



Association between Thyroid Disease and Severe Coronavirus Disease 2019 (COVID-19) Infection: A Meta-Analysis

Juan Xu¹, Yang Li², Quansong Xia², *Qiong Shi²

1. Department of Internal Medicine, The People's Hospital of Guandu District, 63 Yingfeng Road, Kunming 650200, China
2. Department of Clinical Laboratory, The Third Affiliated Hospital of Kunming Medical University, 519 Kunzhou Road, Kunming 650118, China

*Corresponding Author: Email: shiqiong@kmmu.edu.cn

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Abstract

Background: COVID-19 has resulted in an emerging respiratory infection with a pandemics diffusion since December 2019. We aimed to elucidate whether the presence of thyroid disease might increase the risk of severe COVID-19 infection.

Methods: Studies reporting seriously ill in COVID-19 patients with and without thyroid disease combined were searched and 11 relevant studies were subjected to our analysis, and pooled odds ratios (ORs) together with 95% confidence intervals (CIs) were calculated by using STATA and Review Manager Software.

Results: In total, 2,995 COVID-19 patients were included in this study. The pooled ORs were calculated using a fixed-effects model according to the heterogeneity. The pooled results revealed that thyroid disease was associated with severe COVID-19 infection in patients (OR = 2.14, 95 % CI: 1.23–3.72, $P = 0.007$). In the subgroup analysis by type of thyroid disease, hypothyroidism was positively associated with risks of severe COVID-19 infection (OR = 4.78, 95 % CI: 1.59–14.36, $P = 0.005$), however, no obvious difference was found in the risk regarding the severe COVID-19 infection amongst hyperthyroidism or unclassified thyroid disease. In addition, subgroup analysis stratified by ethnic groups demonstrated that thyroid disease was linked to the risks of severe COVID-19 infection in Asian patients (OR = 2.41, 95 % CI: 1.30–4.48, $P = 0.005$) rather than non-Asian (OR = 1.31, 95 % CI: 0.35–4.87, $P = 0.684$).

Conclusion: This study indicates a correlation between thyroid disease and severe COVID-19 infection.

Keywords: COVID-19, SARS-CoV-2, Thyroid disease, Meta-analysis

Introduction

Novel COVID-19, which appeared in December 2019, has a strong ability of early person-to-person transmission and quickly spread to almost all countries worldwide (1, 2). The WHO has named pneumonia caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) COVID-19 and declared it a Pub-

lic Health Emergency of International Concern (3, 4).

Unfortunately, both the severe rate and fatality rate in COVID-19 infection are still increasing quickly. Therefore, identifying the predictors of serious COVID-19 infection is necessary for guiding early intervention treatment. The endo-



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crine metabolic disorders could increase the risk of getting the SARS-CoV-2 (5-7), and the thyroid hormone might be a risk factor for coronavirus infection by modifying the relationship between coronaviruses and integrin $\alpha v\beta 3$ in the target epithelial cells of the airway (8). As SARS-CoV-2 may invade human cells through angiotensin-converting enzyme 2 (ACE2) receptor (1, 9), which was highly expressed in the thyroid and associated with immune signatures in patients (2), however, few studies provide clear evidence regarding the relationship between thyroid disease and SARS-CoV-2 virus infection or the risk of developing more severe COVID-19 disease.

Hence, the purpose of this study was to explore the potential correlation between thyroid disease and serious COVID-19 infection.

