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Association of COVID-19 with thyroid dysfunction and autoimmune thyroid disease: A retrospective cohort study

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ABSTRACT

Background: Since the end of the COVID-19 pandemic, the potential roles of thyroid-inflammatory derangements in driving or being associated with the prognosis of COVID-19 remain controversial. We aimed to clarify the association between COVID-19 infection and thyroid dysfunction, and highlight the impacts of subsequent autoimmune thyroid disease (AITD) on the prognosis of COVID-19.

Methods: The retrospective, multicenter, cohort study enrolled 2,339 participants with COVID-19 from three hospitals located in the north, middle, and south regions of Shaan Xi Province, China, between December 2022 and July 2023. 464 non-COVID-19 patients within the same period were supplemented, divided into groups with and without AITD. At hospital admission (baseline), 3- and 6-month follow-ups, we presented a dynamic description and correlation analysis of thyroid-inflammatory-autoimmune derangements in patients with AITD.

Results: A total of 2,082 COVID-19 patients diagnosed with AITD and 257 cases without AITD were included in the study, and 464 non-COVID-19 patients were supplemented, dividing into 14 AITD and 450 non-AITD cases. We found that COVID-19 infection was closely associated with thyroid dysfunction ($\chi^2 = 1518.129$, $p = 0.000$). AITD patients with COVID-19 showed a higher prevalence of symptoms and comorbidities and longer hospital stays at baseline than non-AITD patients with COVID-19 ($p = 0.000$, $p = 0.000$, and $p = 0.000$). The baseline free triiodothyronine (FT3), free thyroxine, and radioactive iodine uptake at 24 h in AITD cases significantly decreased ($p = 0.000$, $p = 0.000$, and $p = 0.000$), while thyroid stimulating hormone, thyroglobulin, reverse triiodothyronine (rT3), and thyroid antibodies varying elevated from the baseline to the follow-up (baseline: $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, and $p = 0.000$; 3-month follow-up: $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.030$, and $p = 0.000$). C-reactive protein, calcitonin, interleukin-6, -8, -10, and tumor necrosis factor-α rose significantly at baseline ($p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, and $p = 0.000$) in AITD. Interferon-α and interferon-γ at baseline showed a significant decrease ($p = 0.000$ and $p = 0.000$), and remained at low levels after 6 months ($p = 0.000$ and $p = 0.000$). FT3 and rT3 were positively and negatively correlated with hospitalization, respectively (r = -0.208 and 0.231; $p = 0.000$ and $p = 0.000$). ROC curves showed that FT3 and rT3 had better robustness in predicting severe COVID-19 prognosis (AUC = 0.801 and 0.705). Ordered logistic regression revealed that ORs were 0.370, 0.048, and 0.021 for AITD [(subacute thyroiditis, Grave's disease, and Hashimoto's thyroiditis compared to non-thyroidal illness syndrome (NTIS)] with COVID-19 risk, indicating that NTIS was the predominant risk factor for the severity of COVID-19.

Conclusions: A robust association has been identified, wherein COVID-19 infection is closely associated with thyroid dysfunction, and the subsequent AITD may aggravate the poor prognosis of COVID-19.

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Abbreviations

CFR	Global case fatality rate
AID	Autoimmune disease
AITD	Autoimmune thyroid disease
ACE2	Angiotensin-converting enzyme 2
TMPRSS2	Transmembrane serine protease 2
NTIS	Non-thyroidal illness syndrome
Th1	Type 1 T helper
IL-1, -1β, −6, −8, −10, −17	Interleukin-1, -1β, -6, -8, -10, -17
TNF-α	Tumor necrosis factor-α
NETs	Neutrophil extracellular traps
IFN-α, -γ	Interferon-α, -γ
FT3	Free triiodothyronine
FT4	Free thyroxine
TT3	Total triiodothyronine
TT4	Total thyroxine
TSH	Thyroid stimulating hormone
Anti-TPO	Anti-thyroid peroxidase
Anti-Tg	Antithyroglobulin antibody
Tg	Thyroglobulin
TRAb	Thyrotropin receptor antibody
rT3	Reverse triiodothyronine
CRP	C-reactive protein
IgG, A, M, E	Immunoglobulin G, A, M, E
C1 INH	C1 esterase inhibitor
US	Ultrasonography
SPECT	Single photon emission computed tomography
^{99m}Tc	Technetium-99m
^{18}F-FDG PET/CT	Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography
SUV_{max}	Maximum standardized uptake value

1. Introduction

In March 2020, the World Health Organization (WHO) officially declared the global spread of the coronavirus disease of 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which concluded in May 2023. Following the relaxation of China's "zero COVID" policy in December 2022, a significant COVID-19 outbreak occurred among the Chinese population approximately 21 months after the onset of the global pandemic, lasting for approximately six months before rapidly subsiding. Throughout the pandemic, the global case fatality rate (CFR) fluctuated between 1.7 % and 39.0 %, with China experiencing an average CFR of approximately 6.1 % [1,2]. Most COVID-19 patients had mild symptoms, and 20.1 % of cases worldwide were classified as severe or critical, and the data in China ranged from 10.1 % to 53.1 % [3–5].

There was growing evidence indicating that COVID-19 could lead to the overstimulation of the human immune system, resulting in the development of autoimmune diseases (AID) such as autoimmune thyroid disease (AITD), antiphospholipid syndrome, autoimmune thrombocytopenia, and autoimmune hemolytic anemia [6–8]. The upregulations of key receptors angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) in the thyroid follicular cells had been proven to facilitate the invasion of SARS-CoV-2, leading to an exaggerated immune response, which triggered an inflammatory cascade, ultimately leading to thyroid dysfunction and the development of AITD such as non-thyroidal illness syndrome (NTIS), subacute thyroiditis, Hashimoto's thyroiditis, Grave's disease, etc. [9–11]. AITD represented a subset of thyroid-specific AID that was mediated by Type 1 T helper (Th1) lymphocytes [12]. The pathophysiological processes underlying the development of AITD in the context of COVID-19 could be attributed to the following mechanisms: (1) COVID-19 infection triggered upregulation of inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-17 (IL-17), and tumor necrosis factor-α (TNF-α), leading to an exaggerated pro-inflammatory response and the onset of a severe cytokine storm within the thyroid gland; (2) Molecular mimicry between human autoantigens and components of COVID-19, such as the spike protein, nucleoprotein, and membrane protein, resulted in the activation of autoreactive T and B cells through cross-reactivity with thyroid-derived peptides sharing homologous polypeptide sequences [13]; (3) Neutrophil extracellular traps (NETs) were composed of chromatin, microbicidal proteins, and oxidant enzymes that were released by neutrophils, which could exacerbate inflammation and microvascular thrombosis in various organs, including the thyroid gland [14]; (4) Transcriptional modifications of immune genes induced by COVID-19 might potentially exacerbate thyroid autoimmunity in susceptible individuals. The replication of COVID-19 in endocrine cells could result in transcriptional changes in immune genes, ultimately activating type I (interferon-α, IFN-α) and type II (interferon-γ, IFN-γ) pathways [13].

