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ORIGINAL ARTICLE

Factors affecting inflammatory changes in congenital lung malformations

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Abstract

Aim of the study Patients with congenital lung malformation (CLM) may present pulmonary inflammatory changes. However, little is known about the factors influencing local inflammation. The aim of this study was to evaluate the factors that may affect inflammatory changes in CLM.

Methods Patients with CLM operated upon between 2005 and 2021 were included. The grade of inflammation was defined with a purpose-made inflammatory score (IS) ranging from 0 to 5. The association of type of CLM and age at surgery with IS was analyzed. Results are means (standard deviation).

Main results Data from 105 patients with CLM were collected, 56 had congenital pulmonary airways malformation (CPAM), 24 bronchopulmonary sequestration (BPS), and 25 congenital lobar emphysema (CLE). 91 patients (87%) had inflammatory changes. IS was 2.1 (1.5), 1.2 (1.0), and 1.3 (1.5) in CPAM, BPS, and CLE respectively (One-way ANOVA $p=0.0101$). CPAM showed a significantly higher IS as compared with BPS ($p=0.0242$) and CLE ($p=0.0495$). Age at operation significantly correlated to IS ($r^2=0.14$; $p<0.0001$). Patients aged below 6 months at operation had lower IS [1.4 (1.2)] as compared to those over 6 months [2.0 (1.6)] ($p=0.018$). Age at operation significantly correlated with the IS in CPAM ($r^2=0.17$; $p=0.0016$) and CLE ($r^2=0.47$; $p<0.0001$) patients.

Conclusions Patients with CLMs often present inflammatory changes in their lungs. Grade of inflammation significantly correlates with age at surgery and type of anomaly, with CPAMs having the highest grade. These findings support early resection in patients with CLM, especially in case of CPAM.

Keywords Congenital lung malformation · Inflammation score · Pulmonary resection · Pediatric surgery

Background

Congenital lung malformations (CLMs) define a group of rare lower respiratory tract abnormalities, which include congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration (BPS) and congenital lobar and segmental emphysemas (CLE). Bronchogenic cysts (BC) and bronchial atresia belong to CLMs but are less common entities [1–4].

Patients with symptomatic CLM require surgery, while the management of asymptomatic ones remains currently debated. The risks of resection must be balanced against the risks of expectant management [5]. Indeed, the paucity of long term follow-up studies casts doubts on prophylactic surgery with related risks of morbidity and mortality [6, 7]. Some centers advocate a conservative approach, in order to protect the children from the possible surgical complications [8, 9]. Such a "wait and see" approach is based on the possibility of spontaneous regression of CLMs although it has been documented in a very small percentage of cases, and that the CLM may remain asymptomatic all life-long [8]. Instead, some authors encourage early surgical resection in

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the light of the documented possibility of recurrent pulmonary infections, the risk of pneumothorax and neoplastic degeneration [10–13]. The potential better compensatory lung growth and the long-term pulmonary function derived from lung development in infancy are a point in favor of early resection. Other factors supporting surgical management include either subclinical infection or malignancy in asymptomatic lesions [14]. Actually, the development of infectious complications in the CLM leads to more risky and lengthy surgery [6, 15–17].

Also, the optimal timing for surgery is a matter of debate due to the lack of accurate estimation of CLMs natural history and heterogeneity in reported outcomes [18]. In addition, minimally invasive surgery is considered safer and more feasible in older children with asymptomatic lesions [19–21].

Scattered studies have reported inflammatory changes in the lungs of patients with CLMs, which may be an additional factor in favor to preventive surgery [22, 23]. However, little is currently known on the type and the degree of inflammation [22, 23]. Therefore, the aim of the study was to define the degree of inflammation in the resected lungs of patients with CLMs and determine possible factors influencing the development of inflammatory changes.

Methods

All patients consecutively treated for CLM in our hospital between January 1st, 2005 and December 31st, 2021 were included in the study.

To obtain meaningful results, anomalies with less than 10 patients were excluded from the study.

Demographic data, type of anomaly, age at surgery and surgical approach were collected and analyzed.

Histological specimens were retrospectively reviewed by a dedicated pathologist (CC), focusing on the abnormal lung tissue.

