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Thymoma with immunodeficiency, combined diffuse panbronchiolitis, and latent autoimmune diabetes in adults- case report and systematic review

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ABSTRACT

Thymoma with Immunodeficiency (Good's Syndrome, GS) is a rare association between thymoma and immunodeficiency, first described over 60 years ago. Patients with GS typically present with thymomas, reduced or absent B cells in the peripheral blood, hypogammaglobulinemia, and defects in cell-mediated immunity. We report the case of a 67-year-old woman diagnosed with GS following the development of a progressive, severe, refractory pulmonary infection and diffuse panbronchiolitis (DPB). She also had diabetes, characterized by anti-glutamic acid decarboxylase antibody positivity, leading to a diagnosis of latent autoimmune diabetes in adults (LADA). A thorough review of existing literature revealed that GS is often confirmed after multiple episodes of opportunistic infections or autoimmune diseases post-thymoma surgery. Due to their immunodeficiency, GS patients frequently suffer from recurrent infections over extended periods, and some succumb to severe infections. Regular immunoglobulin infusions may be effective in treating GS.

1. Introduction

Good's Syndrome (GS) is a primary immunodeficiency characterized by thymoma, hypogammaglobulinemia, and peripheral B lymphopenia, or in some cases, the absence of B cells [1]. The diagnosis of GS is largely based on clinical indicators, including thymoma combined with hypogammaglobulinemia, marked by decreased levels of IgG, IgA, and IgM, and the absence or reduction of B lymphocytes in peripheral blood. Additional diagnostic criteria involve $CD4^+$ T-lymphopenia, an inverted CD4+/CD8+ T lymphocyte ratio, and other combined B and T lymphocyte abnormalities. Thymoma diagnosis is confirmed via chest imaging or postoperative pathological examination. Immunodeficiency diagnosis encompasses history, physical examination, and laboratory tests, including complete blood count, immunoglobulin levels, lymphocyte subsets, and genetic testing, etc.GS is associated with opportunistic infections like mucocutaneous candidiasis, severe varicella infection, Pneumocystis jirovecii pneumonia, cytomegalovirus (CMV; human betaherpesvirus 5), and recurrent herpes simplex virus (HSV) infections. Autoimmune diseases are common in GS, with frequent manifestations including myasthenia gravis, pure red cell aplasia, and lichen planus [2,3], alongside autoimmune endocrinological, gastrointestinal, dermatological, and rheumatological disorders [1,4]. Latent autoimmune diabetes in adults (LADA) occurs in patients over 35, presenting type 2 diabetes clinical features but possessing type-1-diabetes-associated autoantibodies [5]. Studies indicate diabetes incidence is around 1.4 % in common variable immunodeficiency [4] (95 % confidence interval: 0.8–1.9 %) and approximately 2.2 % in GS [6].

We report the case of a 67-year-old patient diagnosed with GS following the development of a progressive, severe, refractory pulmonary infection and diffuse panbronchiolitis (DPB) after a diagnosis of diabetes, LADA. This case is noteworthy due to the uncommon co-occurrence of LADA and GS. The intricate relationship between GS and LADA in this patient underscores the complexity of diagnosing and managing such interrelated conditions.

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2. Clinical case

A 67-year-old woman was referred to our department in August 2019 due to pneumonia unresponsive to antibiotic treatment, which included β-lactam antibiotics + lactamase inhibitors, macrolides, and fluoroquinolones. She had undergone thymoma surgery 14 years earlier. Initial chest computed tomography (CT) scans at that time showed an 8.0 cm × 5.8 cm mass in the left upper mediastinum with a CT value of 52–87 HU. The mass had moderate and uneven density on enhanced scans, with no other anomalies in the lung tissues. Her medical records indicated albumin concentration at 38.7 g/L (normal range 35.0–55.0 g/L) and a notably low globulin concentration of 19.3 g/L (normal range 25.0–33.5 g/L). Pathological examination confirmed the tumor as a thymoma (type unspecified, Fig. 1G), with no residual thymoma tissue after thymectomy. The low globulin concentration at the time of her original surgery was a crucial finding. Post-discharge, she experienced 13 years of recurrent cough, sputum production, and fever, requiring biannual antibiotic treatment. A repeat chest CT scan revealed scattered patchy exudative changes in both upper lungs, diffuse panbronchiolitis, local bronchiectasis, and multiple mediastinal lymphadenopathy (Fig. 1A and B). An earlier head CT scan showed inflammation in the paranasal area. Her blood tests showed a consistently low lymphocyte count [0.23–1.09 × 10^9/L, (normal range: 1.1–3.2 × 10^9/L)], normal blood glucose levels, low globulin concentration [9.6–12.4 g/L, (normal range: 7–16g/L)], and a negative T cell spot test for tuberculosis (TSPOT.TB), with normal T cell response to mitogen (Phytohemagglutinin). Table 1 details her repeated laboratory test results during hospitalization. In March 2019, she underwent tracheoscopy and bronchoscopic alveolar lavage in another hospital, testing positive for human betaherpesvirus 5 and Haemophilus influenzae by polymerase chain reaction. Given the possibility of fungal infections, she was treated with oral itraconazole for 5 months, which did not yield significant improvement.

