

PAROLE CHIAVE: *stenosi laringotracheale acquisita, interleuchina-1beta, stenosi laringea, stenosi sottoglottica, mediatori dell'infiammazione*

Presentation at conference
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Introduction

Acquired laryngotracheal stenosis (ALTS) remains one of the most challenging problems in otolaryngology. Studies have shown that predominant causes of ALTS include trauma, prolonged endotracheal intubation and tracheostomy [1]. Other less common causes include systemic diseases such as sarcoidosis, Wegener's granulomatosis and relapsing polychondritis [2].

In the United States, there are an estimated 4.9 million cases of ALTS post-intubation and post-tracheostomy per year [3]. Other studies have reported an incidence of laryngotracheal stenosis ranging from 6% to 21% [4,5]. However, in Southeast Asia, the incidence rate of ALTS has not yet been reported. In the authors' centre, there were 28 cases of ALTS from August 2015 to August 2016, 10 of which required multiple surgical interventions.

There is heterogeneity in the proportion of men and women reported. Some studies have reported that ALTS is more common in men [6], whereas others have documented a female predominance [7]. The age distribution may vary according to the aetiology of ALTS. Younger adults are the most common in traumatic groups (34.4 years, CI 23.5-45.3) [8].

Predisposing factors that may contribute to ALTS following intubation include the size of the endotracheal tube, duration of intubation, cuff pressure, re-intubation, history of tracheostomy, percutaneous tracheostomy, gastro-oesophageal reflux, obesity, infection while being intubated and post-radiotherapy for neck or laryngeal tumours [5,9]. ALTS is commonly caused by endotracheal intubation secondary to either mechanical trauma due to the placement of the endotracheal tube or contact pressure. Mucosal oedema and hyperaemia may progress to mucosal necrosis and ulceration that may occur within hours of intubation. Subsequently, this may result in exposure of the perichondrium of the cartilage, leading to perichondritis, which can then progress to formation of scar tissue and stenosis. The formation of a stenosis may also contribute to abnormal wound healing by dense fibrous tissue, which is further attributed to altered fibroblast responsiveness to anti-fibroblastic signals during mucosal repair [10,11].

Motor vehicle accidents (MVA) causing neck trauma and other injuries needing emergency intubation are other common aetiologies of ALTS. The number of MVA cases in Malaysia is increasing [12]. This may hypothetically increase the incidence of ALTS. Surgical interventions with either an endolaryngeal or external approach have remained the standard treatment for ALTS [13]. However, these surgical procedures may cause further scarring, re-stenosis and even mortality, with rates ranging from 1.8% [14] to 5% [15]. The need for multiple surgeries due to re-stenosis is common, ranging between 28% and 70% [16].

The pathophysiology of ALTS is still not well understood. An inflammatory response to injury seems to play an important role in the beginning of the pathogenesis of ALTS. This is regulated by growth factors, cytokines, chemokines and other inflammatory mediators. Acute inflammation, which occurs in the early phase of wound healing, involves mediators of the interleukin-1 cytokine family, including interleukin-1alpha (IL-1α), interleukin-1beta (IL-1β) and interleukin-1 receptor antagonist (IL-1Ra) [17]. A key inflammatory mediator is IL-1β, which is secreted by epithelial cells, macrophages and neutrophils [18]. IL-1β can stimulate the production of other inflammatory mediators such as IL-6, IL-8 and prostaglandin E2 (PGE2) during the inflammatory phase [18]. Animal studies have documented that the specific inflammatory mediators responsible for development of laryngotracheal stenosis may be IL-1β and prostaglandin E2 [18-22]. A human study involving patients with ALTS also reported markedly elevated levels of IL-1β.

To the authors' knowledge, research on adult ALTS is scarce. ALTS studies have mainly focused on animal and Caucasian participants that reported IL-1β as a possible key mediator to abnormal wound healing leading to ALTS. In those studies, IL-1β was measured mainly in tissue or secretions collected from the airway under general anaesthesia. Therefore, the present study aimed to investigate the serum levels of IL-1β and its trend between ALTS (mild and severe) and a healthy volunteer group. The levels of IL-1β in blood were compared levels in tissue of the stenotic segment. To date, there have been no publications of such studies in Southeast Asia or the local population. Hence, the present study may highlight the need for better screening, prevention and treatment for ALTS.