Since the end of the COVID-19 pandemic, some studies have focused on thyroid function and inflammatory immune status in patients with COVID-19 [15,16]. However, the potential roles of thyroid-inflammatory-autoimmune arrangements in driving or being associated with adverse prognosis in COVID-19 patients remain controversial. While some researchers argue that COVID-19 infection does not impact the development and exacerbation of thyroid dysfunction, others have found a significant correlation between thyroid dysfunction and COVID-19 prognosis. In this multicenter retrospective cohort study, we aimed to clarify the association between COVID-19 infection and thyroid dysfunction, and highlight the impacts of subsequent AITD on the prognosis of COVID-19.

2. Materials and methods

2.1. Study design

This retrospective, multicenter cohort study was conducted in three hospitals located in the north, middle, and south of Shaan Xi Province, China. A total of 7,080 participants diagnosed with COVID-19 were enrolled between December 1, 2022, and July 31, 2023, from the Second Affiliated Hospital of Xi'an Jiaotong University (middle region, n = 4,582), Yulin Zizhou County Hospital (north region, n = 1,195), and Hanzhong Mian County Hospital (south region, n = 1,303). The patients who were not infected with COVID-19 during the same period as this cohort study were also collected (n = 464), and divided into two groups with (n = 14) and without (n = 450) AITD. Approval for the study was obtained from the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University.

2.2. Inclusion and exclusion criteria

All eligible participants should meet the following inclusion criteria: (1) A confirmed diagnosis of COVID-19 through a positive RT-PCR assay for SARS-CoV-2 in nasopharyngeal swabs; (2) Radiological confirmation of chest computed tomography or X-ray scans; (3) Hospital admission within 3 days of symptom onset. Participants were categorized into AITD and non-AITD groups based on thyroid function. Follow-up assessments were conducted via phone survey or face-to-face consultation at 3- and 6-months post-baseline. Participants in the study were voluntary, and all individuals or their legal representatives provided informed consent.

To minimize selection bias, individuals might be excluded based on the following criteria: (1) Incomplete medical records (age, gender, symptoms, comorbidities, CFRs, oxygen support, hospital stay, etc.) at baseline and follow-ups (n = 603); (2) Pre-existing AITD (subacute thyroiditis, Hashimoto's thyroiditis, Grave's disease, NTIS, etc.) or history of thyroid surgery (thyroidectomy or lobectomy for the treatment of thyroid cancer, benign nodules, and severe hyperthyroidism) before COVID-19 infection (n = 816); (3) Lack of thyroid-inflammatory-autoimmune tests (thyroid functions, inflammatory indicators, and

autoimmune antibodies shown in Part 2.3 Variables) at baseline and the follow-ups (n = 1,601); (4) Prior use of medications that affected thyroid-related endocrine metabolic system (heparin, glucocorticoids, interferon, antivirals, etc.) before the treatment of COVID-19 infection (n = 676); (5) Individuals with low education levels (primary, junior, senior middle school, etc.) that unable to comprehend or facing severe language barriers during follow-up phone surveys (n = 327); (6) Individuals who were lost (relocation, uncontactable, time constraints, etc.) during the follow-ups in this retrospective, cohort study (n = 718).

2.3. Variables

Individual demographic characteristics, CFRs, symptoms, comorbidities, oxygen support, and hospital stay were documented. Thyroid-inflammatory-autoimmune indicators were assessed at hospital admission (baseline) and during follow-ups, with normal ranges for variables (indicators) provided in **Table S1**.

(1) Thyroid indicators: free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (TT3), total thyroxine (TT4), thyroid stimulating hormone (TSH), anti-thyroid peroxidase (anti-TPO), antithyroglobulin antibody (anti-Tg), thyroglobulin (Tg), thyrotropin receptor antibody (TRAb), reverse triiodothyronine (rT3), and radioactive iodine uptake at 24 h.
(2) Inflammatory indicators: leukocyte, neutrophil, lymphocyte, c-reactive protein (CRP), procalcitonin, IL-6, IL-8, IL-10, and TNF-α.
(3) Autoimmune antibodies: interferon-α (IFN-α), interferon-γ (IFN-γ), immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin E (IgE), and C1 esterase inhibitor (C1 INH).

2.4. Severity of COVID-19

The severity of COVID-19 was determined following the most recent edition of the WHO's diagnosis and treatment guidelines [17]. Patients with COVID-19 were classified as severe if they exhibited at least one of the following criteria: (1) Respiratory rate ≥30 breaths/min; (2) Arterial oxygen saturation ≤93 % at rest while inhaling; (3) Oxygenation index (PaO_2/FiO_2) ≤ 300 mmHg; (4) Lung imaging indicating a lesion progression of ≥50 % within 24-48 h.

Patients were categorized as critical if they met the aforementioned criteria and also fulfilled one of the following criteria [18]: (1) Mechanical ventilation-required respiratory failure; (2) Shock; (3) Combination of intensive care unit monitoring and treatment with multiple organ failures. Therefore, patients were stratified into three categories: mild to moderate, severe, and critical, respectively.

2.5. Diagnosis for subsequent AITD

Once thyroid dysfunction was confirmed in enrolled individuals, then subsequent AITD had been diagnosed. The subsequent AITD was considered to be secondary to COVID-19 infection and mainly manifested as subacute thyroiditis, Grave's disease, Hashimoto's thyroiditis, NTIS, etc. [13]. The diagnostic criteria for subsequent AITD in COVID-19 patients had been established based on the International Classification of Diseases 11th Revision (ICD-11): (1) Subacute thyroiditis: 5A03.1; (2) Grave's disease: 5A02.0; (3) Hashimoto's thyroiditis: 5A03.20; (4) NTIS: 5A06.

2.6. Thyroid imaging

Thyroid imaging was conducted by ultrasonography (US) and single photon emission computed tomography (SPECT) with Technetium-99m (^{99m}Tc), or positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography (^{18}F-FDG PET/CT) scans, if applicable. As to the high expense of ^{18}F-FDG PET/CT scans, a total of 13 patients with AITD underwent this detection.

2.7. Statistical analysis

Descriptive statistics were utilized to present continuous variables in the form of mean ± standard deviation (SD), while categorical variables were expressed as counts and percentages (%). Statistical analyses of continuous variables were conducted by either the Student's t-test or Mann-Whitney U test, while categorical variables were assessed through Fisher's exact test or Chi-squared test. Differences among multiple groups were evaluated using a one-way analysis of variance (ANOVA) test, with Tukey's post-hoc tests applied to further significant findings. Pearson correlation tests were utilized to evaluate the correlations. Ordered logistic regression was employed to investigate the relationship between subsequent AITD and COVID-19 severity. Model selection and building procedures: (1) The model selection of ordered logistic regression: COVID-19 severity included a three-level variable from mild to moderate, severe, and critical, which was called outcome variable (coded 1, 2, and 3), and AITD was called the factor variable (coded 1, 2, 3, and 4); (2) After cases processing summary, model fitting information showed a significant improvement in the fit of the final model; (3) Goodness-of-Fit table showed non-significant test results indicating that the model fitted the data well; (4) Pseudo R-Square values had been calculated; (5) Parameter estimates showed the regression coefficients and significance tests for each of the factor variables in the model; (6) Test of parallel lines indicated non-significance then we interpreted the assumption was satisfied. Receiver operating characteristic (ROC) curve was used to evaluate the predictive abilities of indicators for poor COVID-19 prognosis. Also, the residual analysis and goodness-of-fit tests, such as Hosmer-Lemeshow and Likelihood Ratio tests, were presented. The statistical analysis was carried out by SPSS software (version 25.0, IBM), with statistical significance defined as a two-tailed p-value < 0.05.