Upon admission to our department in August 2019, the patient's vital signs were as follows: heart rate of 80 beats/min, respiratory rate of 18 beats/min, blood pressure at 126/74 mmHg, oxygen saturation in ambient air at 96 %, and a body mass index (BMI) of 18.5 kg/m^2 (height 148 cm; weight 40.5 kg). Moist rales were audible in both lungs. Her routine laboratory results included: hemoglobin concentration at 13.5 g/dL; white blood cell count at 5.24 × 10^9/L; neutrophil count at 4.0 × 10^9/L; lymphocyte count at 1.0 × 10^9/L; and platelet count at 217 × 10^9/L. Tests for urine, feces, coagulation, hepatic and renal function, tumor markers and the autoantibody spectrum for rheumatic immune diseases were normal, with the exceptions of an elevated C-reactive protein level at 48.5 mg/L and a reduced globulin concentration of 15 g/L. Serum immunoglobulin levels were significantly low: IgG at 0.01 g/L, IgM at 0.03 g/L, IgA at 0.01 g/L, and IgE at 10 IU/mL. Complement levels (C3 and C4) were within normal ranges (Table 1). Tests for tuberculosis, cryptococcal capsular antigen, 1,3-β-D-glucan, galactomannan, syphilis, and human immunodeficiency virus returned negative results. Sputum smears were negative for acid-fast bacilli, but the culture tested positive for *Pseudomonas aeruginosa*.

The patient's pulmonary function test indicated a reduced diffusing capacity and significant mixed ventilatory impairment, as evidenced by an FEV1/FVC ratio of 64.94 % (FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity). Blood gas analysis showed a pH of 7.40, PO2 of 68 mmHg, and PCO2 of 39 mmHg. Chest CT scans revealed multiple intrapulmonary patchy blurry shadows in both lung lobes, diffuse panbronchiolitis and slightly enlarged mediastinal lymph nodes (Fig. 1C and D). After the detection of *Pseudomonas aeruginosa* the