Methods

Literature search and data extraction

Articles published up to September 2020 from PubMed, Web of Science, and China National Knowledge Infrastructure were searched by using the key words “thyroid disease” OR “hyperthyroidism” OR “hypothyroidism” OR “clinical characteristics” AND “coronavirus disease 2019”, with no language restrictions. Thyroid disease included in this meta-analysis referred to hyperthyroidism and hypothyroidism. Studies that involved thyroid disease and clinical characteristics of patients with severe and non-severe COVID-19 infection were included. The studies included in this meta-analysis were original studies that reported odds ratios (ORs) with 95% confidence intervals (CIs) or provided useful data to calculate ORs and 95% CIs. Patients entrance the ward of ICU and non-ICU were also categorized into a severe and non-severe subgroup. Studies, which were preprint, were also included and all studies were independently verified against the inclusion and exclusion criteria by two investigators. Useful information was extracted from each included study. In addition, all included literature was evaluated using the Newcastle-Ottawa Scale (NOS) (10). These processes were

also carried out independently by two investigators (Xia and Xu).

Definition of thyroid disease

Manifestations of thyroid disease include hyperthyroidism and hypothyroidism (1). Hyperthyroidism: current recommendations of the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) concur and endorse decreased sensitive thyroid-stimulating hormone (TSH) measurements and elevated free thyroxine (FT4) levels to confirm the diagnosis of hyperthyroidism; (2) Hypothyroidism: an endocrine disorder in which the thyroid fails to secrete adequate amounts of thyroid hormone. An elevated sensitive TSH measurement and a decreased free thyroxine will confirm clinical suspicions of hypothyroid disease (11). Studies included in this meta-analysis did not clarify how researchers define hyperthyroidism, hypothyroidism, and thyroid alteration.

Statistical analysis

Pooled ORs and 95% CIs were estimated by using STATA (v. 12.0; STATA CORP LP, College Station, TX, USA) and Review Manager Software (v.5.2. The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), respectively. Additionally, to assess the heterogeneity between studies, χ^2 -based Q statistics and I^2 metrics were used in this meta-analysis and I^2 values of 25%, 25–50%, or 50% indicated low, moderate, or high heterogeneity, respectively (12). When $I^2 < 50\%$, the pooled ORs were estimated using a fixed-effects model; otherwise, a random-effects model was used. Simple and elementary inequalities were used to calculate the mean and variance for the trials when some relevant articles only reported the median and interquartile range (13). Funnel plots, Begg's tests, and Egger's tests were generated to examine the possibility of publication bias. Begg's test or Egger's test with $P > 0.05$ was considered as no publication bias. Sensitivity analysis was performed by removing one study at a time to assess the stability of these results.

Results

Each paper's first author, country, sample size, and other useable information were available on a database, which was constructed based on the data extracted from 11 relevant studies that met the inclusion criteria (14-24). A total of 2,105 articles related to our keywords were retrieved (Table 1), and Fig. 1 summarized the search strategy of this study. Overall, 2,082 articles were excluded

after the titles, key words, and abstracts were screened. The full texts or entire content of 23 articles were further reviewed, another 12 articles were eliminated (with 10 articles eliminated for not providing usable data and another 2 articles eliminated due to the repetitive articles in different languages); thus, 11 articles remained for further review. In addition, all included studies were evaluated according to the Newcastle-Ottawa Scale, and all included studies were of high quality with a NOS score ≥ 6 (Table 1).

Table 1: Characteristics of the included studies

Study	Country	Sample size	Age (Mean \pm SD)	Thyroid disease type	Study design	Thyroid disease group		Non-Thyroid disease group		NOS Score
						Severe patients	Non-Severe patients	Severe patients	Non-Severe patients	
Ming Xu 2020	China	23	46.2 \pm 9.1	Hypothyroidism	Retrospective cohort	1	0	3	19	7
Ying Sun 2020	China	63	24.3 \pm 9.7	NR	Retrospective cohort	0	3	19	41	6
Sulaiman Almazeedi 2020	Kuwait	1096	47.0 \pm 37.1	Hypothyroidism	Retrospective cohort	3	22	39	1032	6
Jinjin Zhang 2020	China	140	56.5 \pm 10.3	NR	Retrospective cohort	4	1	54	81	7
Hongmei Yue 2020	China	86	42.1 \pm 17.6	Hyperthyroidism	Retrospective cohort	0	1	44	41	7
Min Cao 2020	China	198	50.1 \pm 16.3	NR	Retrospective cohort	1	5	18	174	7
Yanrong Wang 2020	China	55	42.3 \pm 16.8	Hyperthyroidism	Retrospective cohort	0	1	2	52	6
Mohammed Shabrawishi 2020	Saudi Arabia	150	46.1 \pm 15.3	Hyperthyroidism	Retrospective cohort	3	6	13	128	7
Jiyeon Lee 2020	Korea	694	52.1 \pm 18.3	NR	Retrospective cohort	2	6	135	551	6
Antoni SisÓ-Almirall 2020	Spain	322	56.7 \pm 17.8	Thyroid alterations	Retrospective cohort	3	11	53	255	6
Shijiao Yan 2020	China	168	49.6 \pm 19.4	NR	Retrospective cohort	1	1	35	131	6