3. Results

3.1. Characteristics between COVID-19 patients with and without AITD

A cohort of 2,339 COVID-19 patients, comprising 2,082 cases with AITD and 257 cases without AITD, was recruited from three hospitals located in the north, middle, and south regions of Shaan Xi Province, China, between December 2022 and July 2023. Following the application of six stringent exclusion criteria, all patients were monitored from admission to the hospital until 3- and 6-month follow-ups (Fig. 1). We also collected 464 patients who were not infected with COVID-19 during the same period as this cohort study, dividing into groups with (n = 14) and without (n = 450) AITD, and we found that COVID-19 infection was closely associated with thyroid dysfunction (χ^2 = 1518.129, p = 0.000).

The key demographic and clinical features of COVID-19 patients were outlined in **Table 1**. Following hospital admission (baseline), there were no significant differences in age (children, adults, and seniors) or gender between COVID-19 patients with and without AITD (p = 0.794 or 0.995). Patients with AITD exhibited a higher prevalence of symptoms compared to those without AITD (p = 0.000), particularly for common presenting symptoms such as cough (24.11 %), fever (18.94 %), and myalgia (14.49 %), except for nasal congestion, which was present in 0.73 % of patients in both groups (**Table 1**). A higher prevalence of comorbidities was observed in COVID-19 patients with AITD (p = 0.000), with hypertension (21.06 %), cardiovascular disease (20.05 %), and diabetes (11.16 %) being the most common comorbidities in the AITD group (**Table 1**). There was no significant difference in CFRs between the AITD and non-AITD groups (1.45 % vs. 0.09 %, p = 0.434), and the need for oxygen support also did not differ significantly between these groups (15.26 % vs. 1.84 %, p = 0.867). Furthermore, AITD patients had longer hospital stays compared to non-AITD patients (6.64 ±

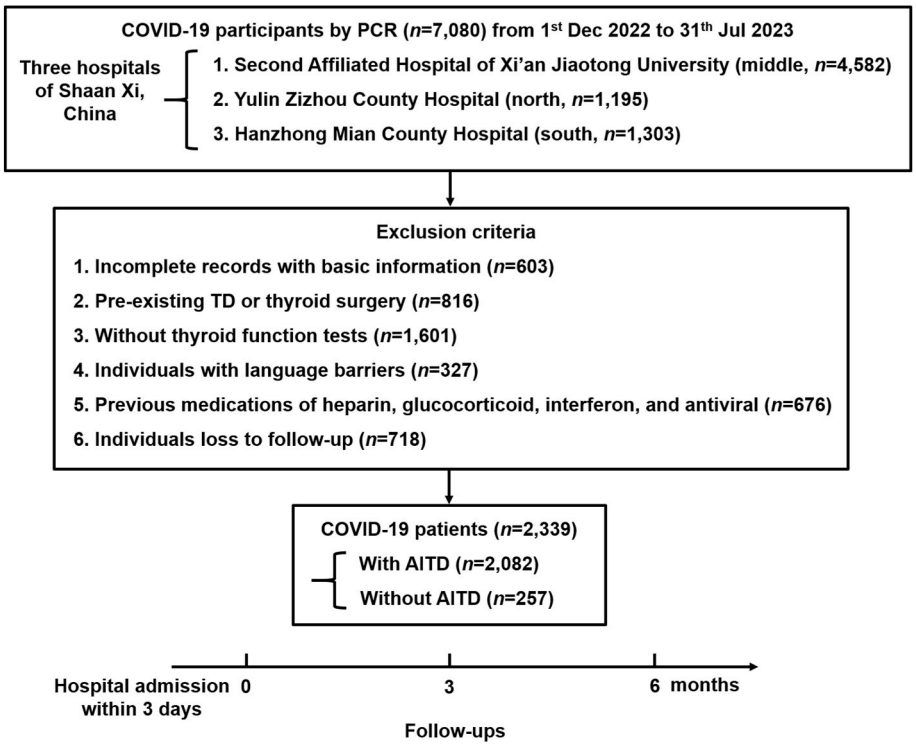

Fig. 1. The flowchart of study design. The eligible individuals were recruited from three hospitals and categorized into groups with and without AITD following strict exclusion criteria. All patients were monitored at hospital admission (baseline) to three- and six-month follow-ups.

5.74 vs. 9.15 ± 8.61, $p = 0.000$) (Table 1).

3.2. Thyroid imaging abnormalities in patients with AITD

Thyroid imaging techniques, including US, SPECT, and ^{18}F-FDG PET/CT, were utilized to identify subsequent thyroid disorders in COVID-19 patients, if applicable. US scans conducted at baseline showed increased thickness, brightness, and vascularity in the thyroid gland of patients with AITD compared to those with normal thyroid function. Follow-up US scans conducted three months later revealed further abnormalities, including thickened light spots, irregular hypoechoic areas, and new nodules (Fig. 2). SPECT scans of AITD patients displayed an indistinct outline and decreased uptake of ^{99m}Tc, consistent with subacute thyroiditis. Subsequently, these findings exhibited clearer outlines and modest enhancement after a 3-month follow-up than the baseline, indicative of resolution following subacute thyroiditis (Fig. 2). Patients with AITD who underwent ^{18}F-FDG PET/CT scans exhibited a significantly higher maximum standardized uptake value (SUV_{max}) at baseline compared to individuals with normal thyroid function ($n = 13$, 2.723 ± 0.052 vs. 0.110 ± 0.042, $p = 0.000$). Following a 3-month follow-up, the average SUV_{max} decreased but remained elevated in comparison to normal thyroid ($n = 13$, 1.305 ± 0.064 vs. SUV_{max} 0.110 ± 0.042, $p = 0.000$) (Fig. 2).