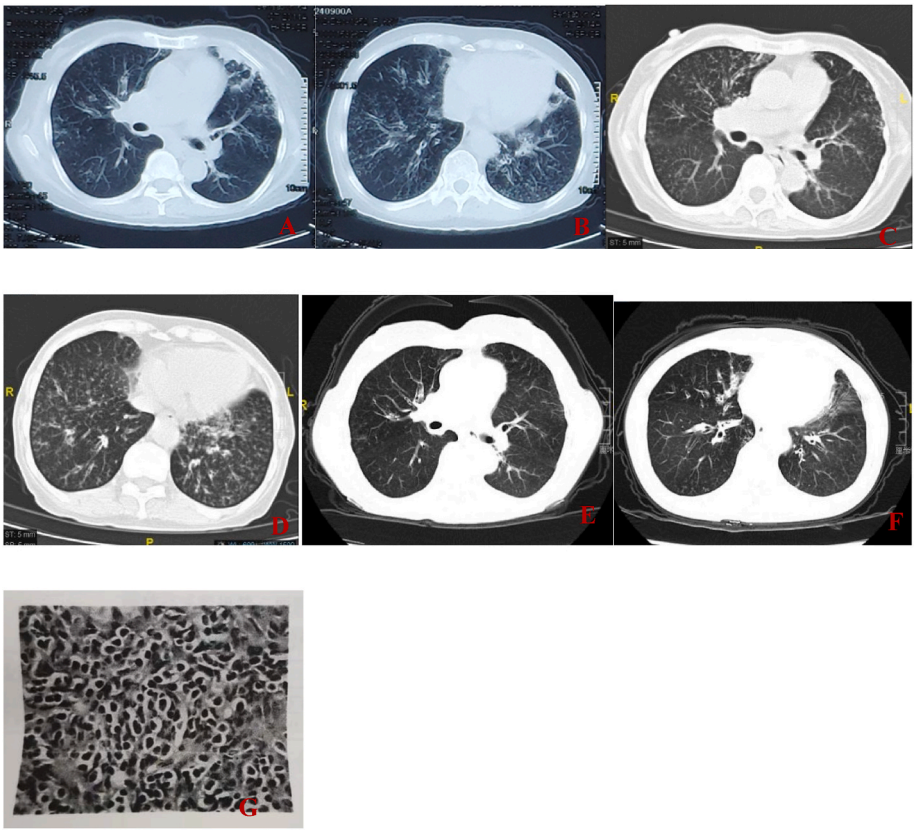

Fig. 1. Chest computed tomography and pathology of the patient. (A) and (B) (Chest computed tomography [CT] in July 2019): scattered patchy exudative changes in both upper lungs, DPB, and local bronchiectasis; **(C) and (D)** (Chest CT in August 2019): multiple intrapulmonary patchy blurry shadows in both lobes and DPB; **(E) and (F)** (chest CT in April 2020): absorption of pneumonia lesions and more diffuse bronchiolitis than previously seen; **(G)** (thymus pathology in February 2005): conforms to the characteristics of a thymoma.

Table 1
Results of repeat laboratory test of hospitalization.

Date	Absolute lymphocyte count (cells/uL)				GLB (g/L) (20–40)	Immunoglobulin levels (g/L)			Complement test (mg/dL)		Differential WBC count (× 10^9/L)	
	$CD4^+$ cells	$CD8^+$ cells	B cells	NK cells		IgG (7–16)	IgA (70–400)	IgM (40–230)	C3 (90–180)	C4 (10–40)	Lymph (1.1–3.2)	Neu (1.8–6.3)
Dec 19, 2018	/	/	/	/	9.6	0.12	0.03	0.05	/	/	1.09	7.11
Mar 21, 2019	/	/	/	/	12.4	/	/	/	/	/	0.23	8.07
Aug 14, 2019	191	615	0	44	15	0.01	0.01	0.03	102	24	1	4
Aug 26, 2019	/	/	/	/	26	13.5	0.01	0.09	/	/	1.6	0.9
Nov 12, 2019	309	847	0	76	18	3.19	0.01	0.04	131	26	1.4	7
Jan 13, 2020	189	466	0	78	15	3.78	0.01	0.04	95	22	0.8	5.4
Apr 8, 2020	240	592	0	90	18	3.23	0.01	0.03	134	28	1.1	6

antibiotic adjustment to cefoperazone sulbactam with etimicin. Following this change in treatment, the patient's respiratory symptoms markedly improved. Given her history of thymoma and the presence of primary immunodeficiency, a diagnosis of GS was confirmed. Intravenous immunoglobulin (IVIG) treatment was initiated (200 mg/kg/day from August 22 to August 26, 2019), with positive results observed.

Post-treatment, an evaluation of the patient's immunoglobulin levels was carried out on August 26, revealing a notable improvement with an IgG level of 13.5 g/L. Following discharge, the patient experienced no further episodes of fever or purulent sputum. She revisited our hospital for IVIG therapy (200 mg/kg for 5 days) on November 12, 2019; January 14, 2020; and April 12, 2020. Before each IVIG treatment, we closely monitored the patient's IgG levels, which consistently ranged between 3.19 and 3.78 g/L, as detailed in Table 1. Follow-up chest CT scans demonstrated significant resolution of the pneumonia lesions and DPB (Fig. 1E and F). While the patient's IgG levels improved, the levels of other immunoglobulins and B cells remained below detectable limits.