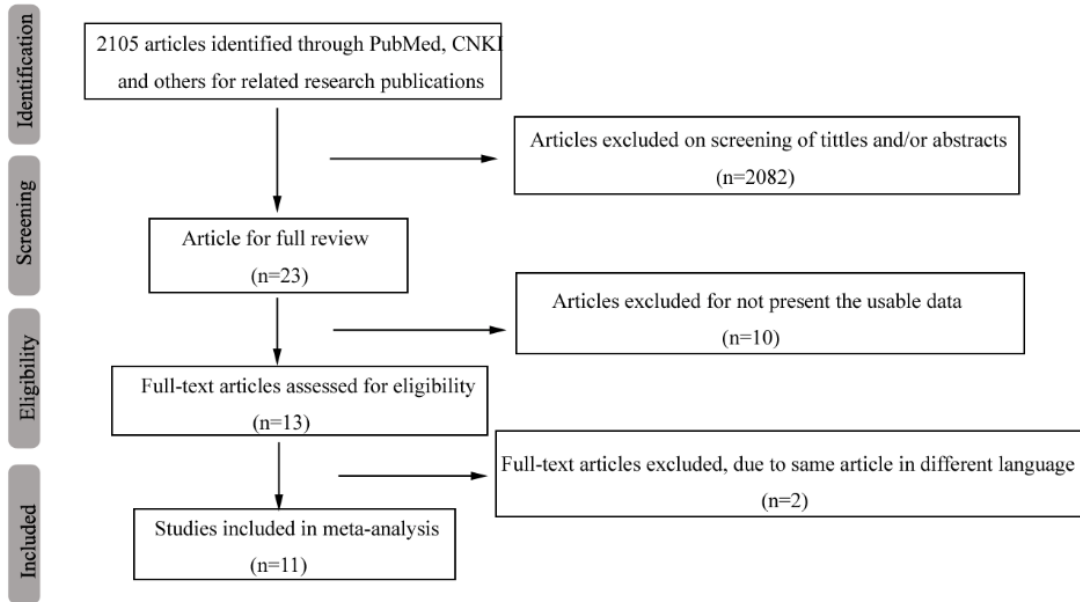


Fig. 1: Flow diagram of the search and selection process in this study.

In total, 2,995 patients with COVID-19 were included in this study. The pooled ORs were estimated using a fixed-effects model. The pooled results revealed that thyroid disease was associat-

ed with severe COVID-19 infection in patients (OR = 2.14, 95 % CI: 1.23–3.72, $P = 0.007$) (Fig.2).