3.3. Alterations of thyroid function and inflammatory indicators in patients with AITD

Table 2 summarized thyroid functions, inflammatory, and autoimmune indicators in patients with AITD at hospital admission (baseline), 3-month, and 6-month follow-ups. Data from patients without AITD were collected at baseline. FT3 and FT4 levels in the AITD group exhibited a moderate decrease compared to the non-AITD group at baseline and the 3-month follow-up ($p = 0.000$, $p = 0.000$, $p = 0.000$, and $p = 0.000$), but no significant differences were observed after 6 months ($p = 0.092$ and $p = 0.144$). The levels of anti-Tg in patients with AITD exhibited a significant increase at baseline and during the initial 3-month follow-up ($p = 0.000$ and $p = 0.030$) compared to individuals without AITD. However, no significant difference was observed at the 6-month follow-up ($p = 0.900$). Interestingly, the TT3 levels in the AITD group demonstrated a marked alteration, with lower levels at baseline followed by an increase at the 6-month assessment compared to the non-AITD group ($p = 0.000$ and $p = 0.002$). Moreover, patients with AITD exhibited elevated levels of TSH, anti-TPO, Tg, TRAb, and rT3 compared to non-AITD individuals at baseline ($p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, and $p = 0.000$), with similar patterns observed at the 3- and 6-month follow-ups ($p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, $p = 0.000$, and $p = 0.000$). Conversely, both groups experienced significant reductions in TT4 and radioactive iodine uptake within 24 h at baseline ($p = 0.000$ and $p = 0.000$), as well as at the 3- and 6-month follow-ups ($p = 0.000$, $p = 0.000$, $p = 0.000$, and $p = 0.000$) (Table 2).

Subsequently, our analysis focused on inflammatory and autoimmune indicators, specifically the blood cell counts and autoantibody levels throughout the study (Table 2). At baseline, individuals with AITD exhibited slightly elevated counts of leukocytes and neutrophils compared to those without AITD ($p = 0.021$ and $p = 0.000$). However, the neutrophil counts in the AITD group decreased significantly throughout the follow-up ($p = 0.013$ and $p = 0.001$). In contrast, lymphocyte counts did not differ significantly between the two groups at baseline ($p = 0.108$) but showed a gradual increase by the end of the follow-up ($p = 0.000$). In the AITD group, levels of CRP and procalcitonin significantly increased at baseline ($p = 0.000$ and $p = 0.000$). After 6 months, CRP levels were considerably lower than the baseline ($p = 0.000$), while procalcitonin levels also decreased but remained elevated than the baseline ($p = 0.000$). Additionally, levels of IL-6, IL-8, IL-10, and TNF-α in the AITD group all significantly increased at baseline ($p = 0.000$, $p = 0.000$, $p = 0.000$, and $p = 0.000$). The recovery of these levels after 6 months was consistent with baseline, except for IL-10. For autoantibodies, we observed a significant decrease in anti-IFN antibodies, specifically IFN-α and IFN-γ at baseline ($p = 0.000$ and $p =$

Table 1
Main characteristics of COVID-19 patients with and without AITD at baseline.

Characteristics		Total (n = 2,339)	With AITD (n = 2,082)	Without AITD (n = 257)	p value
Age (n, %)	–	–	–	–	–
	Children (0–18 years)	100, 4.28 %	87, 3.72 %	13, 0.56 %	0.794
	Adults (19–64 years)	1393, 59.56 %	1240, 53.01 %	153, 6.54 %	
	Seniors (≥65 years)	846, 36.17 %	755, 32.28 %	91, 3.89 %	
Gender (n, %)	–	–	–	–	–
	Male	1210, 51.73 %	1077, 46.05 %	133, 5.69 %	0.995
	Female	1129, 48.27 %	1005, 42.97 %	124, 5.30 %	
Symptoms (n, %)	–	–	–	–	–
	Fever	484, 20.69 %	443, 18.94 %	41, 1.75 %	0.000**
	Cough	589, 25.18 %	564, 24.11 %	25, 1.07 %	
	Dyspnea	109, 4.66 %	55, 2.35 %	54, 2.31 %	
	Myalgia	405, 17.32 %	339, 14.49 %	66, 2.82 %	
	Fatigue	13, 0.56 %	13, 0.56 %	0, 0.00 %	
	Nasal congestion	34, 1.45 %	17, 0.73 %	17, 0.73 %	
	Gastrointestinal manifestation	40, 1.71 %	31, 1.33 %	9, 0.38 %	
	Others	665, 28.43 %	620, 26.51 %	45, 1.92 %	
Comorbidities (n, %)	–	–	–	–	–
	Cardiovascular disease	477, 20.39 %	469, 20.05 %	8, 0.34 %	0.000**
	Hypertension	504, 21.55 %	495, 21.16 %	9, 0.38 %	
	COPD	98, 4.19 %	92, 3.93 %	6, 0.26 %	
	Obesity	4, 0.17 %	4, 0.17 %	0, 0.00 %	
	Diabetes	264, 11.29 %	261, 11.16 %	3, 0.13 %	
	Others	992, 42.41 %	761, 32.54 %	231, 9.88 %	
CFRs (n, %)	–	36, 1.54 %	34, 1.45 %	2, 0.09 %	0.434
Oxygen support (n, %)	–	400, 17.10 %	357, 15.26 %	43, 1.84 %	0.867
Hospital stay (d)	–	8.83 ± 6.34	9.15 ± 8.61	6.64 ± 5.74	0.000**

Data were shown as mean ± standard deviation or sample size (n, %). *$p < 0.05$ and **$p < 0.01$ were considered statistically significant, versus the group without AITD. AITD, autoimmune thyroid dysfunction; COPD, chronic obstructive pulmonary disease; CFRs, case-fatality ratios.

0.000), with these levels remaining low after a 6-month follow-up (p = 0.000 and p = 0.000). Conversely, baseline levels of other autoantibodies, including IgG, IgA, IgM, and IgE, exhibited varying degrees of increase (p = 0.000, p = 0.000, p = 0.000, and p = 0.013), with IgM showing the earliest rise and IgA demonstrating the most substantial growth. Additionally, complement C3, C4, and C1 INH exhibited slight increases at baseline and after 6 months (baseline: p = 0.000, p = 0.000, and p = 0.000; 6-month follow-up: p = 0.000, p = 0.000, and p = 0.000) (Table 2).

3.4. The correlation between subsequent AITD and COVID-19 prognosis

When examining the correlation between the severity of COVID-19 and subsequent thyroid disorders, patients with COVID-19 were categorized based on severity as mild to moderate (78.05 %), severe (13.35 %), and critical (8.60 %). Our study revealed notable variances in thyroid-inflammatory derangements at baseline across different severities of COVID-19 (Fig. 3). Specifically, individuals in the critical group exhibited significantly lower levels of FT3 and TSH (p = 0.000 and p = 0.000), indicating decreased thyroid hormone secretion (Fig. 3A). Conversely, levels of rT3 elevated in both severe and critical cases compared to mild to moderate patients (p = 0.000 and p = 0.000). Meanwhile, critical patients exhibited a slight reduction in FT4 levels compared to those in the mild to moderate group (p = 0.025). In contrast, CRP and IL-6 levels were notably higher in critical cases than in mild to moderate patients (p = 0.013 and p = 0.035, Fig. 3A). Furthermore, a negative correlation was identified between FT3 level and hospitalization through simple linear regression analysis (r = -0.208, p = 0.000). Conversely, a positive correlation was observed between rT3 level and hospitalization (r = 0.231, p = 0.000, Fig. 3B). These findings were further supported by the ROC curve analysis, which demonstrated greater robustness for FT3 and rT3 compared to TSH, CRP, and IL-6 [area under the curves (AUCs) = 0.801, 0.705, 0.667, 0.610, and 0.654 for FT3, rT3, TSH, CRP, and IL-6]. The cutoff values (3.215 and 72.480) and Youden's index (0.497 and 0.383) of FT3 and rT3 were illustrated in Fig. 3C. Except for IL-6, the residual analysis indicated that the models for FT3, rT3, TSH, CRP, and COVID-19 prognosis demonstrated considerable statistical significance. Additionally, the Hosmer-Lemeshow test, employed as a goodness-of-fit measure for logistic regression in this study, yielded p-values of 0.880, 0.711, 0.033, 0.000, and 0.001 for FT3, rT3, TSH, CRP, and IL-6, respectively. Similarly, the p-values for FT3, rT3, TSH, CRP, and IL-6 in the likelihood ratio tests were 0.000, 0.000, 0.562, 0.568, and 0.231, respectively. These results suggested that the models for FT3 and rT3 fitted the data well and accurately predicted the prognosis of COVID-19 (Tables S2–S4).