Materials and methods

Study design and patient recruitment

An exploratory study (cohort study) was conducted over 18 months from 1st January 2017 to 30th June 2018. Twenty patients ≥ 18 years old who were diagnosed with ALTS and attended the otorhinolaryngology (ORL) clinic were recruited. The causes of stenosis were mainly faulty intubation, and one patient had stenosis following blunt laryngeal trauma. Five healthy volunteers ≥ 18 years old were also recruited among the patients' family members and clinical staff.

ALTS patients with the following criteria were excluded: 1) non-Malaysian; 2) laryngotracheal stenosis of other causes such as a tumour, tuberculosis, idiopathic, or congenital; and 3) presence of co-morbidities such as autoimmune or chronic inflammatory diseases including eczema

and allergy rhinitis. Healthy volunteers with co-morbidities or upper respiratory infection or any infection at other parts of the body or surgeries within one month were excluded.
For the ALTS group, the severity of stenosis was diagnosed by performing direct laryngoscopy under general anaesthesia. The degree of stenosis was documented by using Cotton Myer (CM) grading [18]. During clinic visits following diagnosis or surgical interventions, a flexible nasopharyngolaryngoscopy under topical anaesthesia with 2% lidocaine was performed to examine the glottis and subglottic areas. The severity of the stenosis was then documented. Among those not using a tracheostomy tube, the severity of symptoms was graded using the Modified Medical Research Council (MMRC) dyspnoea scale [20]. Based on severity of symptoms and stenosis and the presence of tracheostomy, ALTS patients were categorised as mild or severe stenosis. Criteria for the severe group included CM grading high grade 2, 3, or 4 requiring tracheostomy and undergoing surgical interventions such as T-tube insertion, endolaryngeal laser surgery, dilation and open surgery, i.e. tracheal resection anastomosis (TRA). Successful surgical intervention was defined as either successful decannulation of tracheostomy tube or relief of upper airway obstruction symptoms for patients who were not on tracheostomy tube. Patients with CM grade I who did not require tracheostomy and did not undergo surgical intervention were categorised as mild ALTS. Blood samples were taken four times from each ALTS patient every 6 to 12 weeks. For ALTS patients who required surgical interventions, apart from blood samples, tissue biopsies from the stenotic area were taken under general anaesthesia in the operating theatre. Repeat blood samples were taken within 6 to 12 weeks of post-surgical intervention. For healthy volunteers, one blood sample was taken.

ELISA

IL-1β levels were measured in blood and tissue samples by enzyme-linked immunosorbent assay (ELISA) (RayBio® Human IL-1 beta ELISA kit), according to the manufacturer's instructions. The minimum detectable dose of IL-1β is reported as 0.3 pg/ml, with intra-assay and inter-assay coefficients of variation of < 10% and < 12%, respectively [21].

Statistical analysis

All data were computerised and analysed using SPSS version 23.0 and Graph Pad Prism version 7.0. The mean serum levels of IL-1β for mild and severe stenosis in the ALTS group and the healthy volunteer group were recorded in terms of mean and standard deviation (SD). One-way ANOVA was used to analyse the mean differences in IL-1β levels between groups. A paired t-test was used to compare the serum levels of IL-1β pre- and post-surgical intervention, as well as serum and tissue levels of IL-1β. The correlation between serum and tissue levels was assessed using Pearson's correlation. The trends in serum IL-1β at different time points are reported descriptively.

Results

Demography

The ALTS group included 14 males and 11 females with a mean age of 48.5 years. The majority of the patients were Malay, followed by Chinese and Indian. Five patients had mild ALTS, and 15 patients were classified as having severe ALTS. With regards to CM grading of stenosis, grades I, II, III, and IV were 30%, 25%, 30%, and 15% of the study sample, respectively. Subglottic (60%) was the most common site of stenosis, followed by tracheal (30%), supraglottic (5%) and mixed (5%). Fifteen patients (75%) had mature scars, while five patients (25%) had granulation tissue at the stenotic segment. Most patients presented with a circumferential stenosis and all had mobile bilateral vocal folds.

Surgical interventions performed for severe ALTS

Of 15 patients with severe stenosis, two had a T-Tube inserted, nine underwent transoral laser microsurgery (TLM) and balloon dilation, two underwent TRA and two did not receive any surgical interventions other than tracheostomy during the study period. One had failed TRA and the other was at high risk for cardiac complications for TRA; therefore, a T-tube was inserted for these two patients.

Comparison of mean of IL-1β in mild, severe ALTS and healthy volunteer groups in blood

The mean and SD values of IL-1β for the healthy volunteer, mild and severe ALTS group were 2.310 ± 1.606, 4.127 ± 1.421 and 8.269 ± 5.848 pg/ml, respectively. The level of IL-1β was significantly higher in the severe ALTS group than in the mild ALTS group. It was also significantly higher in the mild ALTS group compared to healthy volunteers ($p = 0.045$) (Fig. 1).