The tissue specimens were routinely fixed in 10% buffered neutral formalin, processed, and embedded in paraffin; 5 µm sections were stained with hematoxylin and eosin (H&E) and examined by light microscopy.

The inflammatory cells were identified in H&E-stained slides, and a semi-quantitative histopathological score was developed to rate the degree of inflammation (inflammation score: IS).

The score ranges from 0 to 5 and it adds: extension of the inflamed tissues in terms of percentage of involved tissue, site of inflammatory infiltrate and type of inflammatory infiltrate (Fig. 1). Chronic inflammation was defined as the presence of mononuclear cells (lymphocytes, macrophages, plasma cells), while inflammatory tissue was defined acute when also polymorphonuclear cells (granulocytes) were found.

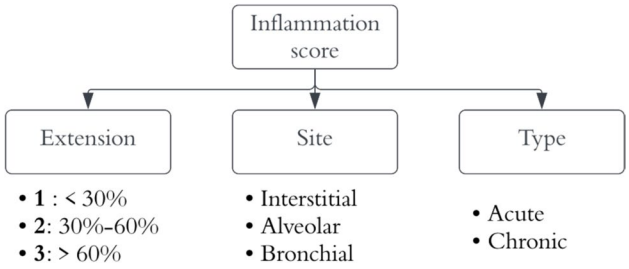

Fig. 1 Parameters used in the histopathological inflammation score. The final score was defined as follows: 0: no inflammation. 1: chronic, interstitial inflammation, extension 1. 2: chronic, interstitial inflammation, extension 2. 3: Chronic, two simultaneous locations, extension 2. 4: chronic, all locations simultaneously, extension 3. 5: acute, all locations simultaneously, extension 3

Every specimen was analyzed by the same pathologist, thereby leading to a uniform evaluation of the specimens.

In hybrid malformations, we defined the prevalent anomaly based on whether it was in communication with the airways or not. Anomalies communicating with the airways were considered CPAM with abnormal systemic blood supply, and those not communicating with the airways were considered BPS with associated cystic anomaly.

This study received Institutional Review Board approval number 260/2021.

Statistical analysis: Data were analyzed using GraphPad Prism 9.0 Macintosh Version (GraphPad Software, San Diego California USA, www.graphpad.com). Continuous variables were analyzed with one-way ANOVA or Fisher's exact test as appropriate. Spearman's test was used for correlations. Receiver operating characteristic (ROC) curve analysis was performed to determine the best cut-off value of age at operation to predict the risk of having an IS ≥ 2. Results are given as mean (standard deviation) or r^2. Two-sided p values are reported and a p value < 0.05 was considered significant.

Results

During the study period, we treated 108 consecutive patients with CLMs. Two patients with a bronchial cyst and one with a pleuropulmonary blastoma were excluded from the study, leaving 105 patients for the analysis: 56 had CPAM (10 with systemic blood supply), 24 BPS (8 with CPAM areas) and 25 CLE. Seven patients (6.5%, all CPAM) had episodes of pulmonary infection before surgery. None of these 7 patients had prenatal diagnosis.

All extra-lobar sequestrations underwent sequestrectomy (last three recent cases treated with thoracoscopy).

Intra-lobar sequestrations and CPAMs were always treated with lobectomy to reduce CPAM recurrence risk, except 4 bilateral CPAMs thus underwent atypical resection to preserve functioning lung tissue. Three recent CPAMs cases were treated with VATS lobectomy.

Mean age at operation was 14 months and mean IS value was 1.7 (1.4) for all CLMs, distributed as displayed in Table 1. Groups' age was not statistically different.

Figure 2 shows the distribution of the IS in our study population.

Only 14 patients (13%) had IS = 0, 50 patients had the inflammation limited to the interstitium and of limited extent (IS = 1), and the remaining 41 patients had moderate to extended degree of inflammation, IS from 2 to 5. Mean IS value was 2.1 (1.5), 1.2 (1.0), and 1.3 (1.5) in CPAM, BPS, and CLE respectively (one-way ANOVA $p = 0.0101$) (Fig. 3).