Following the confirmation of AITD in COVID-19 patients, it was further classified into four main categories: subacute thyroiditis, Grave's disease, Hashimoto's thyroiditis, and NTIS. We observed significant differences in the distribution of COVID-19 severities for subsequent AITD among subacute thyroiditis, Grave's disease, Hashimoto's thyroiditis, and NTIS (χ^2 = 77.32, p = 0.000) (Table 3). The critical COVID-19 patients exhibited the highest proportion of NTIS (6.68 %) and the lowest proportion of Grave's disease (0.19 %). Before the logistic regression, categorical variables were appropriately assigned (Table S5). The ordered logistic regression analysis indicated that the presence of subsequent AITD was associated with an increased risk of severe COVID-19 (Table 3). Specifically, the risks of subacute thyroiditis, Grave's disease, and Hashimoto's thyroiditis concerning critical COVID-19 were found to be 0.370, 0.048, and 0.021 times higher, respectively, compared to NTIS. These results suggested that NTIS in the AITD was the most predominant risk factor for severe COVID-19 (Table 3).

4. Discussion

A rapid and large-scale outbreak of COVID-19 infection in China occurred in December 2022, since the relaxation of the "zero-COVID" policy, and was quickly terminated in just one year. Some studies focused on monitoring thyroid-inflammatory-autoimmune

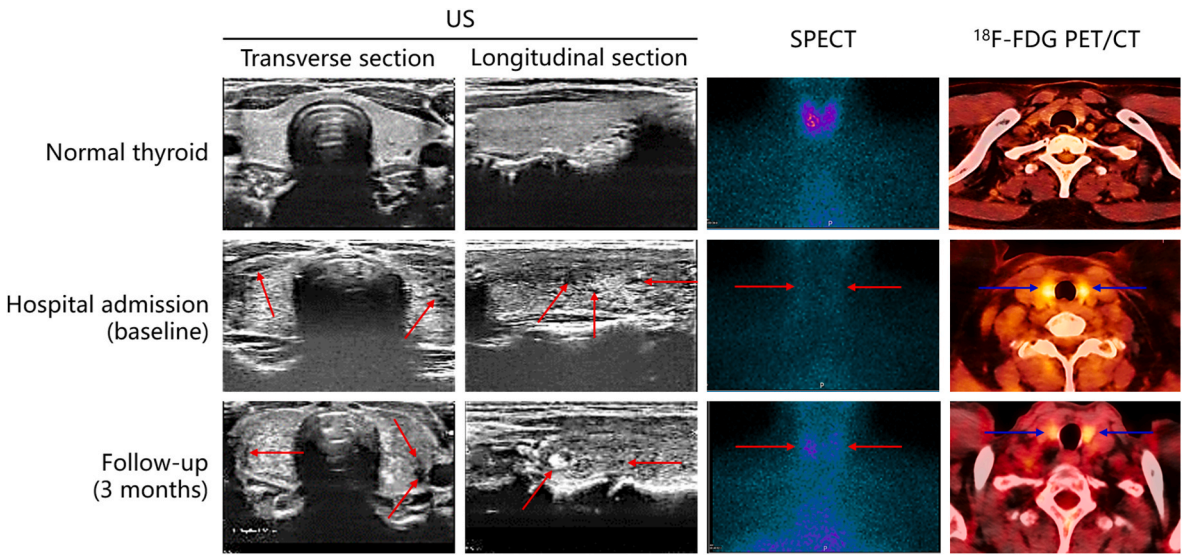

Fig. 2. Thyroid images of AITD patients by US, SPECT, and ^{18}F-FDG PET/CT. Red arrows in US: spots, irregular hypoechoic sites, and nodules; red arrows in SPECT: outlines of thyroid glands by ^{99m}Tc; blue arrows in ^{18}F-FDG PET/CT: areas of increasing glucose metabolism in thyroid glands.

Table 2
Thyroid-inflammatory indicators of COVID-19 patients at hospital admission and follow-ups.