The patient was admitted to our hospital in January 2020 presenting with polyuria. Biochemical examinations revealed significant urine glucose levels (++++), a fasting blood glucose concentration of 18.4 mmol/L, and a glycosylated hemoglobin (HbA1c) level of 12.8 %. These findings led to a diagnosis of diabetes, and she was initially treated with metformin (500 mg twice daily) and acarbose (50 mg three times daily). However, due to inadequate glycemic control on oral metformin and acarbose, her medication regimen was altered to include sitagliptin (100 mg once daily), repaglinide (1 mg three times daily), and miglitol (50 mg three times daily). Further laboratory tests indicated high postprandial blood glucose, low fasting C-peptide levels, and positive glutamic acid decarboxylase antibody (GADA), supporting the diagnosis of LADA. A chest CT scan revealed scattered inflammation in both lungs and a progression of bronchiectasis compared to previous imaging. Consequently, insulin therapy was promptly initiated considering the LADA diagnosis. The patient's poor glycemic control, compounded by interrupted IVIG treatment, led to the progression of pneumonia. She resumed IVIG treatment, augmented with antibiotics, which stabilized her blood glucose levels during hospitalization. However, after discharge, IVIG therapy was discontinued due to financial constraints. Tragically, the patient passed away in January 2021 due to a severe lung infection.

In this case, the specific pathological type of the thymoma was not identified. However, historical data from the patient's medical records suggest that conditions such as diffuse DPB and pneumonia developed after the surgery for thymoma, leading to recurrent respiratory tract infections. Notably, the patient was diagnosed with GS 14 years post-thymoma surgery, despite indications of hypogammaglobulinemia in her preoperative biochemical tests.

Written consent was obtained from the patient presented above.

3. Literature review of Good's syndrome

To better understand GS, we reviewed the symptoms related to GS and respiration.

3.1. Literature search

A comprehensive Boolean search was conducted in PubMed using the keywords "Good's syndrome" or ["thymoma" AND "hypogammaglobulinemia"] or ["thymoma" AND "immunodeficiency"] AND ["pneumonia" or "respiratory infection" or "diffuse panbronchiolitis" or "bronchiectasis"]. This search targeted articles published from January 1, 1992, to December 31, 2021. We meticulously reviewed each publication for presenting symptoms, thymic pathology, CT features, treatment courses, and outcomes. Publications with unclear diagnoses or incomplete data were excluded from our analysis. Ultimately, our search yielded 38 peer-reviewed articles encompassing 39 cases [7–44], as detailed in the subsequent sections.

3.2. Clinical features, treatment, and outcomes

A total of 39 patients diagnosed with thymoma and GS were identified, comprising of 22 males and 17 females. The median age at thymoma diagnosis was 56 years (IQR: 48–64), and for GS diagnosis it was 58 years (IQR: 52–66). The interval between thymoma and GS diagnosis was on average 1 year (IQR: 0–3). Twenty patients presented with reduced immune globulin at thymoma diagnosis, confirming the diagnosis of Good syndrome. The remaining patients received their Good syndrome diagnosis after experiencing recurrent infections following thymoma treatment. The shortest time span between thymoma treatment and Good syndrome diagnosis was 3 months, while the longest was 20 years. Thirty-three patients (84.6 %) underwent intravenous immunoglobulin therapy, and as a result, eight patients (20.5 %) succumbed (Table 2).In 2015, WHO classified thymic epithelial tumors into type A, AB, B1, B2, B3, and C (thymic carcinomas, including neuroendocrine carcinomas of the thymus), indicating that the typing reflects the biological behavior and prognosis of the tumor to a certain extent. Among reported thymomas associated with Good syndrome, the most prevalent pathological type was AB type (11 cases, 44 %), followed by type A (7 cases, 28 %).

The most prevalent respiratory symptoms among these cases were cough (24 cases, 61.5 %), followed by dyspnea (15 cases, 38.5 %), and sputum production (13 cases, 33.3 %). Respiratory system involvement in these patients mainly comprised pneumonia, bronchiectasis,

Table 2
Demographic and clinical parameters.