Table 1 CLMs divisions, mean age at operation and mean inflammation score value

	n (%)	age at operation (mean months) ± SD	Inflammation score value (mean value) ± SD
CPAM	56 (53)	12.5 ± 22.6	2.1 ± 1.5
BPS	24 (23)	15.7 ± 31.0	1.2 ± 1.0
CLE	25 (24)	14.7 ± 36.3	1.3 ± 1.5
All CLMs	105 (100)	14.1 ± 27.9	1.7 ± 1.4

CLMs congenital lung malformations; *CPAM* congenital pulmonary airway malformation; *BPS* extra- and intra-lobar bronchopulmonary sequestration; *CLE* congenital lobar and segmental emphysemas

At ROC curve analysis, the age of 5.5 months was the best cut-off to predict an IS IS ≥ 2 (Fig. 5). Accordingly, patients younger than 6 months at operation had lower IS [1.4 (1.2)] as compared to those older than 6 months of age [2.0 (1.6)] ($p = 0.018$). When focusing in the different anomaly, age at operation was significantly correlated with the IS in CPAM [$r^2 = 0.17$ ($p = 0.0016$)] and CLE [$r^2 = 0.47$ ($p < 0.0001$)] patients.

Discussion

In this study, we found that over 80% of patients operated on for CLM have some degree of inflammation in their affected lungs. Inflammatory changes were associated with the type of malformation and correlated with age at operation. These data may be important in the decision making process while treating a patient with CLMs.

No consensus exists regarding the optimal management of asymptomatic CLMs nor the best surgical timing, if surgery is decided. The rationale behind a "wait and see" approach is the lack of symptoms and the potential, although rare, for spontaneous regression of the lesion. Follow-up is based on imaging studies, mainly periodic thoracic CT scan, and surgery is performed either upon symptoms onset or detection of significant changes in the lesions [19–21, 24]. On the other hand, elective surgical resection is based

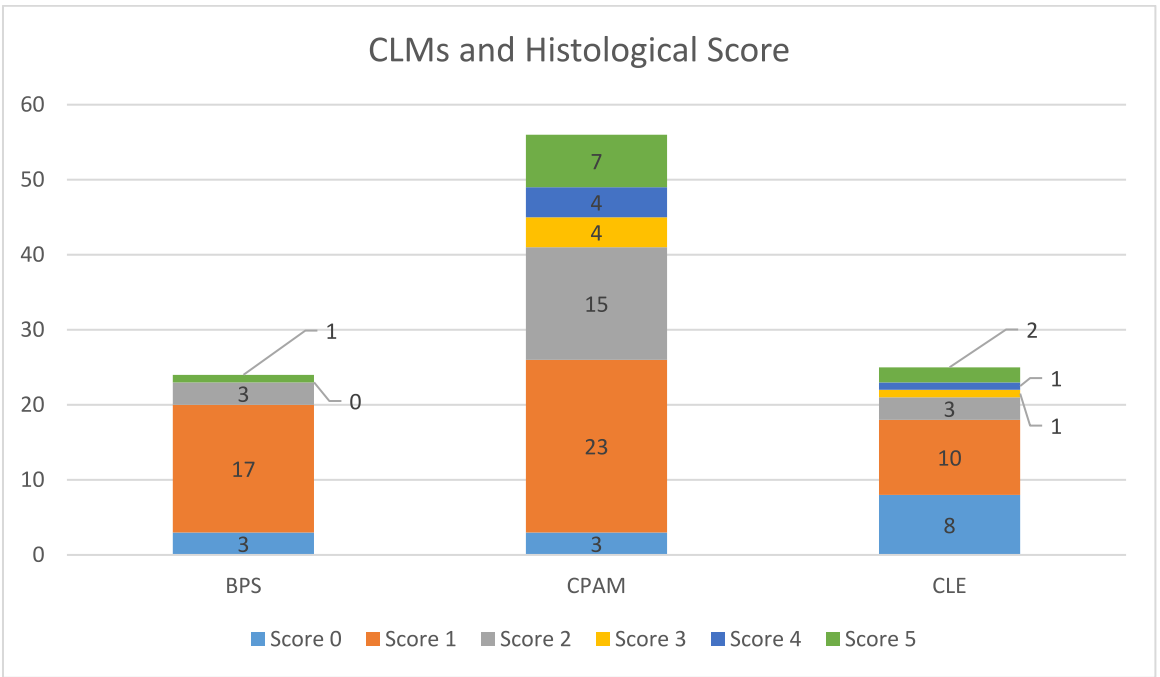

Fig. 2 Histopathological inflammation score in different CLMs. Number of lesions are reported on the y axis