Thyroid-inflammatory indicators	Without AITD (n = 257)	With AITD					
		Hospital admission		3-month follow-up		6-month follow-up	
		(n = 2,082)	p value	(n = 1,614)	p value	(n = 1,542)	p value
FT3 (pmol/L)	4.53 ± 0.72	3.94 ± 1.80	0.000**	4.32 ± 1.53	0.000**	4.43 ± 1.52	0.092
FT4 (pmol/L)	16.71 ± 2.07	16.04 ± 4.25	0.000**	16.06 ± 4.11	0.000**	16.45 ± 4.80	0.144
TT3 (nmol/L)	1.61 ± 0.31	1.36 ± 0.53	0.000**	1.59 ± 0.52	0.390	1.68 ± 0.47	0.002**
TT4 (nmol/L)	104.68 ± 17.29	95.62 ± 27.50	0.000**	100.05 ± 25.20	0.000**	100.02 ± 27.56	0.000**
TSH (μIU/mL)	2.07 ± 0.92	3.59 ± 2.94	0.000**	3.19 ± 2.86	0.000**	3.20 ± 2.74	0.000**
Anti-TPO (IU/mL)	12.76 ± 3.96	52.61 ± 42.87	0.000**	16.23 ± 14.12	0.000**	19.40 ± 16.22	0.000**
Anti-Tg (IU/mL)	21.07 ± 6.55	65.59 ± 20.79	0.000**	22.47 ± 20.08	0.030*	21.15 ± 19.16	0.900
Tg (ng/mL)	1.37 ± 0.94	5.53 ± 3.66	0.000**	24.89 ± 22.54	0.000**	16.46 ± 14.62	0.000**
TRAb (IU/L)	3.54 ± 2.90	7.64 ± 4.17	0.000**	10.78 ± 8.85	0.000**	8.02 ± 6.63	0.000**
rT3 (ng/dL)	52.62 ± 13.95	71.00 ± 48.05	0.000**	61.09 ± 38.59	0.000**	64.51 ± 34.73	0.000**
Radioactive iodine uptake at 24 h (%)	22.76 ± 18.51	12.19 ± 8.14	0.000**	15.32 ± 12.10	0.000**	20.80 ± 7.05	0.000**
Leukocyte (× 10^9/L)	6.21 ± 3.37	6.75 ± 4.58	0.021*	6.29 ± 1.91	0.711	6.18 ± 1.12	0.888
Neutrophil (× 10^9/L)	4.15 ± 3.28	4.95 ± 1.01	0.000**	3.63 ± 1.55	0.013*	3.47 ± 1.11	0.001**
Lymphocyte (× 10^9/L)	1.50 ± 0.64	1.58 ± 1.35	0.108	1.67 ± 0.63	0.000**	1.96 ± 0.46	0.000**
CRP (mg/L)	24.29 ± 19.11	49.33 ± 30.72	0.000**	14.77 ± 14.00	0.000**	10.27 ± 9.24	0.000**
Procalcitonin (ng/mL)	0.34 ± 0.23	0.87 ± 0.42	0.000**	0.47 ± 0.37	0.000**	0.43 ± 0.37	0.000**
IL-6 (pg/mL)	24.44 ± 18.51	57.03 ± 27.12	0.000**	20.05 ± 11.90	0.000**	24.57 ± 10.76	0.913
IL-8 (pg/mL)	18.96 ± 14.94	54.12 ± 11.34	0.000**	17.78 ± 13.49	0.200	17.02 ± 15.56	0.063
IL-10 (pg/mL)	15.17 ± 11.46	18.74 ± 9.78	0.000**	16.21 ± 4.03	0.151	16.96 ± 6.03	0.015*
TNF-α (pg/mL)	47.76 ± 27.18	83.05 ± 30.21	0.000**	64.67 ± 59.79	0.000**	45.01 ± 12.96	0.113
IFN-α (pg/mL)	2.31 ± 1.03	1.82 ± 1.73	0.000**	1.89 ± 0.59	0.000**	1.88 ± 0.15	0.000**
IFN-γ (pg/mL)	6.50 ± 5.77	2.28 ± 0.20	0.000**	2.79 ± 1.18	0.000**	2.75 ± 2.68	0.000**
IgG (g/L)	14.17 ± 5.07	18.30 ± 3.00	0.000**	18.88 ± 3.64	0.000**	17.20 ± 5.14	0.000**
IgA (g/L)	1.87 ± 1.24	4.76 ± 1.95	0.000**	4.01 ± 2.22	0.000**	2.15 ± 1.09	0.001**
IgM (g/L)	1.51 ± 0.50	3.58 ± 4.87	0.000**	1.79 ± 0.53	0.000**	1.67 ± 0.18	0.000**
IgE (IU/mL)	41.58 ± 31.53	46.60 ± 17.90	0.013*	48.68 ± 31.41	0.001**	38.26 ± 21.12	0.105
Complement C3 (g/L)	1.03 ± 0.14	1.12 ± 0.40	0.000**	0.99 ± 0.32	0.001**	0.96 ± 0.15	0.000**
Complement C4 (g/L)	0.21 ± 0.11	0.29 ± 0.03	0.000**	0.23 ± 0.13	0.009**	0.24 ± 0.10	0.000**
C1 INH (g/L)	0.30 ± 0.09	0.37 ± 0.05	0.000**	0.35 ± 0.07	0.000**	0.35 ± 0.12	0.000**

Data were shown as mean ± standard deviation or sample size (n, %). *$p < 0.05$ and **$p < 0.01$ were considered statistically significant, versus the group without AITD. AITD, autoimmune thyroid dysfunction; FT3, free triiodothyronine; FT4, free thyroxine; TT3, total triiodothyronine; TT4, total thyroxine; TSH, thyroid stimulating hormone; Anti-TPO, anti-thyroid peroxidase; Anti-Tg, antithyroglobulin antibody; Tg, thyroglobulin; TRAb, thyrotropin receptor antibody; rT3, reverse triiodothyronine; CRP, c-reactive protein; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; TNF-α, tumor necrosis factor-α; IFN-α, interferon-α; IFN-γ, interferon-γ; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; IgE, immunoglobulin E; C1 INH, C1 esterase inhibitor.

derangements in patients with COVID-19, but the association between COVID-19 infection and thyroid dysfunction remained controversial. In this multicenter retrospective cohort study, we discovered a strong association among COVID-19 infection, thyroid dysfunction, and AITD: COVID-19 infection was closely associated with thyroid dysfunction, and the subsequent AITD might aggregate the COVID-19 severity.

The predominant symptoms we observed in COVID-19 patients with AITD included cough (25.18 %), fever (20.69 %), and myalgia (17.32 %), similar to the global scoping review [19]. Common comorbidities among AITD cases contained hypertension (21.55 %), cardiovascular

