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Case report Free Access

Primary pleural B-cell lymphoma mimicking tuberculosis complicated by pulmonary embolism and suspected rituximab-induced interstitial lung disease

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Abstract

Introduction: Primary pleural non-Hodgkin lymphoma (PPL) is an extremely rare malignancy (<0.3% of non-Hodgkin lymphomas) that frequently masquerades as tuberculosis or mesothelioma, causing diagnostic delay in endemic regions.

Case presentation: A 27-year-old male presented with sub-massive hemorrhagic pleural effusion and sub-centimetric pleural nodules. Pleural fluid analysis showed lymphocyte-predominant exudate with low adenosine deaminase (18 IU/L) and negative tuberculosis tests. Contrast-enhanced computed tomography and thoracic ultrasound demonstrated nodular pleural thickening. Cytology was discordant between cell block (suggesting lymphoma) and fine-needle aspiration (suggesting small-cell lung carcinoma). Immunohistochemistry resolved the diagnosis, showing positivity for CD45 and CD20, confirming B-cell non-Hodgkin lymphoma. Fluorodeoxyglucose (FDG) Positron Emission Tomography demonstrated disease apparently confined to the pleura without nodal or distant organ involvement. The patient received R-CHOP chemo-immunotherapy. Two months later, he developed severe hypoxemia. Computed tomography pulmonary angiography revealed extensive GGOs and interlobular septal thickening consistent with rituximab-induced interstitial lung disease alongside left main pulmonary thromboembolism. Despite high-dose methylprednisolone and anticoagulation, the patient succumbed to respiratory failure.

Discussion: PPL should be considered in patients presenting with hemorrhagic pleural effusion, low pleural fluid adenosine deaminase levels, and pleural nodularity, even in young individuals. When cytological findings are inconclusive or conflicting, pleural tissue sampling and immunohistochemistry are essential for establishing the diagnosis. This case also highlights the potential for life-threatening treatment-associated complications, including suspected rituximab-induced pneumonitis and concurrent pulmonary thromboembolism.

Conclusion: Primary pleural B-cell non-Hodgkin lymphoma is a diagnostic challenge because of its rarity and nonspecific clinical presentation. Early tissue diagnosis with immunohistochemical confirmation is crucial. Clinicians should also maintain a high index of suspicion for severe pulmonary complications during treatment, as concurrent interstitial lung disease and pulmonary thromboembolism may have fatal consequences.

Keywords: Primary pleural lymphoma, Non-Hodgkin lymphoma, Pleural effusion, Tuberculosis, Rituximab-induced lung injury, Pulmonary embolism

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Introduction

Primary pleural non-Hodgkin lymphoma (PPL) represents an exceptionally uncommon extranodal lymphoid malignancy, accounting for less than 0.3% of all non-Hodgkin lymphoma (NHL) presentations (1,2,3). Unlike secondary pleural involvement from disseminated systemic lymphoma, PPL originates primarily within the pleural tissue without widespread lymphadenopathy or extrathoracic organ disease. In tuberculosis-endemic geographical regions, young patients presenting with exudative pleural effusions and pleural thickening are frequently misdiagnosed with pleural tuberculosis or malignant mesothelioma, leading to empirical anti-tubercular therapy and prolonged diagnostic delays (3).

Furthermore, the management of rare thoracic malignancies is fraught with potential treatment-related toxicities. Although chemo-immunotherapy with rituximab-based regimens (such as R-CHOP) has dramatically improved progression-free survival in CD20-positive B-cell lymphomas, rituximab-induced interstitial lung disease (R-ILD) occurs in 3.7% to 10% of treated patients (4,5). When compounded by cancer-associated venous thromboembolism (VTE) and acute pulmonary embolism (PE), these overlapping pulmonary insults create a life-threatening clinical state that poses severe diagnostic and therapeutic challenges.

Herein, we report a rare case of PPL in a 27-year-old male that presented as a hemorrhagic, low-adenosine deaminase (ADA) exudative effusion with pleural nodularity, successfully diagnosed via immunohistochemistry and PET-CT, but complicated by fatal concurrent rituximab-induced pneumonitis and pulmonary thromboembolism.

