






# Cardiorespiratory changes from silica exposure in miners: an integrative review

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## Abstract

Silicosis is a pneumoconiosis caused by exposure to free respirable silica, a compound abundant in nature on the Earth's coast in its free form or combined with other crystallized raw materials. The objective of the research was to discuss the cardiorespiratory alterations caused by silicosis in view of its cardiorespiratory manifestations. This is an integrative review of publications from 2006 to 2022. For the process of searching and selecting articles, descriptors in English, Spanish, and Portuguese and the following databases were used: PubMed from the National Library of Medicine; Virtual Health Library (VHL), LILACS, SciELO, Medline, and Science Direct. It should be noted that silicosis is an occupational disease that needs to be evaluated through imaging tests, radiographs, and computed tomography scans, as well as the integration of physical assessment, occupational anamnesis, history of exposure, and questionnaires for an early diagnosis. As a diagnostic method for this disease, a chest X-ray is an imaging exam in which it is possible to visualize the lesions caused by the disease. That said, the alterations cause a decrease in the functional capacity of the lung, dyspnea, as well as the application of quality of life questionnaires, given the limitations caused. Therefore, prevention is important to reduce exposure to free silica, with awareness of occupational risks, correct use of masks and protective equipment, and control of silica markers in the work environment, respecting exposure limits.

**Keywords:** Silicosis, silica, worker, pneumoconiosis, rehabilitation.

## Graphical Abstract



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## 1. Introduction

Mining is an economic activity responsible for extracting metallic and non-metallic minerals from nature. Among the main products of this extractive industry, there are non-metallic minerals, such as ornamental rocks, commonly used in civil construction, such as quartz, granite, and marble. In its crystalline form, the mineral quartz is composed of silica, one of the vastest components on the earth's surface. When inhaled by miners, free silica causes diseases in the respiratory tract, such as tuberculosis, silicosis, pulmonary emphysema, and chronic obstructive disease (COPD). Given the health risks that this compound causes, the International Agency for Research on Cancer (IARC) has included silica as a carcinogenic agent. Occupational exposure to dust containing silica causes several diseases, the most common being silicosis (Moreira et al., 2020).

Silicosis is a pneumoconiosis caused by exposure and inhalation of free silica. These particles enter the upper airways and reach the lung lobes, causing inflammatory processes and fibrosis. Initially, it is asymptomatic, and as the lesions worsen, symptoms such as dyspnea and asthenia appear and may progress to more severe cases of respiratory failure and chronic bronchitis. Silicosis comes in three forms: acute, subacute, and chronic. In the acute phase, it is associated with a lot of exposure to free silica; it appears in 5 years when the inflammatory response in the lung leads to pulmonary alveolar proteinase. In the subacute phase, 5 years after the initial exposure, radiological changes appear in the form of nodules. Chronic occurs after 10 years of occupational exposure, when the nodules can evolve with the progression of the disease, which, in radiological examinations, show opacities in affected areas (Duarte et al., 2017).

According to the Brazilian Institute of Geography and Statistics – IBGE, mineral activity is categorized as grade 4 in the National Classification of Economic Activities (CNAE) due to the occupational risks to which workers are exposed due to the high capacity to cause damage to the health and safety of these workers. The risks in this sector stem from unhealthy and dangerous activities, which contain chemical, biological, ergonomic, and psychosocial agents (IBGE, 2023).

Silicosis is a pneumoconiosis due to the constant exposure and inhalation of silica particles in the work of miners in closed or open environments, containing SiO<sub>2</sub> in its free form or combined with other crystallized raw materials, such as quartz,

crystalite, and amorphous. Occupational exposure to dust is generally in solid form with particles larger than 1 micrometer. The effect of silica on the human organism depends on the type, exposure time, and individual response of the organism. Generally, when a dust particle reaches the upper airways, it is expelled before reaching the lower airways with the aid of the mucus produced in the tracheobronchial region. However, in occupational exposure, inhalation is constant and lasting and causes atrophy in the tracheobronchial structure mucus generator (Ribeiro, 2010).

Since Brazil is a center of extractivist with an estimated three million workers in the labor market, with an environmental and public health impact, public policies were implemented to combat silicosis. Measures for adopting environmental control include changes in the work process, the replacement of silica in industrial processes, and actions aimed at raising awareness among employers and workers (Dias et al., 2017).