Comparison of mean IL-1β between blood and tissue samples in severe ALTS

The level of IL-1β in tissue samples was found to be significantly higher than in blood samples. ($p \leq 0.05$) (Fig. 2). The level of IL-1β in serum was strongly correlated with the level of IL-1β in tissue ($r = 0.74$, $p = 0.035$).

Comparison of mean serum level of IL-1β pre- and post-intervention in severe ALTS

Mean and SD of IL-1β for the pre- and post-intervention group were 10.62 ± 6.814 and 4.756 ± 3.061 pg/ml, respec-

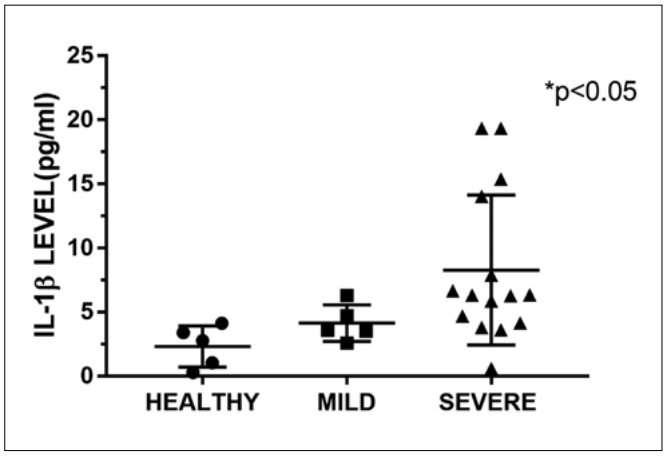

Figure 1. Differences in mean IL-1β between mild, severe ALTS and healthy volunteer groups in blood samples (p = 0.045).

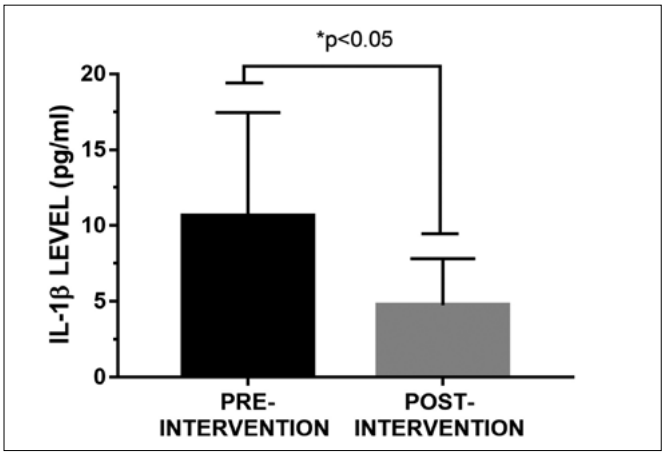

Figure 3. Comparison of the mean values of IL-1β in the severe ALTS group pre-and post-intervention.

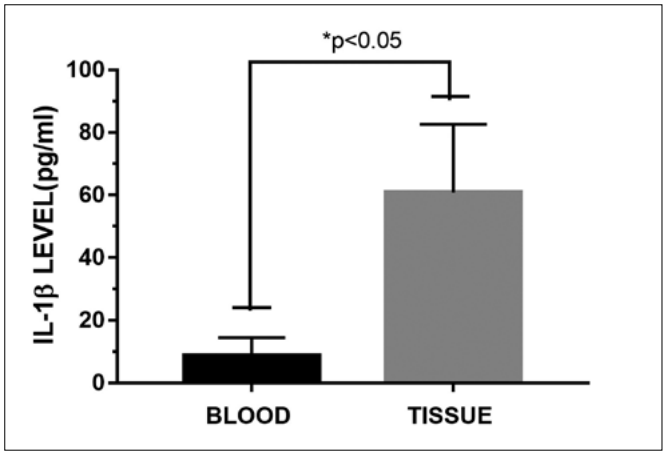

Figure 2. Comparison of mean IL-1β between blood and tissue samples in the severe ALTS group.

tively. Using Paired t-test, a significant reduction of IL-1β after surgical intervention was observed ($p \leq 0.05$) (Fig. 3).

Examples of cases in the severe ALTS group showing trends of IL-1β over time

T-tube procedure

The level of IL-1β in patients who underwent T-tube insertion was noted to be stagnant at around 4 to 5 pg/ml. Although stagnant, the level was higher than mean IL-1β in healthy volunteers.