Case presentation

A 27-year-old male garment shop owner presented to the respiratory medicine outpatient department of a tertiary care university hospital in Northeast India with a 2-week history of left-sided pleuritic chest pain, progressive breathlessness, dry cough, and loss of appetite. He was a non-smoker with no prior chronic medical illness, but reported close household contact with his sister who had been diagnosed with tubercular lymphadenitis 1 month prior. Physical examination revealed a thin-built male with stable vital signs (blood pressure 120/74 mmHg, pulse rate 86 beats/min, respiratory rate 20 breaths/min, and oxygen saturation 96% on room air). Chest percussion demonstrated a stony dull note over the left infrascapular and infra-axillary zones, accompanied by significantly diminished breath sounds.

Chest radiography (PA view) showed a left-sided sub-massive pleural effusion with contralateral tracheal displacement (Figure 1). Diagnostic thoracentesis yielded gross hemorrhagic pleural fluid. Pleural fluid biochemistry and cell analysis revealed an exudative effusion by Light's criteria, with a total protein 5.2 g/dL (paired serum protein: 6.9g/dl, ratio 0.75), lactate dehydrogenase (LDH) 1580 U/L (paired serum LDH: 290U/L; ratio 5.45, upper limit of normal for serum LDH: 220 U/L), glucose 79 mg/dL, albumin 3.2 g/dL, and total nucleated cell count 300 cells/cu.mm (82% lymphocytes, 18% polymorphs) with abundant red blood cells (Table 1).

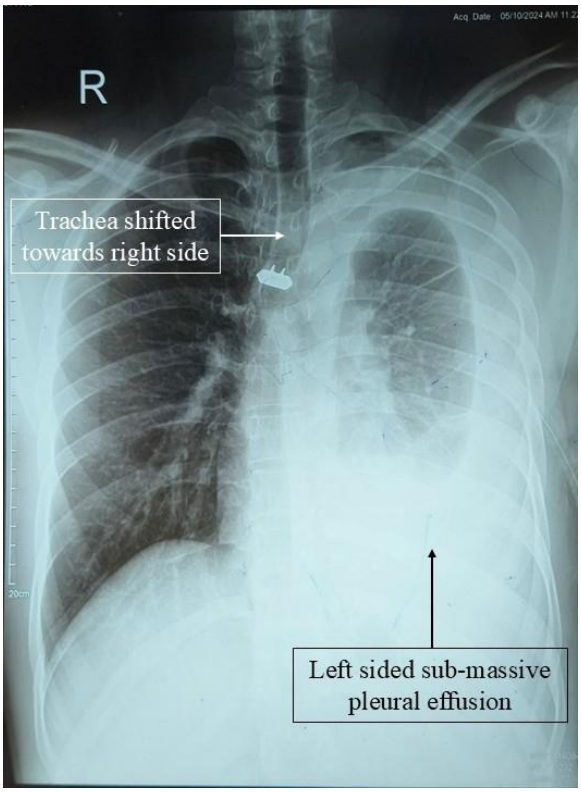


Figure 1. Chest radiograph (PA view) at initial presentation showing a left-sided sub-massive pleural effusion with contralateral tracheal and mediastinal displacement.

Table 1. Pleural fluid analysis and serial hematologic parameters at initial presentation and ICU readmission.

Parameter	Initial Presentation	ICU Readmission (2 Months Post-R-CHOP)	Units
Pleural Fluid Protein	5.2	Not applicable	g/dL
Pleural Fluid LDH	1580	Not applicable	U/L
Pleural Fluid Glucose	79	Not applicable	mg/dL
Pleural Fluid ADA	18	Not applicable	IU/L
Pleural Fluid Cell Count	300	Not applicable	cells/cu.mm
Hemoglobin	11.3	10.8	g/dL
Total Leukocyte Count (TLC)	10100	11400	cells/cu.mm
Platelet Count	238000	215000	cells/cu.mm
Serum NT-proBNP	Not measured	63	pg/mL

Adenosine deaminase (ADA) was low at 18 IU/L (reference cut-off >40 IU/L for tuberculosis(6)). Pleural fluid acid-fast bacilli (AFB) smear, cartridge-based nucleic acid amplification test (CBNAAT/GeneXpert) for *Mycobacterium tuberculosis*, and fluid cytology for malignant cells were all negative. Complete blood count showed hemoglobin 11.3 g/dL, total leukocyte count 10,100 cells/cu.mm (78% neutrophils, 17% lymphocytes, 3% eosinophils, 2% monocytes), and platelet count 238,000 cells/cu.mm. Serological testing for HIV, Hepatitis B, and Hepatitis C was negative. A 24F intercostal drainage (ICD) tube was placed in the 4th intercostal space within the triangle of safety to relieve dyspnea, and fluid was sent for cell block preparation.