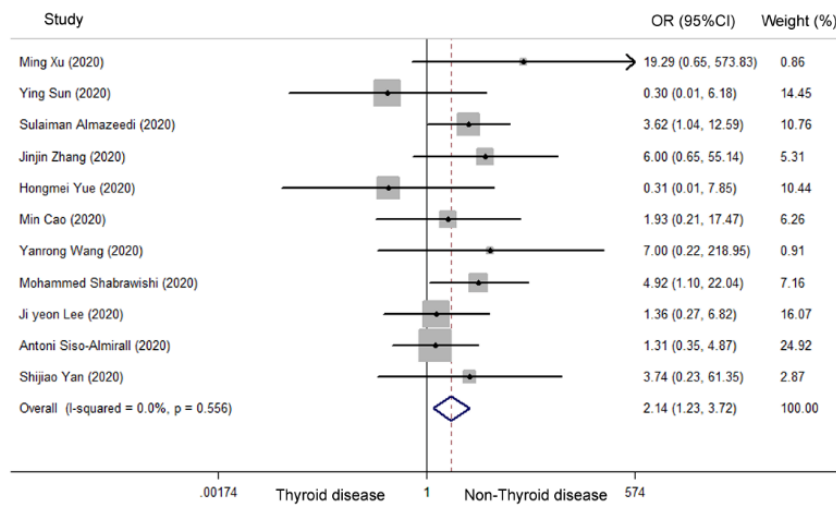


Fig.2: Forest plot of severe infection in COVID-19 patients with or without Thyroid disease.

In the subgroup analysis by type of thyroid disease, hypothyroidism was positively associated with risks of severe COVID-19 infection (OR =

4.78, 95 % CI: 1.59–14.36, $P = 0.005$), however, no obvious difference was found in the risk regarding the severe COVID-19 infection amongst

the hyperthyroidism (OR = 2.42, 95 % CI: 0.69–8.56, $P = 0.170$), thyroid alterations (OR = 1.31, 95 % CI: 0.35–4.87, $P = 0.684$), or unclassified thyroid disease (OR = 1.80, 95 % CI: 0.74–4.39, $P = 0.196$) (Fig.3). As reports uncovered that ACE2-expressing lung cells were more abundant in Asian males, which was linked to COVID-19 infection (25). Next, subgroup analysis stratified

by ethnic groups was also conducted and a fixed-effects model was used. Our results demonstrated that thyroid disease was linked to the risks of severe COVID-19 infection in Asian patients (OR = 2.41, 95 % CI: 1.30–4.48, $P = 0.005$) rather than non-Asian (OR = 1.31, 95 % CI: 0.35–4.87, $P = 0.684$) (Fig.4).

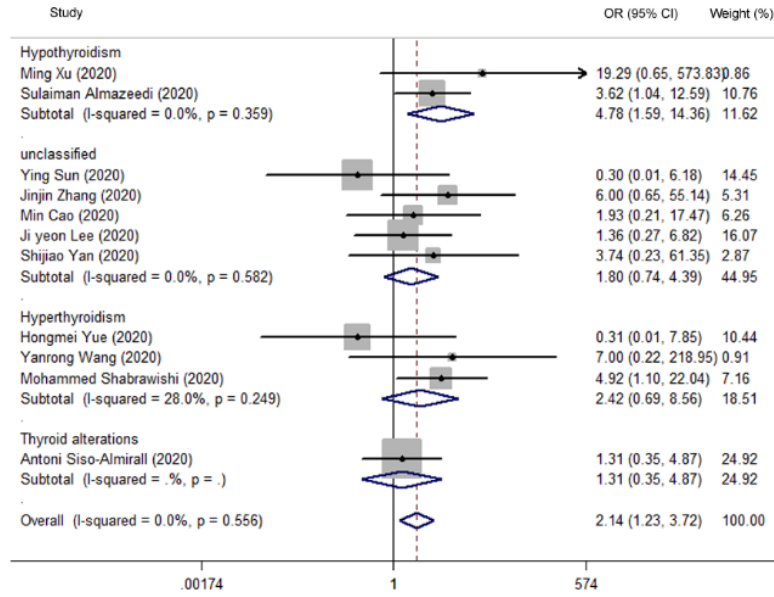


Fig.3: Forest plot that demonstrates the association of thyroid disease with severe COVID-19 disease: subgroup analysis by type of thyroid disease

