Role of pulmonary function testing in inflammatory bowel diseases (Review)

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Abstract. Inflammatory bowel disease (IBD) is a term used to describe chronic inflammatory entities of the gastrointestinal system with an unclear etiology. Extra-intestinal manifestations beyond the involvement of the gastrointestinal tract can also occur. Several studies have investigated the alterations of pulmonary function tests (PFTs) in patients with IBD. To the best of our knowledge, the present review article is the first to summarize all the types of PFTs that have been performed in patients with IBD. Contradictory data exist regarding the association of PFT alterations with disease activity. PFT abnormalities can develop in individuals with IBD who have no clear clinical signs or radiological evidence, suggesting that PFTs may be useful in detecting latent respiratory involvement. The most prevalent finding in the PFTs of adults and children with IBD is an impairment in the diffusing capacity for carbon monoxide, although evidence on the other tests, particularly spirometric values, and their connection with disease activity is inconsistent.

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Contents

1. Introduction

Inflammatory bowel disease (IBD) is a term used to describe chronic entities characterized by inflammation, mainly affecting the gastrointestinal system. The underlying etiology of this condition remains unclear. Crohn's disease (CD) and ulcerative colitis (UC) represent the two main types of chronic IBDs (1). In spite of CD and UC being different entities, both may present with any of the following manifestations: Abdominal pain, tenesmus, diarrhea, steatorrhea, fever, rectal bleeding, severe cramps or muscle spasms in the pelvic area and weight loss (2).

Extra-intestinal manifestations or complications beyond the involvement of the gastrointestinal tract occur at an incidence of 21-41% (3). These manifestations can occur concurrently with intestinal inflammation or may develop independently of the intestinal activity. They can significantly affect the quality of life of patients, causing severe morbidity and involving several organs (4). Frequent extra-intestinal manifestations include anemia, osteoporosis, cutaneous lesions, as well as

ocular, liver and articular diseases (5). Ulcers in the oral cavity and thromboembolic disease can also occur (6). However, pulmonary involvement is relatively infrequent (7).

The spectrum of lung involvement in IBDs is broad, spanning from subclinical abnormal involvement to interstitial lung disease (ILD) (8). Other pulmonary manifestations are airway disease (panbronchiolitis, bronchiolitis obliterans organizing pneumonia and bronchiectasis), inflammatory tracheal stenosis, pulmonary vasculitis, thromboembolic disease, pleural disease, apical fibrosis, sarcoidosis, enteric-pulmonary fistulas, Langerhans cell histiocytosis, manifestations resembling Wegener's granulomatosis and adverse drug toxicities (9).

Lung abnormalities in IBDs can be present years following the onset of the disease, occurring commonly during active disease, infrequently independent of disease activity, and even in patients in the post-colectomy period (10). The underlying pathogenesis of lung abnormalities in IBDs may be associated with the fact that both the colonic and respiratory epithelial cells share a common embryonic origin. The respiratory and gastrointestinal systems contain submucosal lymphoid tissue and play a key role in host mucosal defense (11). The similarity in mucosal immunity leads to similar pathogenic alterations, which may be caused by epithelial cell exposure to common inhaled or ingested antigens, leading to lymphoid tissue sensitization and an inflammatory process (12). The activated inflammatory cells in the gastrointestinal tract are capable of producing numerous circulating cytokines that can regulate the endothelial cell adhesion molecules, modify leukocyte migration, enhance the production of toxic reactive oxygen metabolites and induce lung parenchyma damage (13). Recent research has demonstrated that there is a pathological connection between the lung and bowel with the longer course of the disease, the greater extent of the disease, and the more severe the pulmonary function damage is in individuals with UC (14). Animal experiments have also noted that rat models of UC exhibited lung pathological injury (14-16).

Although pulmonary involvement in IBDs is rare, the prevalence of pulmonary function test (PFT) abnormalities in patients with IBDs has been reported to be 17-55%, indicating that occult pulmonary disease may be detected using PFT variables (17). Some studies have examined possible changes in pulmonary function parameters in patients with IBD and their association with disease activity (18,19). According to some reports, PFT alterations in patients with IBD are related to disease activity (20,21), whereas other authors have found that active disease does not affect the values of PFTs (22). Moreover, apart from traditional PFTs, additional PFTs, such as bronchoprovocation challenge and the measurement of exhaled nitric oxide (NO), have been performed in patients with IBDs and have been associated with disease activity (23,24). The present review article is the first, to the best of our knowledge, to summarize all the types of PFTs that have been performed in patients with IBD and to discuss the association of their results with the activity of the disease.