Contrast-enhanced computed tomography (CECT) of the thorax revealed irregular, nodular enhancing thickening along the left costal and diaphragmatic pleura associated with left pleural effusion and sub-centimetric mediastinal lymph nodes, highly suspicious for a primary pleural neoplasm (? mesothelioma). Thoracic ultrasound (TUS) confirmed multiple lobulated, hypoechoic pleural mass lesions (Figure 2). Ultrasound-guided transthoracic fine-needle aspiration cytology (FNAC) and cell block cytology were performed.

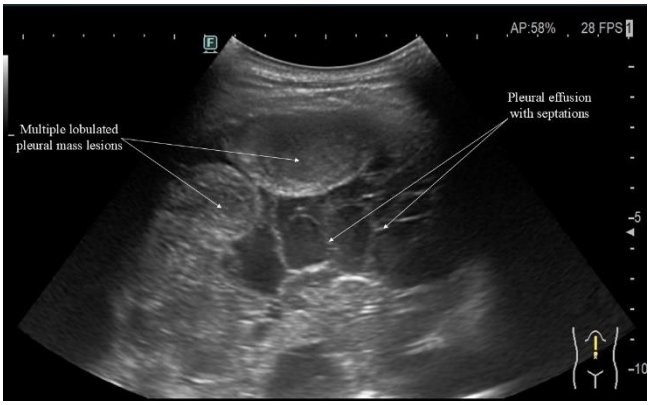


Figure 2. Thoracic ultrasound (TUS) image demonstrating multiple lobulated, hypoechoic pleural-based mass lesions accompanied by a septated left pleural effusion.

Diagnostic cytology revealed a striking morphological discordance. Cell block cytology demonstrated monomorphic tumor cells arranged in sheets with irregular nuclear membranes, vesicular chromatin, and scanty cytoplasm, favouring non-Hodgkin lymphoma with a differential diagnosis of small-cell lung carcinoma (Figure 3).

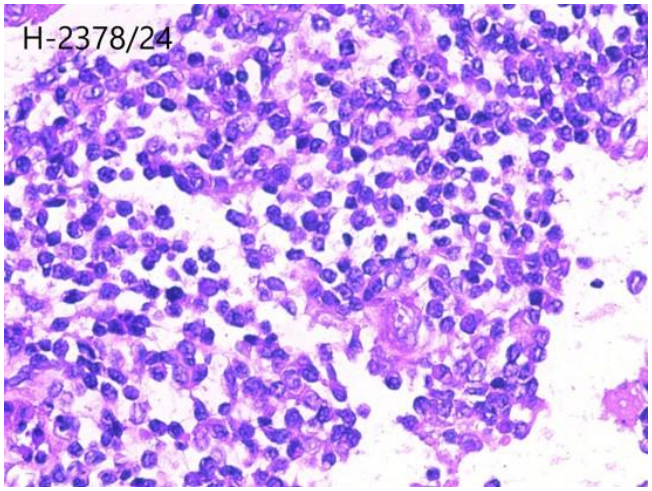


Figure 3. Cell block cytology section (H&E stain) showing tumor cells arranged in monomorphic sheets with irregular nuclear membranes, vesicular chromatin, and scanty cytoplasm, suggestive of non-Hodgkin lymphoma (Original magnification x400).

Conversely, FNAC smears showed non-cohesive hyperchromatic nuclear sheets without visible cytoplasm or nucleoli, favouring small-cell lung carcinoma over hematolymphoid malignancy (Figure 4).