The exposure of workers to silica causes health risks, with silicosis being the main one, due to its epidemiological importance. Some activities have a higher potential risk of exposure to this compound. Activities involving polishing, grinding, cutting, sawing, and pulverizing are at greater risk, as the production of dust particles is intense. Of the 3 million formal workers, it is estimated that about 30% are exposed to silica during their workday. The most exposed sectors are ore extraction, civil construction, non-metallic minerals, rubber, and metallurgical industries (Dias et al., 2017).

Given the above, how can the physiotherapist intervene in the face of cardiorespiratory changes presented by patients with silicosis? Therefore, this research aims to discuss the cardiorespiratory alterations due to silicosis, highlighting the effect of exposure to silica on cardiorespiratory manifestations. The study also describes the prevention methods that can be used against this disease and understand the anatomy and physiology of the cardiorespiratory system, such as discussing the performance of a physiotherapy evaluation in patients facing respiratory changes due to this pathology, in addition to the methods of diagnosing this disease, its etiology and understanding how the physiotherapy professional works in these cases, either as an intervention with the disease installed or as prevention and health promotion.

Therefore, this research deals with an integrative literature review, having extreme relevance, both academic and scientific, as well as social, for bringing up issues of the current scenario of world health, about silicosis, which is a public health problem and the cardiorespiratory changes that occupational exposure can trigger in patients with this disease, as well as the role of the physiotherapist in the face of these changes.

## 2. Materials and Methods

The present study deals with bibliographical research of the integrative review type. This methodology guides the research as follows: formulation of the research question; elaboration for collecting fingers; selection; analysis of included studies; interpretation of results and description of the integrative review; and presentation of the critical literature analysis. The study was performed through the PICO strategy, acronym of the words Population (P), Interest (I), and Context (CO), which was used to elaborate the guiding question of this integrative review. The controlled descriptors used in the search strategy were selected through the DECS (Health Sciences Descriptors) (Mascarenhas et al., 2019).

For the search process and selection of relevant articles that answered the research question, descriptors in English, Spanish, and Portuguese were used in the following databases: PubMed of the National Library of Medicine; Virtual Health Library (VHL) coordinated by BIREME and made up of databases produced by the VHL network, such as LILACS, SciELO, Medline and Science Direct. With the following descriptors “mineiro pneumoconiosis,” “silicic acid,” silicosis,” “worker,” “occupational diseases,” and “pulmonary lung abscess.” As inclusion criteria, articles published in full and available online in the databases, in Portuguese, Spanish, and English, about the proposed theme, in a time frame between 2006 and 2022, from March to May 2022, were selected to discuss scientific evidence in recent years.

Exclusion criteria were case reports, articles unrelated to the research objectives, and duplicate articles. With the selection of articles, after the steps of identification, screening, and eligibility, 46 articles were included. This study was outlined by the analysis of the articles carried out by the descriptive and qualitative approach through the synthesis of the evidence of each publication (Table 1).

**Table 1** Outline of the *corpus* acquisition process.

Schematization of the corpus acquisition process	
<b>Identification</b>	180 Studies: databases: LILACS, BIREME, SciELO, Science Direct, Medline, PubMed.
<b>Screening</b>	100 Articles after removing duplicates; 80 after identification by title and abstract.
<b>Eligibility</b>	40 Publications do not match the criteria specified after analyzing the texts.
<b>Inclusion</b>	40 Works were read in full and selected for further evaluation, and 6 were chosen for results and discussion.

## 3. Results and Discussion

From the analysis of the selected studies (Table 2), it is observed that silicosis is caused by the inhalation of respirable silica particles, which are deposited in the respiratory system in the form of silicotic nodules. There are three forms of disease presentation: acute, subacute, and chronic. It is an incurable disease. However, measures to control exposure to SiO<sub>2</sub>, education on the correct use of individual use equipment, and changes in work processes are alternatives for worker protection and prevention (Dias et al., 2017).

When a particle is inhaled in the respiratory system, as it passes through the upper airways, it is trapped by mucus and movement. When the worker is exposed to dust containing silica particles at a physiologically respirable level, this particle, when deposited in the lower respiratory system in the region of the alveoli and macrophages, cannot phagocytize this particle and causes local inflammation. The inflammatory mechanism activates fibroblasts, promoting the formation of parenchymatous fibrosis. The scar tissue resulting from this process impairs the elastic capacity of the lung, and the affected areas impair gas exchange (Alves et al., 2019).