TLM and balloon dilation

There was a decrease in the level of IL-1β following TLM and balloon dilation procedure. The improvement of CM grading was observed together with a reduction of IL-1β. However, the IL-1β level documented after taking the 4th blood sample was slightly higher than that in healthy volunteers.

Tracheal resection and anastomosis

There was a marked reduction in IL-1β levels following successful surgical intervention with TRA. A reduction was observed together with improvement in CM grading of the stenosis (Figs. 4, 5). However, the IL-1β level was still higher than in healthy volunteers.

Tracheostomy

In a severe ALTS patient who had not undergone surgical intervention during the study period and was on tracheostomy, there was a fluctuation of the IL-1β level, and the mean value was higher than in healthy individuals. CM grading was maintained as Grade 2.

The trend of IL-1β level in mild ALTS and its correlation with CM Grading compared with mean of IL-1β in healthy individuals

The level of IL-1β was found to be low and was not above 4 pg/ml, which correlated with the severity of the stenosis, but still higher than in healthy individuals.

Discussion

ALTS is a condition commonly caused by emergency intubation injury [1]. Moderate to severe cases of ALTS are tracheostomy tube dependent, and those who suffer complete stenosis will be aphonic. This reduces the quality of life and is highly likely to cause job loss. Treatment for moderate to severe ALTS, especially with poor prognostic factors, remains one of the most challenging conditions to treat in otolaryngology. To date, there is still a lack of studies to identify preventive or curative medical treatment for ALTS.

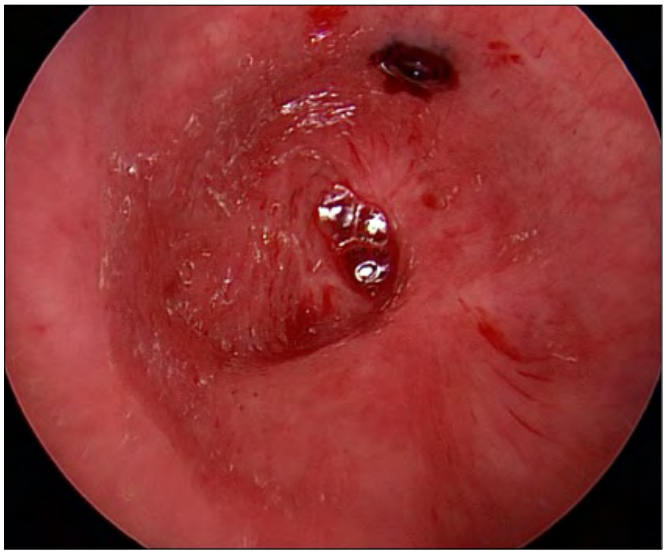

Figure 4. Findings before open surgery with TRA.

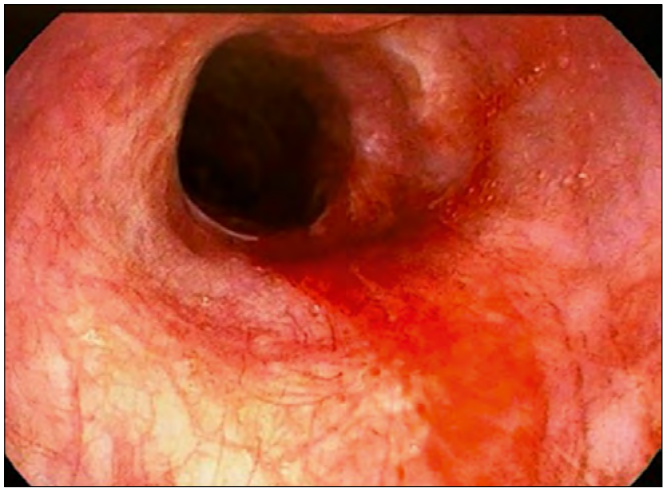

Figure 5. Findings after open surgery with TRA.

The majority of studies have been performed in animals and are very scarce in humans. Preventive or curative medical treatment may be possible by identifying the key mediators of the inflammatory response in a high risk group of patients who have the propensity of developing ALTS.