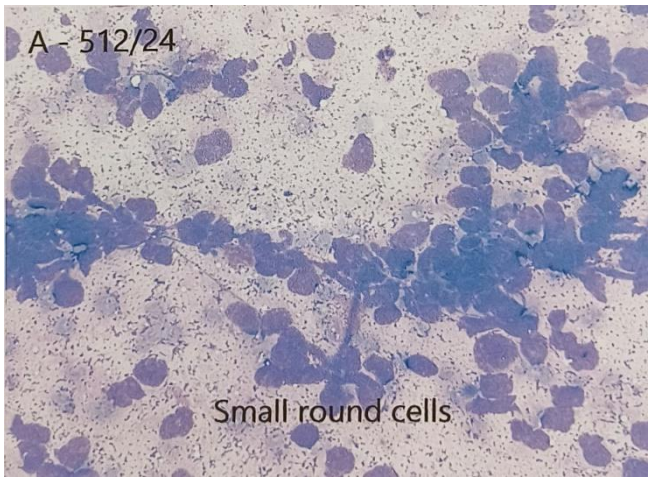


Figure 4. Transthoracic fine-needle aspiration cytology (FNAC) smear showing non-cohesive clusters of hyperchromatic tumor cells lacking distinct nucleoli or visible cytoplasm (Original magnification x400).

To resolve this conflict, immunohistochemical (IHC) panel testing was conducted. The tumor cells showed strong, diffuse membranous positivity for leukocyte common antigen (CD45) and B-cell marker CD20, while T-cell marker CD3 and epithelial marker cytokeratin AE1/AE3 were negative (Figure 5), indicating diagnosis of B-cell Non-Hodgkin Lymphoma. As FNAC and cell block sample adequately established the diagnosis, and patient didn't give consent to undergo any more invasive procedure, core needle biopsy even though planned, could not be performed.

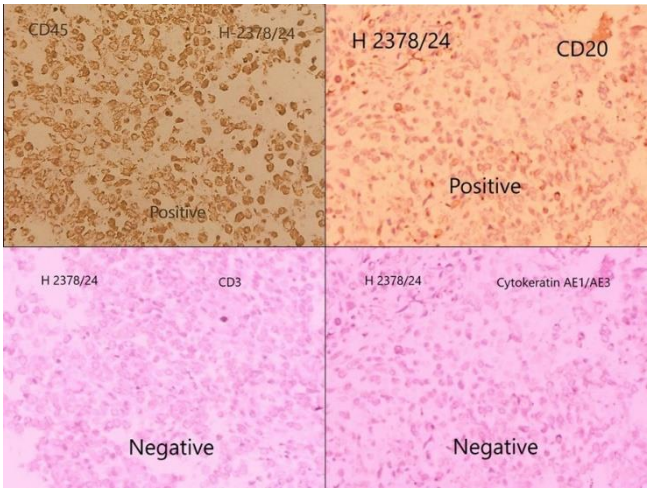


Figure 5. Immunohistochemical (IHC) panel showing diffuse membranous positivity for CD45 (leukocyte common antigen) and CD20 (B-cell marker), alongside negative staining for CD3 (T-cell marker) and Cytokeratin AE1/AE3 (epithelial marker), establishing B-cell non-Hodgkin lymphoma (Original magnification x400).

Whole-body 18F-fluorodeoxyglucose (FDG) PET-CT scan demonstrated a large, intensely FDG-avid heterogeneous enhancing pleural-based mass (6.3 × 10.9 cm, SUVmax 7.1) in the left basal region abutting the diaphragm. Sub-centimetric highest mediastinal, upper paratracheal, subcarinal, and hilar lymph nodes exhibited non-to-faint FDG uptake, reported as reactive lymphadenopathy (Figure 6).With no extrathoracic lymphadenopathy or organ involvement, a diagnosis of Primary Pleural B-cell Non-Hodgkin Lymphoma was confirmed. The patient was initiated on chemo-immunotherapy with the R-CHOP regimen (rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m², and oral prednisolone 100 mg daily for 5 days), scheduled on a standard 21 day cycle.