2. Spirometry

Spirometry calculates the maximal air volume that a patient can inspire and expire using maximal effort, estimating volume or flow as a function of time. The most common measurements are the forced vital capacity (FVC), which represents the air volume exhaled during a forceful and complete expiration and the forced expiratory volume in 1 sec (FEV1), which is the air volume exhaled in the first second during an FVC maneuver (25). Another variable that can be measured during the FVC maneuver is the mean forced expired flow as lung volume decreases from 75 to 25% of vital capacity $FEF_{(25-75)}$, which is associated with changes in the small airways (26).

Alterations in the values of FEV1, FVC and $FEF_{(25-75)}$ have been found in patients with IBDs (9,10,19,23,27-36). More specifically, obstructive dysfunction was observed in some studies (17,19,29,33,37), and obstructive and/or restrictive ventilatory defects were observed in others (10,21,22,27,35), and some investigators have demonstrated isolated reductions in the absolute values of FEV1, FVC and $FEF_{(25-75)}$ (9,21,28,30-32,34,36). In some studies, these abnormalities were associated with disease activity (9,10,19,21,25,34,36), whereas other studies have mentioned no association between an impairment in spirometric values and the activity of IBDs (22,30-33,35). Of note, in the study by Ellrichmann *et al* (37), patients with active IBD presented with significant obstructive abnormalities in their PFTs, with obstruction being related to inflammatory activity. However, treatment with anti-tumor necrosis factor (TNF) antibody induced a significant improvement in obstructive dysfunction (37). On the other hand, some studies did not reveal alterations in the spirometric values of patients with IBDs compared to healthy controls (18,38-40).

3. Diffusing capacity for carbon monoxide

Diffusing capacity for carbon monoxide (DLCO) testing is used to differentiate patients with exertional dyspnea, spirometric obstruction and spirometric restriction, and to detect ILD, pulmonary vascular diseases, occupational pulmonary diseases and or pulmonary side-effects of radiation or drugs (41). Reduced DLCO values have been noted in the majority of studies investigating PFT performance in patients with IBD (9,10,13,18,19,32-36,38). In several studies, alterations in DLCO, consistent with ILD, have been observed and this lung involvement has been shown to be associated with IBD activity (9,10,13,19,34-36). In addition, in the study by Marvisi and Fornasari (13), there was a strong association between DLCO values and histopathological grading, suggesting that DLCO testing may reflect IBD activity.

4. Lung volumes

Total lung capacity (TLC) and residual volume (RV), which represents the air volume left in the respiratory system at the end of a maximal expiration, can be calculated either by gas dilution or whole-body plethysmography (42). The RV/TLC ratio reflects the resting pulmonary hyperinflation (43). Functional residual capacity (FRC) represents the air volume that remains in the respiratory tract after a normal exhalation. Increased lung volumes result in increased FRC (44).

The RV, TLC and RV/TLC ratio have all been found to be elevated in patients with IBD and to be related to disease activity (10,22,40). Additionally, FRC has been found to be greater in patients with IBDs compared with healthy controls

and during the exacerbation of the IBDs than during the remission phase (24). Elevated lung volumes in patients with IBD may represent bronchial or bronchiolar inflammation, and an increase in RV/TLC may be a useful tool for investigating lung involvement in these patients (45).

5. Bronchoprovocation challenge testing

Methacholine challenge testing is the most frequent type of bronchoprovocation testing using the acetylcholine derivative, methacholine, to cause bronchoconstriction. Methacholine has limited side-effects. Airway hyperreactivity is detected by a decrease in FEV1. The provocative dose (PD20) or concentration (PC20), which results in a 20% decrease in FEV1 in a positive test, is recorded. This test is used to aid with the diagnosis of asthma (45-47).