Parameter	N (%)
Gender (male)	22(56.4 %)
Age at diagnosis of thymoma (years), Median (IQR)	56(48–64)
Age at diagnosis of GS (years), Median (IQR)	58(52–66)
Time from thymoma to GS diagnosed (years), Median (IQR)	1(0–3)
Respiratory symptoms	
Cough	24(61.5)
Sputum	13(33.3)
Chest tightness	13(33.3)
Shortness of breath	2(5.1)
Dyspnea	15(38.5)
Constitutional symptoms	
Fever	13(33.3)
Weight loss	15(38.5)
Night sweats	3(7.7)
Fatigue	4(10.2)
Decreased appetite	3(7.7)
Involvement of other organ systems	
Digestive system	15(38.5)
Hematopoietic system	7(17.9)
Endocrine system	1(2.6)
Nervous system	2(5.1)
Body cavities	8(20.5)
Integumentary system	6(15.4)
Musculoskeletal system	3(7.7)
Urinary system	2(5.1)
IVIG	33(84.6)
Died	8(20.5)

Numbers for continuous variables represent medians (interquartile range); IVIG : intravenous immunoglobulin.

empyema, pulmonary tuberculosis, pulmonary nodules, and other infections. The predominant imaging features in these cases were bronchiectasis (17 cases, 43.6 %), followed by infiltration (9 cases, 23.1 %), consolidation (6 cases, 15.4 %), nodules (6 cases, 15.4 %), and other abnormalities (Table 3). The primary pathogens observed in these cases included *Pseudomonas aeruginosa* [8,16,23,30,37], Human beta-herpesvirus 5 (CMV) [6,11,16,18,27,31], Pneumocystis jiroveci (PJP) [10,18,25,32,33,38], Candida albicans [11,15,25,30,38], among others.

In the reviewed cases, the predominant systemic symptoms included weight loss in 15 cases (38.5 %) and fever in 13 cases (33.3 %). Additionally, other organ systems were frequently affected. The digestive system was involved in 15 cases (38.5 %), body cavities in 8 cases (20.5 %), and the hematopoietic system in 7 cases (17.9 %), among others.

Table 3
Pathology of thymoma and imaging features.

Parameter	N (%)
Pathology	
A (Medullary, spindle cell thymoma)	7(28)
AB (Mixed thymoma)	11(44)
B1-3(Cortical thymoma)	5(20)
C (Thymic carcinoma)	2(8)
Imaging features	
Bronchiectasis [7–23]	17(43.6)
Consolidation [15,17,30–32]	6(15.4)
Ground glass opacities [7,32,34,39]	4(10.2)
Nodules [26,33–37]	6(15.4)
Infiltration [14,16,20,24–29]	9(23.1)
Hydrothorax [38,40–42]	4(10.2)
Volume loss [9,19]	2(5.1)
Bronchitis [10,37]	2(5.1)
Mass [11]	1(2.6)
Cavitary [26,39,43]	3(7.7)
Fibrosis [15,19]	2(5.1)
Lymphadenopathy [44]	1(2.6)

Pathology reports were available for 25 of the 39 patients.

Pure red cell aplasia emerged as the most commonly encountered hematological disorder, while occurrences of pure white cell aplasia or polycythemia vera were relatively rare. Notably, fungal infections in the digestive tract were also reported [31].Skin and mucous membrane changes predominantly manifested as dermatomycosis [8,11,12,21], with other instances including lichen planus [17,23], tuberculosis, and skin abscess [34]. In the endocrine system, cases of hypothyroidism were noted [12]. Regarding diabetes mellitus (DM), one patient was diagnosed with diabetes prior to the diagnosis of GS [29].

4. Discussion

GS represents a rare conjunction of thymoma and immunodeficiency, first identified over 60 years ago. Typically, GS affects individuals aged between 40 and 70 years, most of whom present with thymomas. Research on GS largely comprises single-case studies or small case series. The most extensive cohort study to date involved 78 patients from the UK [45], and a systematic review before 2010 encompassed 152 cases [6]. In the systematic review before 2010, thymoma was diagnosed before hypogammaglobulinemia, infection, or diarrhea in 42 % of patients, while in 38 % of patients, these diagnoses were nearly simultaneous, occurring within a span of 2 months. Interestingly, this body of research did not report radiographic pulmonary lesions in patients with GS. The case described here is unique in its combination of Good's Syndrome with DPB and LADA, alongside distinct lung radiographic features.