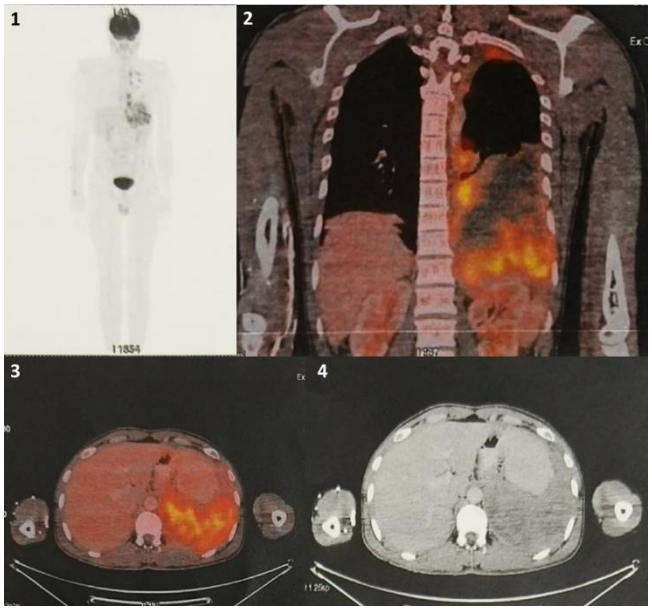


Figure 6. Whole-body 18F-FDG PET-CT scan showing an intensely FDG-avid heterogeneous left basal pleural mass (6.3 × 10.9 cm, SUVmax 7.1) with non-avid reactive mediastinal lymph nodes and no extrathoracic disease.

Two months after completing two cycles of R-CHOP, the patient presented again to the emergency department with rapidly progressive breathlessness and dry cough. Physical examination revealed bilateral lung crackles and severe hypoxemia (SpO2 90% on 10 L/min oxygen via non-rebreather mask). Chest radiograph demonstrated bilateral reticular opacities. He was transferred to the intensive care unit (ICU) and intubated. Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was normal (63 pg/mL), ruling out doxorubicin-induced cardiomyopathy. Urgent CT pulmonary angiography (CTPA) revealed a filling defect in the left main pulmonary artery extending into lobar and segmental arteries, confirming acute pulmonary thromboembolism. Concurrently, lung window images demonstrated extensive ground-glass opacities (GGOs) with interlobular septal thickening in the right lung parenchyma, alongside residual left pleural mass (8.5 × 3.25 × 10.04 cm) (Fig. 7), establishing dual complications of rituximab-induced interstitial lung disease (R-ILD) and acute pulmonary embolism. High-dose intravenous methylprednisolone (1 g/day) was initiated for R-ILD and Low Molecular Weight Heparin (LMWH, 1 mg/kg twice daily) for PE. Systemic thrombolysis was planned for PE, however, despite full ICU support, the patient's oxygenation deteriorated, and he died on the 8th day of admission.

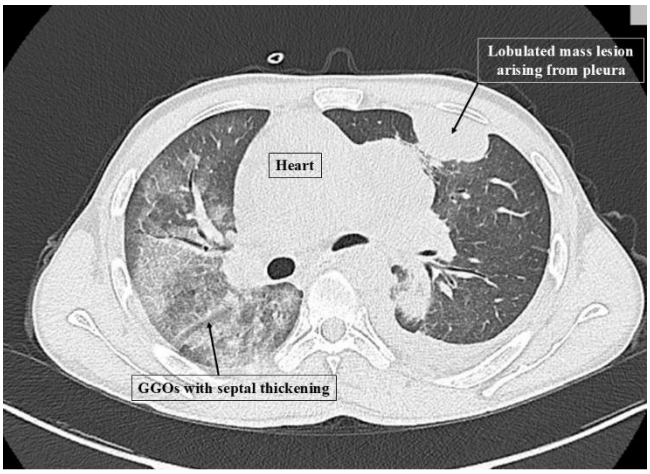


Figure 7. Diffuse ground-glass opacities with interlobular septal thickening in the right lung parenchyma indicative of rituximab-induced pneumonitis.

Discussion

Primary pleural non-Hodgkin lymphoma is an exceedingly rare disease entity, accounting for <0.3% of all non-Hodgkin lymphomas (NHLs) (1,3). PPL typically occurs in the setting of long-standing chronic pyothorax (pyothorax-associated lymphoma) or severe immunocompromise such as HIV infection (7,8). Its presentation in a young, immunocompetent individual without preceding empyema or asbestos exposure is exceptionally rare (4). In tuberculosis-endemic countries, young patients with lymphocytic exudative effusions are frequently placed on empirical anti-tubercular therapy. However, pleural fluid ADA levels <40 IU/L while alone don't definitively exclude pleural tuberculosis with absolute certainty negative pleural fluid AFB smears and negative CBNAAT argued against tuberculosis (6), mandating immediate image-guided tissue biopsy to avoid therapeutic misdirection.