Azevedo and Schütz (2021) state that prevention, in addition to dust control, involves modifications in the work process when drilling rocks, instead of dry, the wet method drilling process, as well as following control measures followed by the norms of activity of risk of mineral extraction. Continuing education is the path to professional training. It promotes safety in carrying out activities. In addition, environmental control measures and risk assessment methods for exposure to lipogenic material are implemented.

According to Silva et al. (2018), it is understood that the inhaled dust dose is cumulative, and two factors are important to understand this factor: exposure time and dust concentration. In this study, it was observed that the duration of exposure

component is data related to the prevalence of silicosis in workers, in which a lower prevalence of silicosis was obtained in workers who were exposed for shorter periods. It is foreseen by law that workers' retirement in underground mines is at least 15 years.

**Table 2** Main characteristics of the six studies selected for the results and discussions.

Study Titles	Methods	Considerations	Reference
Predictors of health-related quality of life among semi-precious stone miners exposed to silica dust	In a cross-sectional study with 348 male miners (129 with silicosis) who underwent an interview and spirometry, HRQoL was assessed using the World Health Organization Quality of Life questionnaire (WHOQOL-BREF) and the Saint George's Respiratory Questionnaire (SGRQ).	The study revealed impaired HRQL in miners of semi-precious stones assessed using both the SGRQ and the WHOQOL-BREF questionnaires, of which the SGRQ outperformed. Respiratory symptoms, functional impairment, and cigarette pack-years were the most important determinants of workers' overall HRQoL.	Souza et al. (2021)
Silicosis in quarries: the subtle difference between knowing and fall ill. Interventions in Workers' Health in the exploitation of ornamental stones	Participant observation of work processes in two quarries, carried out in two different years (2008 and 2009), complemented with documental analysis.	There is a need for incentives for investment in training qualified labor and cutting-edge technologies in the sector, a change that is urgent for workers' health in producing ornamental stones to combat silicosis.	Azevedo & Schütz (2021)
Lung function and functional exercise capacity in underground semi-precious stone miners	Medical and occupational data were collected in a cross-sectional study with 193 current miners from Ametista do Sul, Rio Grande do Sul, Brazil. The diagnosis of silicosis was established by the history of dust exposure and chest X-ray findings. All workers performed spirometry and the 6-minute walk test (6MWT).	Results show impaired lung function and preserved exercise capacity in current miners exposed to silica. Length of time working in mining, presence of silicosis, and lower education were factors associated with reduced lung function.	Souza et al. (2020)
Changes on the silicosis profile in underground gold mining in Minas Gerais, Brazil	Cross-sectional study with 1,020 miners from the region of Nova Lima/MG, evaluated between 1995 and 2011.	There was a significant drop in the occurrence of silicosis in the analyzed period. Since the disease is known to be dose-dependent, the decrease in exposure levels, obtained by improvements in occupational environments, is expected to be reflected in these results. Such measures must continue to be adopted in mining and other areas of activity to reduce the occurrence of the disease.	Silva et al. (2018)
Evaluation of pulmonary function and respiratory symptoms in pyrochlore mine workers	Observational cross-sectional study carried out with workers in the production sector of a pyrochlore mining company. To assess respiratory symptoms, occupational exposure factors, and smoking, the British Medical Research Council respiratory symptoms questionnaire was applied, and lung function was assessed using a portable spirometer.	The frequencies of respiratory symptoms and spirometric changes were low when compared to studies involving exposure to occupational dust. No significant associations were observed between respiratory symptoms and spirometric values.	Borges et al. (2016)
Long-term therapeutic effects of whole lung lavage in the management of silicosis	A total of 70 patients with silicosis were randomly and equally divided into WLL and control groups based on chest X-ray, silicosis staging, age, and time of work exposure to dust. Comparative analysis was performed to assess the long-term therapeutic effect of WLL. In addition, 157 patients with silicosis treated by WLL underwent long-term follow-up.	WLL is an effective therapy for silicosis, especially for early silicosis and accelerated silicosis. However, WLL should be used with caution in the treatment of advanced silicosis.	Zhang et al. (2012).