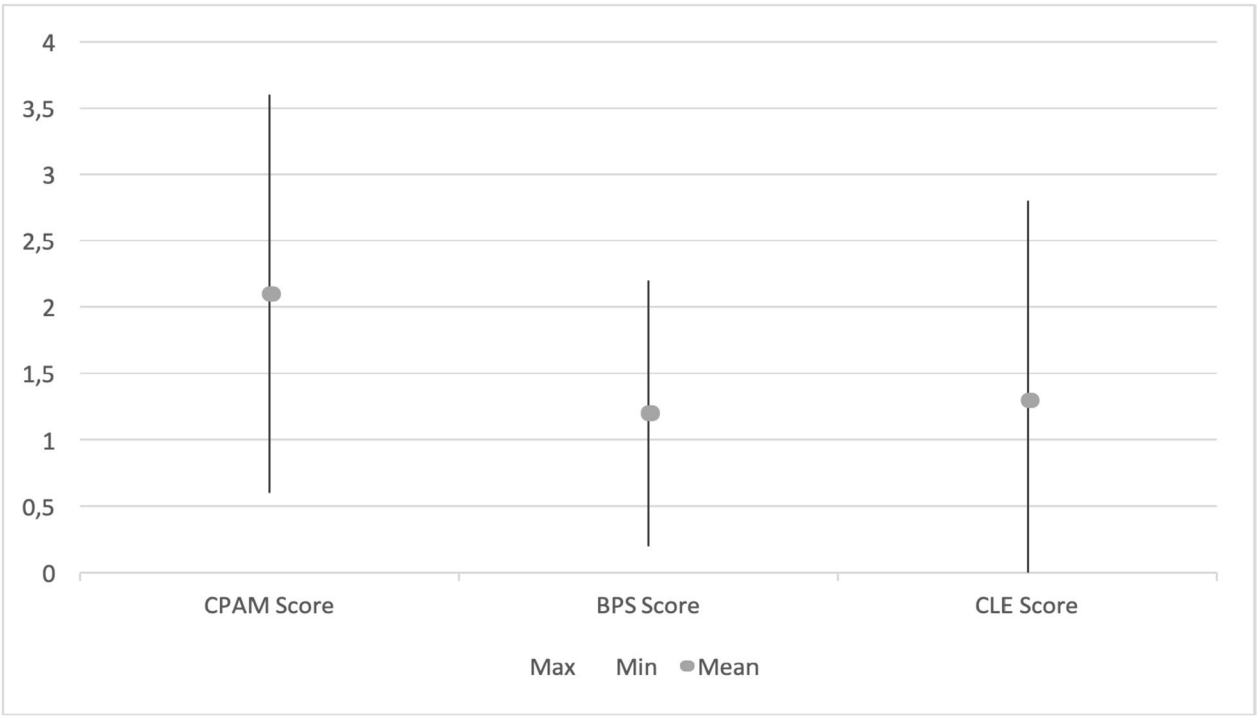

Fig. 3 CLMs mean inflammation score value. Number of lesions are reported on the y axis. CPAM showed a significantly higher IS as compared with BPS ($p=0.0242$) and CLE ($p=0.0495$), while IS was not statistically different between BPS and CLE. Overall, age at operation was significantly correlated to the IS ($p<0.0001$, $r^2=0.14$) (Fig. 4), even when patients with pre-operative pneumonia were excluded from the analysis $r^2=0.13$ ($p=0.0002$)