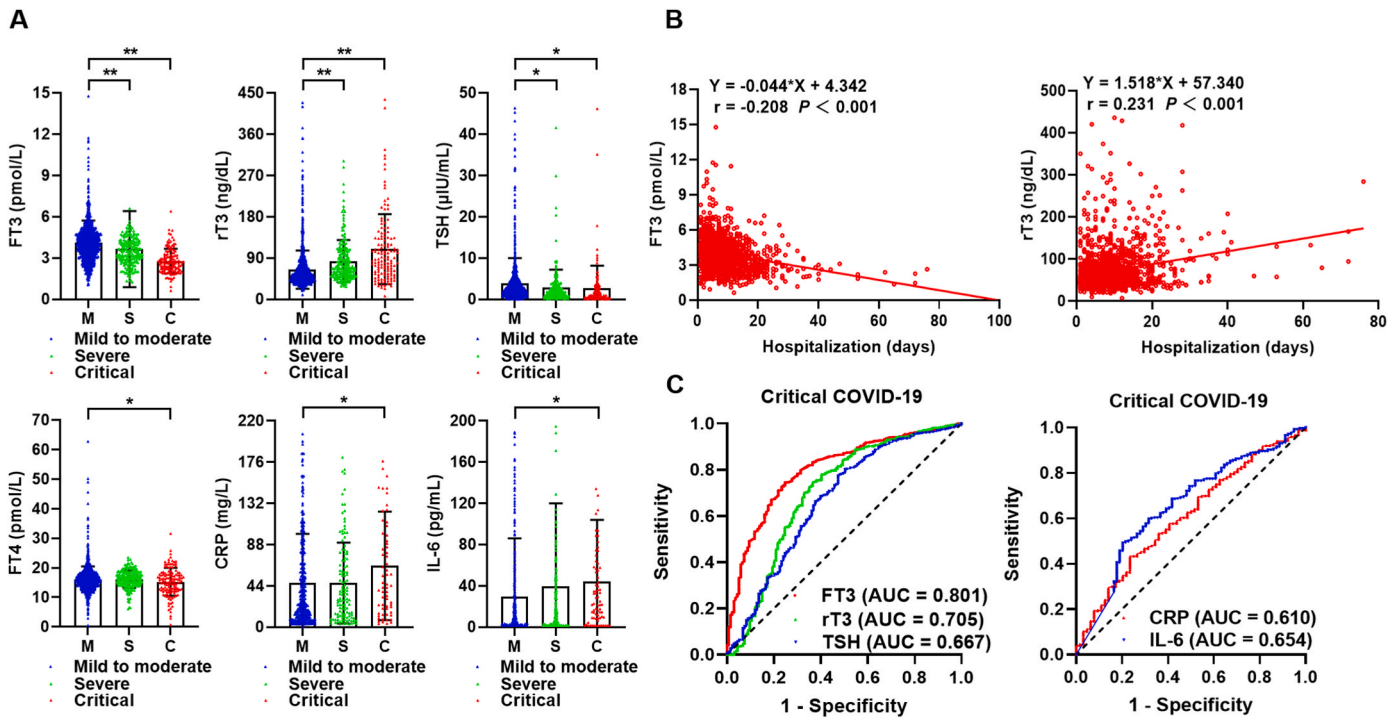

Fig. 3. The impacts of thyroid-inflammatory indicators on COVID-19 severity. (A) FT3, rT3, TSH, FT4, CRP, and IL-6 alterations in the groups of COVID-19 severities; (B) FT3 and TSH correlations with hospitalization in COVID-19 patients; (C) ROC curves of FT3, rT3, TSH, CRP, and IL-6 in critical COVID-19 patients. Data were shown as mean ± SD, $*p < 0.05$, $**p < 0.01$.

Table 3
Ordered logistic regression of subsequent AITD for COVID-19 severity.

AITD (n, %)	COVID-19 severity (n = 2,082)			Ordered logistic regression					
	Mild to moderate (n = 1,625)	Severe (n = 278)	Critical (n = 179)	*B*	*SE*	*95 % Wald CI*	*Wald*χ^2	*p* value	OR (95 % CI)
Subacute thyroiditis	562, 26.99 %	75, 3.60 %	11, 0.53 %	−0.994	0.157	(-1.301, −0.687)	40.234	0.000**	0.370 (0.272, 0.503)
Grave's disease	49, 2.35 %	6, 0.29 %	4, 0.19 %	−0.874	0.442	(-1.741, −0.007)	3.902	0.048*	0.417 (0.175, 0.993)
Hashimoto's thyroiditis	257, 12.34 %	43, 2.07 %	25, 1.20 %	−0.406	0.175	(-0.749, −0.062)	5.368	0.021*	0.667 (0.473, 0.939)
NTIS	757, 36.36 %	154, 7.40 %	139, 6.68 %	0.000	–	–	–	–	1.000 (-, -)

$*p < 0.05$ and $**p < 0.01$ were considered statistically significant, versus the group NTIS; AITD, autoimmune thyroid dysfunction; NTIS, nonthyroidal illness syndrome.

disease (20.39 %), and diabetes (11.29 %), which were consistent with the studies based on epidemiology worldwide [20]. Furthermore, our study revealed that individuals with AITD experienced longer average hospital stays than those without AITD, albeit slightly shorter than the global average of more than 10 days, with durations ranging from 21 days in South America to 9 days in Africa [21].

The onset of the COVID-19 infection was found to be a precipitating trigger for thyroid dysfunction. However, the absence of routine thyroid function tests in COVID-19 patients often resulted in a lack of comprehensive data, particularly regarding antibody levels. Drawing on prior research, our extensive analysis of thyroid-inflammatory derangements in patients with AITD was conducted across multiple medical facilities. It was observed that thyroid function and inflammatory indicators gradually normalized within 6 months following acute COVID-19 infection, albeit not completely reverting to baseline levels in our study. The thyroid function manifestations observed in patients with AITD were complex, with decreased levels of FT3 and FT4 at both baseline and after 3 months. This was accompanied by an increase in rT3, indicating that NTIS likely played a significant role in the acute COVID-19 infection. Typically, NTIS manifested as decreased levels of FT3 and TT3, while TSH levels remained stable or decreased, suggesting a decline in hypothalamic thyrotropin-releasing hormone secretion and a chronic, severe illness resulting in impaired thyroid function [22]. It was important to acknowledge that TSH levels in patients with AITD exhibited considerable variability across various studies. Notably, significant disparities in TSH levels were observed between AITD and non-AITD patients both at baseline and during subsequent evaluations. Interestingly, our findings revealed a notable elevation in TSH levels, contrary to typical findings. A previous report suggested a potential increase in TSH levels of up to 20 μIU/mL during the recovery from NTIS, primarily driven by the negative feedback loop resulting from decreased thyroid hormones [23], which might partially explain why we observed an increase in the TSH level among AITD patients. Limited research had been conducted on alterations in thyroid antibodies, but our study confirmed elevated levels of anti-TPO, anti-Tg, and TRAb in AITD patients, demonstrating that COVID-19 infection overstimulated the immune response and resulted in increasing thyroid antibodies. Furthermore, radioactive iodine uptake at 24 h in AITD patients showed a significant decrease at baseline, which persisted even after 6 months, and was closely associated with COVID-19-induced thyroiditis. Based on our findings, baseline FT3 levels might serve as an indicator of the severity of COVID-19 prognosis, with elevated rT3 levels emerging as a

significant prognostic factor in cases of severe COVID-19. Conversely, the utility of TSH and FT4 levels in gauging the severity of COVID-19 appeared to be limited.

In addition, our study found that AITD patients exhibited thyroid dysfunction alongside a significant cytokine storm induced by COVID-19, leading to an elevated cytokine storm both initially and during subsequent assessments, aligning with existing studies [24,25]. Additionally, AITD patients displayed normal lymphocyte counts, slightly elevated leukocyte and neutrophil counts at baseline, and a decreased leukocyte-neutrophil/lymphocyte ratio during the follow-ups. These findings, consistent with those of a retrospective cohort study conducted at two prominent hospitals, were associated with a heightened risk of poor outcomes in COVID-19 patients [26]. The proliferation of these cells might be linked to an exaggerated response by the human immune system. The elevated levels of leukocytes and neutrophils could be attributed to the excessive release of chemokines by the immune response, as well as secondary bacterial infections [27,28]. The increase in lymphocyte counts primarily represented a crucial aspect of the immune response to COVID-19. Activated B lymphocytes generated neutralizing antibodies that attached to extracellular viral particles and led to their eradication, while CD8-positive T lymphocytes identified and eliminated infected cells, and then prevented host infection [29,30].