Given the health risks that silica dioxide causes, the Agency for Research on Cancer (IARC) considered it a carcinogenic agent. Occupational exposure to dust containing silica causes several diseases, the most common of which is silicosis. Therefore, exposure control measures were taken in Ordinance No. 426, of October 7, 2021, of the Ministry of Labor and Employment in Brazil, when it reiterates, in NR-15, referring to unhealthy activities and operations, the parameters of exposure to silica and provides the calculation of the percentage of silica in the breathable dust of the work environment, considering a weekly working day of 48 hours, is

equivalent to 0.10 mg/m<sup>3</sup> as a tolerance limit (Ribeiro, 2010). However, the tolerance limit in the United States, as in other countries, the NIOSH (National Institute for Occupational Safety and Health) considers this exposure limit of 0.05 mg/m<sup>3</sup> in the period of work of 40 hours per week (Hoy & Chambers, 2021).

As described by Silva et al. (2018), silicosis remains a public health problem, especially in developing countries. Some sectors present greater risks of exposure: metal mining; extraction and processing of rocks; construction; sandblasting.

A study conducted by Li et al. (2022) states that there is no protocol for early diagnosis, while treatment for silicosis and therapeutic interventions are limited. There are some proposals for invasive lung lavage therapy, when the patient is in the early stages of the disease, being used to relieve chest pain and improve shortness of breath. Chambers et al. (2021) corroborate this idea through the radiological data of patients with silicosis associated with artificial stones when a significant improvement in symptoms and functional capacity, lung function, and mortality was obtained using total lung lavage.

According to Zhang et al. (2012), the long-term therapeutic effect of lung lavage was combined in a controlled trial with 157 participants diagnosed with silicosis. In this trial, the group undergoing lung lavage therapy achieved better results in terms of significant improvement in the clinical picture of cough and sputum compared to the control group. The result of this study shows the effectiveness of this therapy, especially for the early stages of silicosis.

Regarding drug therapy, in some countries, such as the USA, pirfenidone and nintedanib were approved for use in patients with idiopathic fibrosis and are recommended for use in patients with silicosis. In China, tetrandrine was approved for the treatment of silicosis; this drug has anti-inflammatory effects contributing to improved lung function. However, Li et al. (2022) reveal that further studies are needed to ensure the effectiveness of these drugs. In more severe cases with chronic silicosis, the only indicated treatment is lung transplantation. Nonetheless, survival is short, and about 76% have a 3-year survival after lung transplantation.

Barnes et al. (2019) show that using ILO criteria, plain radiography is the most used for screening and diagnosing silica in workers. In accelerated silicosis, it presents fibrotic and diffuse alterations, which do not appear on radiographs. Moreover, they consider chest tomography better than simple radiographs to detect coalescence changes in silicotic nodules early.

According to Magalhães et al. (2020) and Duarte et al. (2017), the prevalence of silicosis is related to the time of exposure; that is, the longer the time of occupational exposure to SiO<sub>2</sub>, the greater the chances of the individual developing the disease. The average onset of the disease is between 10 and 18 years of exposure. Still, with intense exposure for short periods, the disease can occur in less time, in 5 years. Therefore, it is evidenced as a public health problem. Studies show that the symptom of this

pathology is mainly cough and chest pain. As it progresses, it presents other symptoms, such as mucopurulent sputum, dyspnea, asthenia, and chronic respiratory failure.

That said, knowing about pulmonary alterations, dyspnea, and reduced tolerance to exercise can lead to worker withdrawal from their activities and work. In addition, it affects the quality of life and health of these workers, especially those in the advanced stages of the disease. In a cross-sectional study with 348 members of a cooperative of miners, all male, of these, 129 have a diagnosis of silicosis and have undergone a Quality of Life questionnaire from the World Health Organization (WHOQOL-BREF) and the Saint George's Respiratory Questionnaire (SGRQ), quality of life and the 6MWT. With this study, it was possible to observe that miners with silicosis presented HRQL, which is the quality of life related to impaired health. Another evaluative instrument was also used, the SGRQ, which is specific for COPD, having three domains, with a score from 0 to 100. The evaluation through the HRQoL questionnaire is important to understand beyond the physical dimension but also the impact of biopsychosocial (Souza et al., 2021).