The present study was a human study in which the serum levels of IL-1β were measured in patients diagnosed with mild or severe ALTS as well as in healthy volunteers. This study was intended to obtain information concerning ALTS that has not been previously reported in human studies. Previous studies documented IL-1β as the key inflammatory mediator in ALTS [18,19]. Those studies mainly measured IL-1β in tissue samples taken from the upper airway, which normally can only be done when performing direct laryngoscopy under general anaesthesia. This would not be ideal if this inflammatory marker were to be used as a screening tool for patients who will potentially develop ALTS. Identification of inflammatory markers using blood samples would be an easier and less invasive method as a screening tool. Hence, the present study measured the levels of IL-1β in blood samples from healthy volunteers and those with mild to severe ALTS to compare the differences. Furthermore, the trend of IL-1β level was studied at four different time points with 6- to 12-week intervals between each point, and the mean level was compared between pre- and post-surgical interventions to illustrate the impact of the inflammatory mediator. As far as we know, no previous literature has investigated the serum levels of IL-1β in these patients. This study is also the first published data from Southeast Asia and may become the basis for future studies.

In the present study, the mean serum level of IL-1β in healthy volunteers was 2.310 ± 1.606 pg/ml. When this was compared with ALTS patients, the mean IL-1β level was significantly higher in the latter ($p < 0.05$). The mean of IL-1β was also higher in the severe ALTS group than in the mild ALTS group ($p < 0.05$). In the mild ALTS group, the levels of IL-1β remained low (≤ 4 pg/ml) throughout the study period, which correlated with severity of the stenosis. The level of IL-1β was found to be in a downward trend in severe ALTS following successful TLM and open surgery. However, the level was unchanged in patients with T-tubes and fluctuant in patients on tracheostomy. The serum level of IL-1β in patients who were still on T-tubes was noted to be stagnant at around 4 to 5 pg/ml, which, however, was still higher compared to healthy individuals.

The level of IL-1β in tissue samples was shown to be significantly higher than in blood samples. However, a significant positive strong correlation between blood and tissue samples was seen in this study ($r = 0.74$), and this result shows that blood samples may be used instead of tissue samples in ALTS.

In a study by Puyo et al., significant tracheal inflammation was detected in short-term intubations. This further justifies the abhorrent risks of persistent inflammation faced by patients who were intubated longer and hence high levels of IL-1β [23]. To our knowledge, numerous studies have been performed to determine IL-1β levels in ALTS, but the levels were mainly measured from specimens taken from tissue or secretions of the upper airway. Results of these studies showed that subglottic injury was associated with increased levels of IL-1β [18,19,22]. Another study also compared the levels of IL-1β in ALTS in humans and animals [19]. Granulation tissue was taken from 10 patients with early symptomatic subglottic stenosis and compared to mucosal tissue from

the control bronchus of the same patients. The expression levels of 24 different cytokines were measured by polymerase chain reaction (PCR). The results showed that IL-1β was markedly elevated in the granulation tissue compared to the mucosa of the normal bronchus. In the same publication, the authors also demonstrated increased IL-1β in animal models of induced subglottic injury compared to the control group.

While previous studies have documented increased levels of IL-1β in tissue, the present study measures IL-1β levels in blood, which is a less invasive approach and thus a more feasible screening tool. Additionally, we compared healthy and ALTS groups, and mild and severe groups of ALTS, pre- and post-surgical intervention, and correlated the level of IL-1β with clinical findings, which were not mentioned in the previous studies. This makes this research a novel and innovative study, allowing it to be used as a baseline for in-depth research including clinical trials in the future.

Some recent studies have demonstrated that IL-4 is elevated in ALTS. This is based on the role of cytokines in other fibroproliferative diseases such as idiopathic pulmonary fibrosis and cardiac fibrosis [24]. However, there have been no comparisons between IL-1β and IL-4. Further investigation is recommended to compare these two groups of interleukins in the future for a better understanding of the pathophysiology of ALTS.

Some limitations were identified in this study. The small number of patients included and the variation in the duration of onset of ALTS before recruitment may limit the strength of the results. For future studies, including patients undergoing emergency intubation in a larger cohort study is recommended to confirm our findings. It would also be interesting to investigate the association of genetic predisposition and high IL-1β in the development of stenosis.

Conclusions

This study documented that the normal mean serum levels of IL-1β was 2.310 ± 1.606. Levels of IL-1β were generally higher in the adult ALTS group than in healthy volunteers. Serum IL-1β was also positively correlated with tissue levels, and thus blood may be used for future studies on key inflammatory mediators in ALTS.

Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

NA: research proposal, data collection, data analysis, manuscript writing. YL: data collection, data analysis, manuscript writing. ANMH: manuscript writing. MA: data collection, data analysis, manuscript writing. ASM: manuscript writing. MMB: research idea and design, data collection, data analysis, manuscript writing.

Ethical consideration

This study was registered with the Secretariat for Research and Innovation and received full ethics approval with project code FF-2017-036.

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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