Increased bronchial responsiveness to the administration of methacholine has been described in patients with IBDs with no respiratory symptoms, no abnormal findings on chest computed tomography and normal FEV1 values (24,48,49). In addition, significantly increased bronchial responsiveness has been observed in patients with CD and extra-intestinal manifestations, and in patients with CD treated with azathioprine, possibly due to a side-effect of azathioprine (24). There is solid evidence in the existing literature of the association between airway inflammation and bronchial hyperresponsiveness (48). However, neither the decrease in FEV1 nor the PD20 values have been found to be associated with the disease activity or duration (24,48).

6. Exhaled nitric oxide measurement

The contribution of NO to the pathophysiology of the respiratory system has been extensively studied. There is conflicting evidence concerning the exact role of NO in respiratory diseases. In pathological conditions, NO is a pro-inflammatory factor with immunomodulatory properties, predisposing to the development of airway hyperresponsiveness. On the other hand, in physiological situations, NO weakly mediates smooth muscle relaxation and is protective against airway hyperresponsiveness. Exhaled NO originates from the airway epithelial cells. The clinical usefulness of NO measurement is most important in allergic airway disease (50).

Increased exhaled NO has been found in patients with IBDs (23,51-54). It has also been described that increased exhaled NO is positively associated with disease activity, as estimated by validated activity indexes (23,51,52). Exhaled NO levels have been found to have a fair association with systemic inflammatory biomarkers in patients with CD, with the exception of fecal calprorectin (51). Moreover, increased exhaled NO levels have been observed in patients with IBDs and lung involvement compared to those without pulmonary involvement, indicating that increased exhaled NO values may be used for identifying patients with IBDs who require the further evaluation of the respiratory system (52).

By contrast, Ikonomi *et al* (53) study found that patients with IBDs had almost the same exhaled NO levels as the controls, and this finding was attributed to the fact that gastrointestinal mucosal activity was not reflected in the amount of exhaled NO.

7. Pulmonary function testing in children with IBD

Few studies have reported the performance of PFTs in children with IBDs. As regards the spirometric values, a significant deterioration during disease activity compared to remission status concerning FEV1, FVC and $FEF_{(25-75)}$ with a negative association between the disorder's activity and these parameters has been reported (55). As previously demonstrated, although expiratory flows were impaired, no important differences were found between the acute and quiescent phases (56). Moreover, in another study, maximum expiratory flows at 50 and 25% of vital capacity were mildly decreased in patients with CD (57). On the contrary, Welsh *et al* (58) mentioned spirometry measurements within normal limits and without significant associations with the duration of the disease and hospitalizations in children with IBDs.

DLCO is the most frequently reported abnormality in PFTs of children with IBDs, as it has been observed to be significantly impaired in all relevant studies regarding PFTs in these patients (55-58) and has been associated with disease activity (55,56). Lung volumes have been noted to be decreased (54) or normal in testing with plethysmography (58) and in one study, RV/TLC ratios were mildly increased in children with UC (57), while there was no association with the disease severity (55,57,58). Increased bronchial responsiveness with no association with treatment or the duration of the disease has been demonstrated in children with CD (59), while levels of exhaled NO have been found to be elevated in children with IBDs, with no association with intestinal disease activity or respiratory symptoms, indicating a latent lung involvement in the systemic disease (60).

The prolonged process of inflammation and lung damage caused by circulating factors and immune complexes, the common embryological origin of both gastrointestinal and respiratory epithelium, the similarity of the mucosal immune response and activated inflammatory cells in the gastrointestinal tract produce several circulating mediators capable of causing lung tissue damage, leading to affection of the alveolocapillary membrane and alveolar damage. These mechanisms can explain why lung involvement leads to abnormalities in the interstitium and airways that are presented early by abnormal PFTs even in asymptomatic children with IBDs (55). In the study by Furlano *et al* (57), the PFT changes that were observed did not last over a median of 34 months of follow-up. This suggests that lung involvement in children with IBDs is variable and changes over time (57). The findings of the performance of PFTs in IBDs are illustrated in Figs. 1-6.