Borges et al. (2016), in their observational cross-sectional study, surveyed 147 workers at a mining company and obtained the following result: 22.44% of the workers had respiratory symptoms such as cough and dyspnea, while 17.69% of them showed changes in spirometric data.

Similarly, Souza et al. (2020) conducted a survey that included 193 mining workers who performed activities such as drilling, cutting, and removal of debris and detonation. In these individuals, a 6-minute walk test and spirometry were performed. A percentage of 26.4% of these had radiographic alterations that indicated silicosis. Normal spirometric data were found in 75.1% of these workers, an abnormal pattern suggestive of a restrictive ventilatory deficit was 13%, and a mixed pattern was 2.6%. These studies indicate that, with the progression of the disease, the patient can affect pulmonary functional capacity, and the longer the exposure time and dust accumulation, the more restrictive the individual's airflow.

Thongtip et al. (2021) argue that biomarkers can indicate the development of adverse health effects. Through biomonitoring to assess exposure, silica does not have enough support in the literature. What complicates the biomonitoring of silica is that it is an exposure biomarker that cannot be evaluated in

urine tests, for example, because silicotic nodules with SiO<sub>2</sub> are present in the lungs. Therefore, one way to assess and monitor exposure to this toxic compound is through the presence of silicic acid in the air. Thus, with the difficulty of using exposure biomarkers, environmental monitoring is recommended as the best way to assess exposure/occupancy to SiO<sub>2</sub>.

Occupational exposure to dust containing free respirable silica is known to cause an inflammatory and pulmonary response. Therefore, the biomarkers present in this immune and fibrosis response can be associated with the diagnosis and prognosis when there is a fibrotic lung lesion in individuals with silicosis. Studies have found high levels of interleukins in workers exposed to SiO<sub>2</sub> (Thongtip et al., 2020).

For Austin et al. (2021), early diagnosis is a challenge, especially when the disease is in its early stages, often asymptomatic, with undetectable tests such as radiography and spirometry, especially silicosis, as it is similar to other lung diseases such as sarcoidosis and pulmonary tuberculosis. As Thongtip states, there is a diagnostic barrier concerning the lack of adequate biomarkers for the disease. In addition, low adherence to health services and inadequate occupational health measures contribute to the lack of an assertive and early diagnosis.

According to Austin et al. (2021), spirometry is a pulmonary function test commonly used to diagnose pulmonary diseases, monitor risk to the pulmonary health of workers, especially those exposed to particulate matter, and a parameter to evaluate therapeutic interventions used. Although spirometry helps assess lung damage, it is not accurate enough to detect damage before significant changes occur. Therefore, studies using spirometry associated with occupational health questionnaires and other methods, such as chest X-rays, are necessary for this respiratory surveillance. Therefore, respiratory surveillance encompasses these imaging tests associated with clinical history and questionnaires.

Dias et al. (2017) and Silva et al. (2016) consider that the clinical evaluation encompasses occupational aspects of the worker's history, type of environment, time of exposure, and habits, such as smoking. Silva et al. (2016) also argue that the main respiratory symptoms are: cough, expectoration, and the presence of wheezing, and these should be analyzed in the clinical evaluation. Physical examination is important to analyze the patient's main

complaint, the time and intensity of exposure to silica, and signs and symptoms. Inspect the type of chest, pulmonary auscultation for the presence of adventitious sounds, and respiratory rhythm. They also observe signs of respiratory distress, systemic signs such as cyanosis, and digital bloating, which may indicate alterations caused by the pathology.

According to Dias et al. (2017) and Khemakhem et al. (2022) and collaborators, silicosis is developed after years of exposure to dust containing SiO<sub>2</sub> particles, and it usually takes 10 years to have a diagnosis. However, the clinical presentation can vary and is classified into three distinct forms. Acute or accelerated silicosis develops between 3 and 10 years of exposure. The higher the occupational exposure level, the greater the risk of developing progressive lung fibrosis. Chronic or classic is developed from 10 years of exposure to low levels of silica dust. The problem is the progression of the disease, with complications associated with bacterial infections. The most common complication is tuberculosis. Hoy and Chambers (2021) point out that one of the causes of morbidity and mortality of workers exposed to this type of fine particulate matter is the development of infection by *Mycobacterium tuberculosis*.