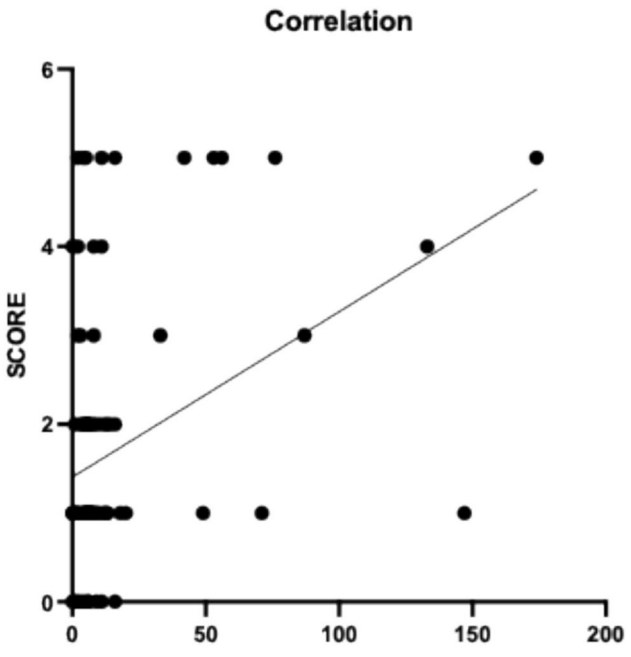

Fig. 4 Correlation between age at surgery and histopathological score

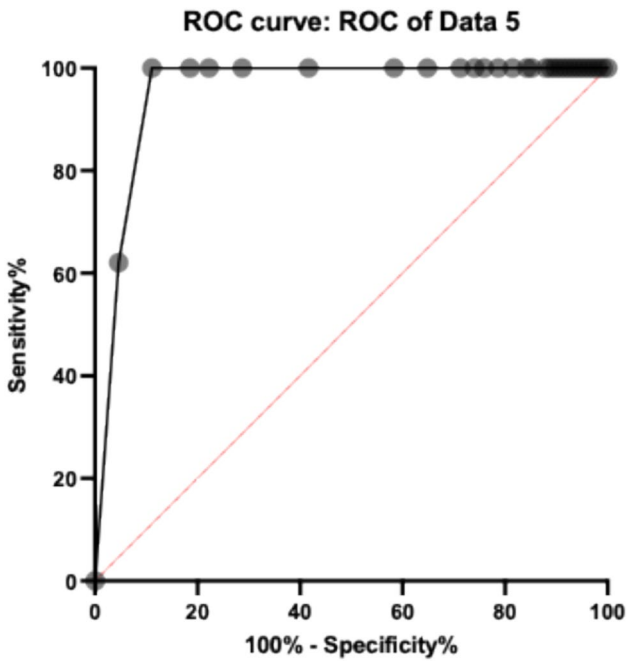

Fig. 5 ROC Curve analysis: the age of 5.5 months was the best cut-off to predict an IS IS ≥ 2

on risk of pneumothorax and neoplastic degeneration and, more frequently, the possibility of recurrent pulmonary infection that will make surgical resection more complex and with a higher complication risk [10–13, 25]. Our findings of inflammatory changes in the lungs of the majority of patients treated for CLMs, even if they never previously experienced clinically evident pneumonia, are similar to what was reported from previous studies. In 13 patients operated on for asymptomatic CPAM, Calvert and Lakhoo found signs of infection or inflammation in 5 [16]. In 2009, Pelizzo et al. found that 19 out of 24 patients operated upon for CPAM within the first 3 months of life had inflammatory infiltrates [26]. More recently, Durell et al. found that 16 out of 69 asymptomatic patients operated upon for CLMs had neutrophil/macrophage infiltration (9 patients) or microabscesses (7 patients) [14]. Similarly, Till and co-workers [27] found evidence of clinically silent infectious infiltrates in lung tissue of patients operated on for asymptomatic CLM. Also Liu et al. [28] report that 32% of patients with CLMs have hidden infections in their lungs although no infectious agent is described, but only inflammatory infiltrate. Lastly, in 2022, Engall et al. [29] found that 59% of asymptomatic patients who underwent surgical resection of a CLM had histological evidence of inflammation. Taken together, these findings suggest that a significant proportion of patients with CLMs harbor inflammatory infiltrates or infectious microfoci in their lungs, even if asymptomatic, that may predispose to subsequent clinically evident lower respiratory tract infection. Additionally, it is long known that chronic inflammation may foster cancer development [30]. If neoplastic transformation of CLMs remains a possibility, the persistence of inflammatory changes in the lungs of patients with CLMs may participate in this transformation. These findings are a further point in favor of surgical resection of CLMs, even in asymptomatic patients.