8. Mechanisms responsible for alterations in PFTs in patients with IBDs

In addition to the mechanisms responsible for the spirometry measurements alterations described above, an elevated percentage of alveolar lymphocytes has been mentioned in bronchoalveolar lavage obtained from asymptomatic patients with CD, indicating a shift in the proportions of alveolar cells compatible with alveolitis (39). This finding was significantly associated with a decrease in spirometry parameters (39). Another theory suggests that lymphocytes that are sensitized from the gastrointestinal tract may lead to

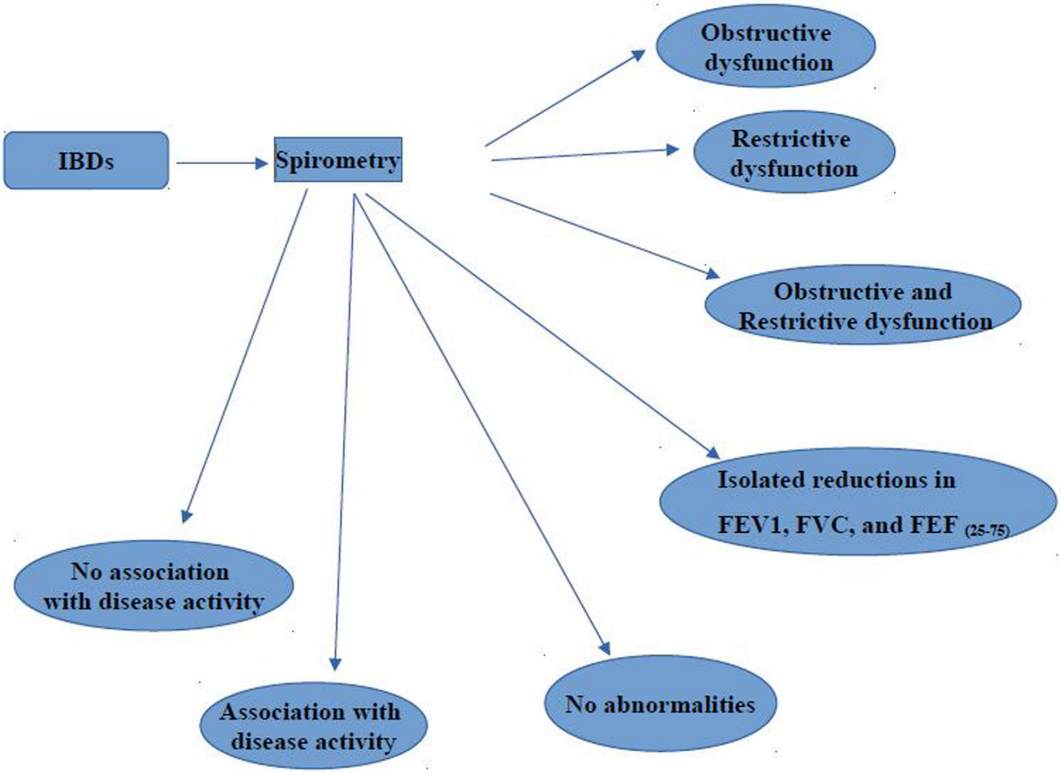

Figure 1. Findings from spirometry in inflammatory bowel diseases. IBDs, inflammatory bowel diseases; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; $FEF_{(25-75\%)}$, mean forced expired flow as lung volume decreases from 75 to 25% of vital capacity.

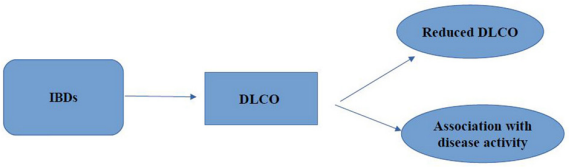

Figure 2. Findings from measurement of diffusing capacity for carbon monoxide in inflammatory bowel diseases. IBDs, inflammatory bowel diseases; DLCO, diffusing capacity for carbon monoxide.

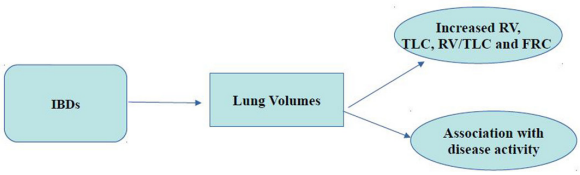

Figure 3. Findings from measurement of lung volumes in inflammatory bowel diseases. IBDs, inflammatory bowel diseases; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity.