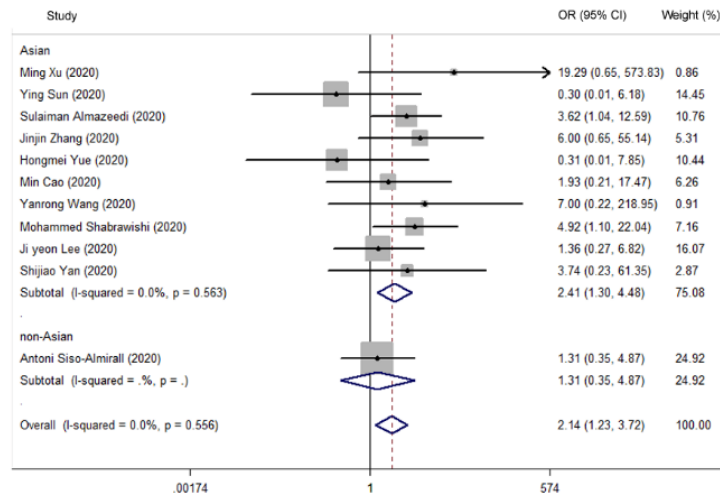


Fig. 4: Forest plot that demonstrates the association of thyroid disease with severe COVID-19 disease: subgroup analysis stratified by ethnic groups

We also analyzed the sensitivity by removing one study at a time to assess the stability of these results. The pooled ORs were not distinctly changed, with stable results. Funnel plots were drawn by Review Manager Software to determine the risk of bias, and it was symmetric (Fig. 5),

indicating no clearly identified publication bias. Next, STATA software was used to perform Begg's test and Egger's test to evaluate publication bias. No significant publication bias was found via statistical methods (Begg's test $P = 0.983$; Egger's test $P = 0.959$).

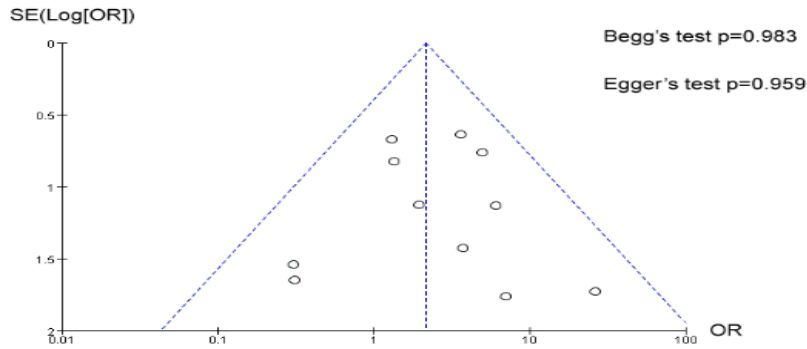


Fig. 5: Funnel plot analysis to detect publication bias

Discussion

Thyroid disease is usually caused by autoimmune conditions and almost 80% of these diseases are determined by genetic factors, while environmental factors accounting for 20%. Viral infections including those with Epstein Barr and Hepatitis C viruses have already been judged potential environmental triggers (26, 27). Nevertheless, the relationship between thyroid disease and SARS-CoV-2 virus infection or the risk of developing more severe COVID-19 disease is not fully understood at present.

In this study, altogether 2,995 COVID-19 patients were included. The pooled results showed a significant association between thyroid disease and severe COVID-19 infection (OR = 2.14, $P = 0.007$). Some reasons might explain why thyroid disease caused severe COVID-19 infection. Firstly, thyroid hormones have been demonstrated to play a pivotal role in the regulation of innate immune response in some reports (28). Therefore, the disorders of thyroid hormones in thyroid disease may cause dysregulation of innate immune response, which was considered especially im-