Our study also revealed that the subsequent AITD resulting from thyroid dysfunction might exacerbate the severity of COVID-19. COVID-19-related AITD was a thyroid-specific autoimmune disease mediated by Th1 lymphocytes, such as NTIS, subacute thyroiditis, Hashimoto's thyroiditis, Grave's disease, etc. [13,31]. Our multicenter retrospective cohort study identified a range of AITD types, with NTIS being the most prevalent across all severity categories of AITD. NTIS represented an adaptive thyroid response to stress, critical illness, and malnutrition. Prior research indicated a prevalence of NTIS ranging from 30 % to 64 % [32]. Similarly, NTIS in our study was observed in 46.58 %, 55.40 %, and 77.65 % of cases classified as mild to moderate, severe, and critical COVID-19, respectively. The ordered logistic regression showed that NTIS was supposed to be the most prevalent risk factor for critical COVID-19. Subacute thyroiditis was identified as the second most pervasive AITD either in mild to moderate or severe COVID-19 patients, which was characterized by transient hyperthyroidism, reduced uptake of ^{99m}Tc in SPECT images, and a notable decrease in radioactive iodine uptake at 24 h, ultimately leading to permanent hypothyroidism. Further research had indicated a potential development of Grave's disease and Hashimoto's thyroiditis several months following subacute thyroiditis [31,33], with the scholar noting a significant increase in anti-TPO and anti-Tg in cases of Hashimoto's thyroiditis [33]. Furthermore, levels of anti-TPO and anti-Tg increased significantly, as did TRAb level in our study. Therefore, the occurrence of AITD in COVID-19 patients with thyroid dysfunction should be continuously evaluated.

The pathophysiological mechanisms of AITD in the context of COVID-19 infection were primarily focused on four key points: hyperactivation of the human immune system, molecular mimicry between host and viral antigens, NETs, and alterations in the transcription of virus-induced immune genes [13,31,34]. The immune response to COVID-19 in humans was characterized by an excessive proinflammatory cytokine storm driven by CD4-positive T helper cells, which were responsible for the production of a significant proportion of proinflammatory mediators, including IL-1, IL-6, IL-8, TNF-α, and IFN-γ [31]. The study demonstrated that the JAK-STAT, NFKB1/RELA, and IFNAR1 pathways, among other inflammation signaling pathways, played a significant role in the development of a severe cytokine storm in COVID-19, which was found to be associated with thyroid neoplasia and AITD [9,35]. Moreover, it had been proposed that molecular mimicry might serve as an additional potential mechanism through which COVID-19 could induce AITD, as antibodies targeting the S-protein of COVID-19 had demonstrated significant immunologic cross-reactivity with human thyroid peroxidase and glutamic decarboxylase, but limited cross-reactivity with thyroglobulin, leading to the formation of AITD [36]. Neutrophils played a crucial role in innate immunity through the activation of NETs. Once neutrophils released the NETs, which included not only histones, chromatin, and DNA, but also secreted toxic enzymes, which increased the damage to the thyroid gland [13]. The observed differences in immune gene transcription between the virus-free and virus-infective thyroids due to SARS-CoV-2, which showed heightened activation of the innate immune response, were attributed to the up-regulation of both the type I and type II-related IFN pathways [37]. It was evident that AITD following COVID-19, such as subacute thyroiditis, might be a result of the SARS-CoV-2 virus replicating within the thyroid gland [35]. The prolonged inflammation and damage observed in this condition could potentially be linked to heightened macrophage activity induced by the IFN pathway [38]. Additional research was imperative for elucidating the molecular mechanisms underlying COVID-19-related thyroiditis and identifying potential molecular targets for mitigating autoimmune responses. Thus, enhanced comprehension of COVID-19 and its associated complications could facilitate the implementation of early preventive measures to decrease the incidence and severity of AITD.

The study was constrained by several limitations, predominantly arising from inherent biases associated with a retrospective design, including hindsight bias, survivorship bias, outcome bias, confirmation bias, and nostalgia bias. Mitigating these retrospective biases necessitated the implementation of strategies such as structured reflection and a conscious recognition of the limitations imposed by hindsight. These strategies included documenting decisions in real-time, conducting structured retrospectives, creating a time gap for reflection, etc. Another key bias in our study was the selection bias caused by overly stringent exclusion criteria. This bias potentially led to a sample that was not representative of the broader population, thereby limiting the generalizability of our findings. To mitigate this selection bias, several strategies were considered, including the implementation of broader inclusion and exclusion criteria to capture a more diverse range of participants, randomization, stratified sampling, expanding the sample size, etc. To improve the generalizability of our findings on thyroid dysfunction, AITD, and COVID-19, we proposed the following strategies in the future study: (1) Ensure diverse and representative sampling by including participants from various demographic groups, geographic regions, and with differing levels of COVID-19 severity; (2) Conduct multi-center studies through collaboration across different countries to collect data that can be more broadly applicable; (3) Report detailed contextual information, including healthcare systems, public health measures, and cultural factors; (4) Promote replication of studies in different settings and populations to validate findings and assess their applicability. Additionally, non-routine assessments of thyroid functions at baseline, resulting in potential selection bias and incomplete test results, particularly for antibody indicators, such as TRAb, were also worth noting. While thyroid dysfunction in AITD patients typically resolved within six months without intervention, the limited follow-up introduced uncertainty regarding long-term alterations in thyroid function post-COVID-19 recovery, so it was imperative to monitor the long-term effects of COVID-19 on thyroid functions. Furthermore, the data collection on thyroid functions and inflammatory indicators in AITD patients was influenced by various factors such as demographics, clinical settings, and health system resources, leading to potential heterogeneity in the data. The strengths of the study included the enrollment of COVID-19 patients from multiple centers and the exclusion of potential confounding variables, such as drug treatments impacting thyroid functions. Also, the study collected both morphological (ultrasonography images) and functional thyroid assessments (nuclear medicine images) to accurately assess thyroid functions.

5. Conclusion

In this multicenter retrospective cohort, a robust association among COVID-19 infection, thyroid dysfunction, and AITD has been observed:

COVID-19 is closely associated with thyroid dysfunction, while subsequent AITD may aggravate the poor prognosis of COVID-19. The most prevalent AITD correlated with COVID-19 is NTIS, followed by subacute thyroiditis, Hashimoto's thyroiditis, and Grave's disease. The baseline FT3 may serve as a valuable indicator for assessing the severity of COVID-19, and elevated rT3 emerges as a significant prognostic factor in COVID-19 severity. Conversely, TSH and FT4 levels appear to be limited in gauging the COVID-19 prognosis. Our study has evaluated the effects of COVID-19 on thyroid functions and assessed the subsequent AITD on COVID-19 prognosis. Therefore, more research is required to determine the long-term prognosis of COVID-19 on a large scale.

CRediT authorship contribution statement

Jia Di: Writing – review & editing. **Xiaodong Ma:** Software. **Tao Wu:** Project administration. **Eryue Qiao:** Data curation. **Mojtaba Salouti:** Writing – review & editing. **Yu Zhong:** Resources. **Qian Xia:** Resources. **Danfeng Kong:** Visualization. **Min Hao:** Project administration. **Qingwei Xie:** Conceptualization. **Zhuang Ge:** Formal analysis. **Dongzheng Liu:** Validation. **Juanyi Feng:** Project administration. **Xianghong Zheng:** Writing – review & editing.

Ethics approval and consent to participate

This study was obtained from the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University and carried out under the Declaration of Helsinki.

Consent for publication

All authors gave their consent for publication.

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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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtauto.2024.100255.

Data availability

Data will be made available on request.

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