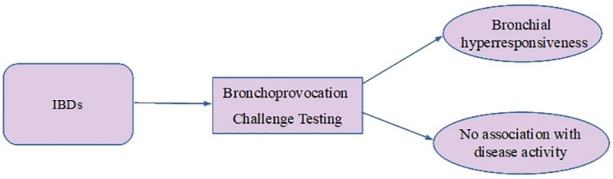

Figure 4. Findings from bronchoprovocation challenging testing in inflammatory bowel diseases. IBDs, inflammatory bowel diseases.

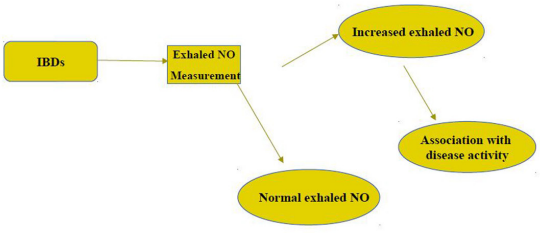

Figure 5. Findings from the measurement of exhaled NO in inflammatory bowel diseases. IBDs, inflammatory bowel diseases; NO, nitric oxide.

inflammation in the mucosa of other tissues. According to a study by Mohamed-Hussein *et al* sputum lymphocytosis in patients with UC, was significantly associated with a decrease in spirometry parameters (21). Moreover, the loss of body proteins and the reduction in body mass index in patients with IBD have been found to be related to reductions in spirometry parameters, indicating a poor nutritional status as a possible factor resulting in abnormalities in spirometric values (21,61).

It has been indicated that subclinical alveolar inflammation or ILD may be present in patients with active IBD, since a reduced DLCO of the lungs is an early manifestation of ILD, and supports the hypothesis that DLCO testing may be utilized as a non-invasive indicator of gastrointestinal inflammation in patients with IBD (13). As regards the question of whether the lungs are target organs in IBDs, the reply seems to be positive. The pathogenesis of IBD causing ILD is unclear.