Standard cytological examination of pleural fluid is notoriously non-diagnostic in PPL, yielding positive results in fewer than 25% of cases (4). In our patient, initial FNAC and cell block preparations yielded discordant impressions between small-cell carcinoma and non-Hodgkin lymphoma. Immunohistochemistry proved crucial in establishing lineage: positivity for CD45 and CD20 confirmed B-cell lymphoma, while

negativity for cytokeratin AE1/AE3 and CD3 ruled out epithelial carcinoma and T-cell malignancy(5). Furthermore, PET-CT staging was essential to confirm the primary pleural origin, demonstrating high FDG avidity isolated to the pleura (SUVmax 7.1) with non-avid reactive mediastinal nodes and no distant metastases (7).

A critical educational aspect of this case is the development of dual, fatal treatment-related toxicities. Rituximab-induced ILD is a well-documented but under-recognized pulmonary toxicity, typically manifesting 1 to 3 months after chemo-immunotherapy initiation due to massive B-cell lysis and secondary cytokine release (TNF-alpha, IL-6, interferon-gamma) (9,10). Radiologically, R-ILD presents with ground-glass opacities and interlobular septal thickening (11). Simultaneously, active malignancies induce a prothrombotic state through tumor-derived tissue factor expression and procoagulant cytokine release, predisposing patients to venous thromboembolism (12,13). The concurrent occurrence of diffuse parenchymal lung injury and acute central pulmonary artery thrombosis produces profound, synergistic ventilation-perfusion mismatch that is frequently refractory to combined corticosteroid and anticoagulant therapy.

Primary pleural lymphoma (PPL) predominantly affects older adults in their 6th to 8th decades or immunocompromised individuals with chronic pyothorax or HIV infection (4). Its occurrence in young, immunocompetent individuals is exceptionally rare (4). A review of previously reported cases of primary pleural lymphoma in immunocompetent young patients showed marked heterogeneity. Comparison of age, histology, presentation, treatment and outcome of previously reported cases is presented in Table 2.

Table 2. Comparison of previously reported cases of primary pleural lymphoma in immunocompetent young patients.

Author	Age/Gender	Histological subtype	Presentation	Treatment	Outcome
Karadeniz et al. (14)	2.5 years/ Female	T-cell Lymphoblastic Lymphoma	Fever, Severe dyspnea, Massive pleural effusion	Modified LSA2-L2 protocol + Cranial Radiotherapy	Initial complete remission; isolated CNS relapse at 11 months; died of neutropenic sepsis
Ravikumar et al. (15)	12 years/ Female	DLBCL	Fever, nonproductive cough, pleural effusion, pleural peel	Surgical decortication + 6 cycles of MCP 842 chemotherapy	Remission for 13 months; terminal local relapse with respiratory failure
Elsayed et al. (16)	34 years/ Male	Plasmablastic Lymphoma	Pleural effusion with pleural thickening	CHOP chemotherapy	Deceased
Steiropoulos et al. (17)	37 years/ Female	Classical Nodular Sclerosis Hodgkin Lymphoma	Exertional dyspnea, pleural effusion	Systemic chemotherapy (regimen not mentioned)	Complete clinical regression of effusion and long term remission

Conclusion

Primary pleural lymphoma should be included in the differential diagnosis even in young patients presenting with hemorrhagic exudative pleural effusions, low pleural fluid ADA, and pleural nodularity in tuberculosis-endemic settings. Early image-guided biopsy with immunohistochemistry (CD45/CD20) is essential for diagnostic resolution. Furthermore, clinicians must maintain high vigilance for treatment-related toxicities during rituximab-based chemo-immunotherapy, as concurrent rituximab-induced ILD and pulmonary thromboembolism carry an extremely high risk of rapid clinical deterioration and death.

Author contribution

SB and **TCS** contributed to the conceptualization of the case report. **SB** and **TT** contributed to data curation and investigation. **SB**, **TCS**, and **SH** contributed to the formal analysis and methodology. **SB** and **TT** wrote the initial manuscript. **TCS** and **SH** contributed to critical review and editing of the manuscript. SH and SB provided supervision and project administration. All authors reviewed and approved the final version of the manuscript.

Conflicts of interest

There are no conflicts of interest.

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