Previous studies indicate that GS does not typically present with specific imaging findings. Pneumonia, attributable to various pathogens, can manifest differently on radiographs, exhibiting features like consolidation, diffuse ground-glass opacities, the tree-in-bud sign, cavitation, bronchiectasis, and pleural effusion. Certain case reports [9,36] document lung imaging that shows diffuse centrilobular nodules, the tree-in-bud sign, and bronchial wall thickening, aligning with the radiographic characteristics of DPB.

The patient's prolonged symptoms of cough, sputum production, and dyspnea, combined with results from blood gas analysis, pulmonary function tests, and imaging, led to a diagnosis of diffuse DPB [46]. DPB is a chronic, progressive disease primarily affecting the bronchioles in the respiratory tract. In patients with GS, recurrent bacterial infections, reduced B-lymphocyte immunity due to thymoma, and hyperreactivity of lymphocytes associated with HLA-B54 are considered potential etiological factors for DPB [47]. DPB often progresses to bronchiectasis [9], and some cases exhibit coexistence of centrilobular nodules with bronchiectasis [11].

A UK retrospective survey identified bronchiectasis in 35 out of 78 GS patients (45 %) [45]. Our literature review indicates that bronchiectasis is a frequent radiographic finding in GS patients with pulmonary involvement. Since some patients with GS experience recurrent lower respiratory tract infections over the years between thymoma and GS diagnosis, bronchiectasis may emerge as a late radiographic sign. This condition likely results from the development of bronchial inflammation and structural damage. This observation emphasizes the importance of considering bronchiectasis in the differential diagnosis of respiratory symptoms in patients with a history of thymoma, especially in the context of GS.

In our case, the low globulin concentration observed during the initial thymoma surgery indicated the presence of hypogammaglobulinemia, which was recognized and addressed at the time of the surgery. This early identification likely prevented a prolonged diagnostic delay typically associated with recurrent infections in patients with GS. Previous studies have corroborated that low globulin levels are a reliable predictive marker for hypogammaglobulinemia [3]. Therefore, the detection of reduced globulin levels at the time of thymoma surgery in this patient was a critical factor that facilitated an earlier intervention and management of potential complications associated with GS.

In the context of GS, implementing aggressive anti-infection therapy

and immunoglobulin supplementation may significantly enhance patient outcomes. Reports of GS coexisting with endocrinopathies, particularly diabetes, are relatively rare. In most cases where diabetes is reported, it is described as an underlying disease, but details on adjunctive tests and glycemic control are seldom provided. It appears that the onset of diabetes is independent of GS [48–50]. Latent autoimmune diabetes in adults (LADA) was first described by Tuomi et al., in 1993 [51] as having phenotypical characteristics similar to type 2 diabetes and immunological features akin to type 1 diabetes. LADA diagnosis typically relies on three criteria: the patient's age at onset, presence of islet autoantibodies indicating autoimmune activity, and eventual insulin dependence [52]. Compared to type 2 diabetes, LADA patients exhibit lower insulin secretion levels and a faster progression to insulin dependence [53]. In the case presented, the patient's diabetes symptoms became more pronounced during intravenous immunoglobulin therapy, as indicated by laboratory findings. Although prior studies have suggested that IVIG use can result in false-positive GADA results, it has been noted that the impact on GADA results is minimal when testing is performed four weeks after IVIG administration [54].

5. Conclusions

For patients experiencing recurrent lower respiratory tract infections post-thymectomy, it is essential to conduct close monitoring of immunoglobulin levels and pulmonary status. In our case, while we could not definitively confirm an association between LADA and GS, the co-occurrence of these conditions cannot be dismissed as mere coincidence. Moreover, poor glycemic control in such patients is often linked to pulmonary infections, which further complicates the diagnosis and treatment of GS.

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CRediT authorship contribution statement

Yijiao Xu: Investigation, Writing - original draft. **Lumin Wang:** Funding acquisition, Writing - review & editing. **Zhisheng Chen:** Supervision, Writing - original draft. **Qingwei Zhang:** Data curation, Formal analysis. **Yun Shen:** Formal analysis, Visualization. **Yanrong Ye:** Resources. **Jiaxin Liu:** Methodology. **Huijun Zhang:** Resources, Validation, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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