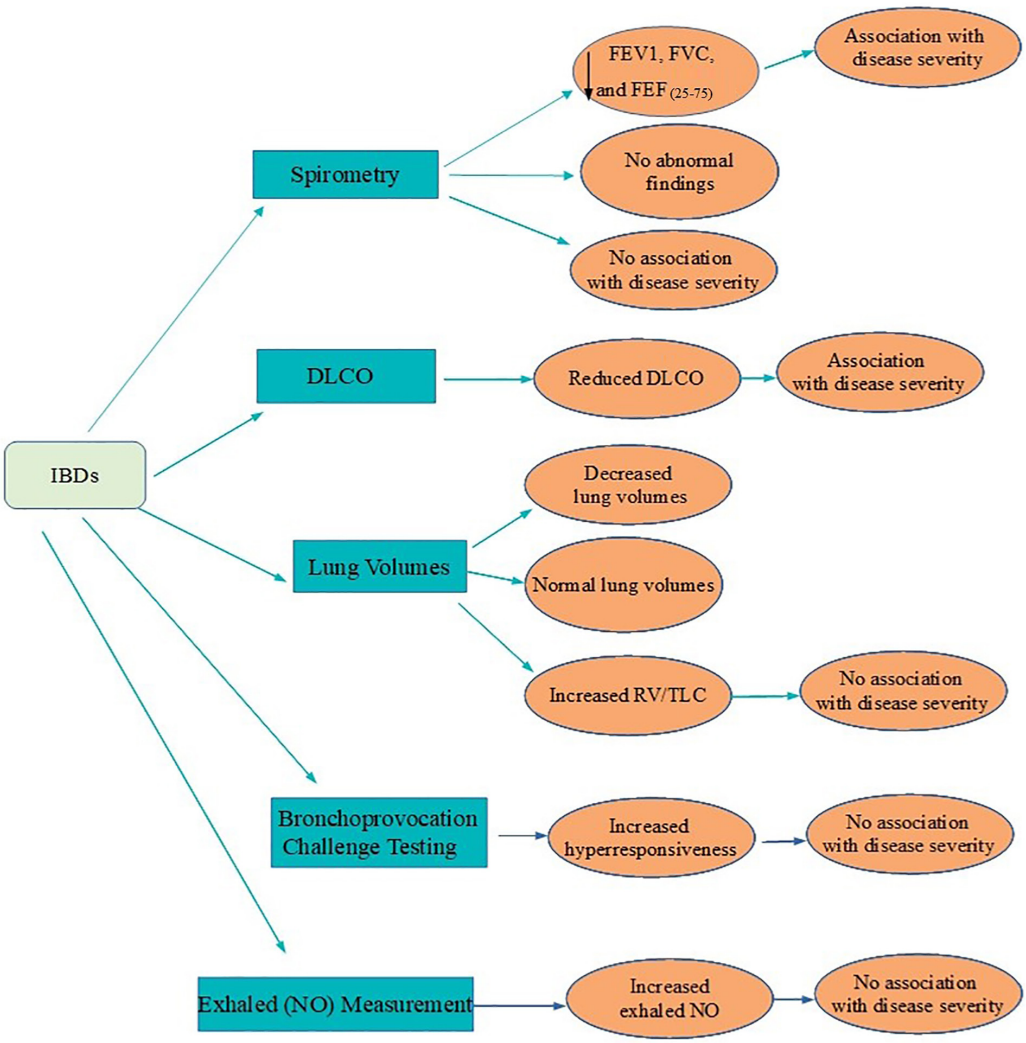

Figure 6. Findings from pulmonary function test in children with inflammatory bowel diseases. IBDs, inflammatory bowel diseases; DLCO, diffusing capacity for carbon monoxide; NO, nitric oxide; RV, residual volume; TLC, total lung capacity.

However, similarities in both morphology and development exist between the colonic and the bronchial epithelium (13). The activated inflammatory cells in bowel tissues produce circulating cytokines, such as interleukin (IL)-1, IL-2, IL-6 and TNF-α, which mediate inflammatory processes, resulting in lung tissue damage (13). This hypothesis is also supported by alveolar lymphocytosis in the bronchoalveolar lavage of asymptomatic patients (39). Furthermore, in a series of cases by Marvisi and Fornasari (13), a low incidence of positive p-ANCA tests was observed, and the researchers suggested the possible pathogenetic contribution of these antibodies in the context of neutrophil enzymatic release and lung damage.

Increased bronchial responsiveness can also be explained by the inflammation of the small airways induced by the recruitment of lymphocytes in bronchi, activated in the gastrointestinal tract (24). Abnormal findings from bronchoprovocation challenge testing have also been noted in patients with IBD receiving azathioprine (24). Azathioprine is the nitroimidazole derivative of 6-mercaptopurine and the nitroimidazole moiety is responsible for hypersensitivity reactions (62). Therefore, a side-effect of azathioprine cannot be excluded as a mechanism of increased bronchial responsiveness in these patients (24).

Active IBD is associated with the increased activity of inducible NO synthase (iNOS), which results in an increase in mucosal and plasma NO levels. Pro-inflammatory mediators and products of bacteria are present in increased amounts in tissues with inflammation in patients with IBD. Due to increased intestinal permeability, the release of these mediators into the systemic circulation is facilitated, inducing the expression of iNOS in other organs, including the lungs, leading to airway inflammation and increased exhaled NO levels (63). This fact is in accordance with the presence of increased counts of airway eosinophils and lymphocytes in patients with IBD (64).

9. Conclusions and future perspectives

PFT abnormalities can occur in patients with IBDs without any obvious clinical manifestations or radiological findings, reflecting the possible importance of PFTs in the detection of latent respiratory involvement. An impairment in DLCO is the most common finding in the PFTs of adults and children with

IBDs, while there are conflicting data regarding other tests, particularly spirometric values, and their association with disease activity. However, according to the existing literature, there is no evidence to support the use of PFTs for monitoring IBD activity. Moreover, according to the existing literature, there is no difference between UC and CD as regards the association with PFTs. In addition, the existing literature refers to the comparison of variables of PFTs in remission and activity of the diseases and not in different stages. Thus, larger prospective studies are required to clarify the role of PFTs as diagnostic tools for recognizing subclinical pulmonary damage and determining the activation of IBDs.

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Availability of data and materials

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Authors' contributions

CD, KT, PP and DM conceptualized the study. VEG, DAS, AG, SC, PS, NT and DM analyzed the data from the literature for inclusion in the review and wrote and prepared the draft of the manuscript. DAS and DM provided critical revisions. All authors contributed to manuscript revision and have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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