Through a study, Dale et al. (2021) sought to examine physical training in individuals with non-malignant dust-related respiratory diseases. In this study, they showed the effectiveness of physical training programs that include muscle strength training for upper and lower limbs in two groups and obtained an improvement in the exercise capacity and quality of life of the participants. In short, chronic respiratory diseases have similar involvement characteristics, including shortness of breath, reduced functional exercise capacity, and quality of life.

These functional impairments result in absence from work, early retirement, and reduced quality of life. Pulmonary changes make ventilatory mechanics difficult due to these factors. Thus, with reduced exercise capacity, patients tend to physical reconditioning. It is known that weekly resistance training of the lower limbs promotes physiological changes in patients with COPD. Therefore, the practice of physical training is an important intervention for managing these patients, contributing to improving muscle and cardiorespiratory function and reducing symptoms (Dale et al., 2021).

In this context, physical exercises associated with other physiotherapeutic treatments in

patients with pulmonary disease can cause a response to systemic levels, reducing dyspnea, promoting gain in muscle strength, and increasing oxygenation. In addition to cardiorespiratory function, physical training improves symptoms, pain, and breathing patterns (Souza et al., 2012).

Marrara et al. (2012) showed in their study that conventional physiotherapy, when associated with therapies with physical exercises, brings more benefits. In this context, the evaluation by the 6-minute walk test was observed to improve the functional capacity of the participants. The training protocol performed 3x a week based on training on the treadmill, with alternating speed and intensity for 6 months, resulted in an improvement in the dyspnea condition of the patients submitted to the test.

Zhao et al. (2020) evaluated the efficacy and safety of pulmonary rehabilitation for pneumoconiosis by meta-analysis. In that study, they observed that interventions based on the association of physical training, health education, and pulmonary rehabilitation could effectively treat respiratory diseases, promoting improvement in lung capacity and respiratory symptoms. However, although pneumoconiosis is considered an incurable disease, interventions such as pulmonary rehabilitation must be included as a treatment for pneumoconiosis, given the improvements provided.

In a review survey, Yu et al. (2019) show that multidisciplinary interventions with pulmonary rehabilitation are widely used to treat chronic lung diseases, including resistance training, exercises, muscle training, oxygen therapy, and nutritional and educational monitoring. This study evaluated the response of using pulmonary rehabilitation in idiopathic fibrosis and obtained effective results in improving functional lung capacity and quality of life associated with health with this therapeutic approach.

According to Cox et al. (2021), the COVID-19 pandemic brought the possibility of telerehabilitation with rehabilitation programs in remote format and the possibility of an alternative for the treatment of chronic respiratory diseases. In short, this study carried out with patients with respiratory diseases was evaluated remotely with the physical training program at home. There were no significant differences in the rehabilitation programs

with exercises about the functional capacity and quality of life of the participants.

#### 4. Conclusion

The studies surveyed herein outline a need for creating public policies and the insertion of a multidisciplinary team in the prevention of silicosis through healthcare measures and in the promotion and rehabilitation of individuals w Although pneumoconiosis is considered an incurable disease, interventions are needed, such as pulmonary rehabilitation being included as a treatment for pneumoconiosis, given the improvements provided. However, more in-depth studies are suggested, realizing the relationship between pathology and physiotherapeutic action. There was a remarkable lack of publications relating to physiotherapeutic interventions in silicosis and scientific publications that prove and analyze the alterations and the performance of physiotherapist professionals. Thus, the research obtained good results about the general and specific objectives, managing to understand the physiotherapeutic and therapeutic interventions used, considering that silicosis has cardiorespiratory manifestations, as well as discussing the evaluation and diagnostic methods of this disease and its etiology, as well as understanding the professional performance of the physiotherapist who can act in the prevention and promotion of workers' health. Evidence shows that pulmonary rehabilitation and training interventions are essential for improving patients' functional capacity and health-related quality of life with silicosis.

#### Authors' Contributions

Conceptualization, A.K.S.L., A.A.S.R., and M.P.S.S.; Methodology, M.E.J.S., and R.C.R.S.; Investigation, A.K.S.L., and M.P.S.S.; Formal Analysis, A.A.S.R., and M.P.S.S.; Writing – Original Draft, M.E.J.S., and A.A.S.R.; Writing – Review & Editing, R.C.R.S., A.A.S.R., and M.P.S.S. All authors read and approved the final manuscript.

#### Competing interests

The authors declare that they have no competing interests.

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