In this study, we aimed to identify factors facilitating the development of inflammation in the lungs of children with CLMs. We found that the type of anomaly and the age at operation had an influence on inflammatory infiltrate degree. Patients with CPAM had the highest IS, which was significantly higher than that of patients with BPS or CLE. It is tempting to speculate that anatomical aspects of the anomaly may have an influence on the development of inflammatory infiltrate. Specifically, in patients with CPAM, the connection with the upper airways may facilitate the colonization of the abnormal lung from potentially infectious agents, which may then stagnate within the cysts, thereby stimulating the inflammatory response. In their 16 patients with CLMs who developed inflammatory or infectious infiltrate, Durell et al. did not focus on the type of anomaly [4]. Pelizzo et al. described only patients with CPAM; they found a higher prevalence of inflammatory infiltrate in patients with Stocker type II CPAM [31]. Liu et al. reporting 518 asymptomatic patients treated for CLMs found that those with intra-lobar BPS had the highest prevalence of inflammatory infiltrate [28], suggesting that the anatomical location of the anomaly within the lung lobe that communicates with the environment facilitates the invasion from microorganisms. The partial discrepancy between our findings and that from previous studies suggests that a more complex mechanism may be involved in the inflammatory changes in the lungs of patients with CLMs. A recent study by Tan and co-workers [32] aiming to identify the characteristic gene expression patterns and the marker genes essential to CPAM found several candidate genes for the development of CPAM. Interestingly, some of the genes expressed differently between the cysts and the normal lung tissue were also significantly enriched in immune-related functions and inflammatory responses, suggesting that that malformation of the lung rather than infection induced the inflammatory reaction. This study was limited to CPAM. Therefore, it is not possible to define if the same, or a similar, mechanism may be involved also in other types of CLMs.

We also found that age at operation was significantly correlated with IS. When we analyzed the different type of anomaly separately, the significant correlation remained for CPAM and CLE patients, not for BPS patients, further supporting the possibility that the connection with the environment may represent a trigger for the inflammatory process and the longer this trigger acts the higher the inflammation. With ROC curve analysis, we found that the best cut-off age at surgery allowing to predict an IS of 2 or higher was 5.5 months. This is not the first study suggesting a direct correlation between time and inflammation in the lungs of patients with CLMs. Calver and Lakhoo in a small series of patients operated upon for CPAM found a higher incidence of inflammation/infection with surgery performed after 6 months of age [16]. Liu et al. report that among 518 children operated on for CLMs, the age of those with inflammatory infiltrate is significantly higher than those without [29]. Additionally, the prevalence of inflammatory infiltrate increases with age. Similarly, Engall et al. [29] found that after 10 months of age, the prevalence of inflammatory changes was significantly higher and they report a significant correlation between age at resection and previous treatment for lower respiratory tract infections. Therefore, time is a factor that influences both prevalence and degree of inflammation in the lungs of patients with CLMs, and the risk of lower respiratory tract infections. Earlier resection may protect children with asymptomatic CLMs from development of pulmonary inflammation and the associated risks. It is not possible to define the exact ideal age for operation. Our data suggest before 6 months of age, while others found that the cut-off was 10 months of age.

Our study has some limitations. The first is the retrospective nature of the study. The second is that we used a score

not previously validated. We used a semi-quantitative score over qualitative data to enhance descriptive/qualitative tissue data. In addition, each progressive level of the score had well-defined descriptors in every parameter (extension, site, type of inflammation). Finally, every specimen was analyzed by the same pathologist, thereby leading to a uniform evaluation of the specimens. The score was not tied to predict the outcomes. Therefore, we did not analyze the outcomes based on the IS. In present study, we wished to evaluate if patients with CLMs had inflammatory changes in their lugs and their degree, and if type of malformation and age at surgery may have impacted on these.

In conclusion, a significant proportion of patients with CLMs have inflammatory infiltrate in their lungs. The type of CLM and the age at operation may have an influence on the development of pulmonary inflammatory changes and on their degree. This information should be taken into consideration during counselling parents of a fetus with a CLM and for the postnatal management of these patients. Further studies, with larger and diverse population samples, are required to confirm these findings and eventually drive the optimal management of these complex clinical entities.

Author contributions A.Z., C.O., F.T. and F.M. wrote the main manuscript text and prepared figures and Tables. All authors reviewed the manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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