portant in antiviral immunity of our body to fight off the SARS-CoV-2 virus. Secondly, the disorder of innate immune response also led to elevated levels of cytokine, decreased levels of NK cells, and increased levels of neutrophil, which were closely related to severe COVID-19 infection (29). In this study, the results of subgroup analysis based on thyroid disease types demonstrated that hypothyroidism was positively associated with risks of severe COVID-19 infection instead of hyperthyroidism or other unclassified thyroid diseases. Even though some reports demonstrated that thyroid hormones may contribute to target cell uptake of coronavirus and regulate the expression of cytokine genes, some of which are components of the 'cytokine storm' of viral infections (8, 30), furthermore the changes in serum TSH and total triiodothyronine (T₃) levels may be important manifestations of the courses of COVID-19 (31). However, due to the limited number of patients with thyroid disease enrolled in this study, this might be the reason that hyperthyroidism did not showed any statistical significance. Hence, considering the limitation

of sample size, the results of subgroup analysis should be interpreted with caution.

The report uncovered that ACE2-expressing lung cells were more abundant in Asian males, which was linked to COVID-19 infection (25). To discover if the severity of COVID-19 infection was different in thyroid disease patients with different ethnic backgrounds, subgroup analysis stratified by ethnic groups was also conducted in this study, and results demonstrated that thyroid disease was linked to the risks of severe COVID-19 infection in Asian patients (OR = 2.41, $P = 0.005$) rather than non-Asian. On the other hand, an elevated level of pro-inflammatory cytokines was examined in patients with thyroid disease (32, 33), which were associated with the development of severe COVID-19 infection (34). However, there is still no clear evidence that if the level of pro-inflammatory cytokines were different in thyroid disease patients with different ethnic backgrounds. Furthermore, enrolled patients in this study were mainly Asian and the proportion of non-Asian patients was low, therefore, more studies of thyroid disease patients with COVID-19 in different ethnic backgrounds, such as Caucasian, African, and others should be conducted in the future.

From a pathophysiological point of view, previous researches examining the pathology of thyroid in Severe Acute Respiratory Syndrome suggested some mechanisms of thyroid organ damage such as host immune overreaction, immune deficiency related to infection, destruction of lymphocytes, and inhibition of the innate immune response (35, 36), which indicate that Severe Acute Respiratory Syndrome might lead to thyroid dysfunction. Furthermore, as the expression level of ACE2 was highest in thyroid among other organs, which is used as a host cell receptor to invade human cells by SARS-CoV-2 and prompt a reliable mechanism for pathophysiology of thyroid disease in COVID-19 (2, 37). Based on the above available findings add to our results that COVID-19 infection might lead to thyroid dysfunction followed thyroid dysfunction caused severe COVID-19 infection, in turn, and this is a vicious cycle. So, a prompt evaluation of thyroid

hormones may ameliorate disease progression in patients with COVID-19 by early diagnosis and appropriate therapy. However, due to the lack of usable data about thyroid hormone level and the results of thyroid function tests were not available, there is no direct evidence to show the association between COVID-19 severity and thyroid hormone level itself.

Limitations

Though we tried to explore the possible relationship between thyroid disease and risk of severe COVID-19 infection, some limitations of this meta-analysis should be noted. First, the severity of COVID-19 has known to be affected by many other clinical factors, such as age, gender, and diabetes, however, due to the lack of usable data, we could not control the well-known confounding factors of COVID-19 infection by performing multi-regression analysis, which may lead to bias risk. Hence, more studies with a large sample size and detailed data must be pursued in the future. Second, some studies included in this meta-analysis did not clarify the manifestations (hyperthyroidism or hypothyroidism) of thyroid disease. Variations in the definition for thyroid dysfunction, timing of the thyroid dysfunction, as well as if the dysfunction was treated, would greatly affect the results. Furthermore, in case of patients with thyroid dysfunction, thyroid hormone level could be normal when thyroid hormone or anti-thyroid drugs were used. Nevertheless, due to the lack of usable data about thyroid hormone level, there is no direct evidence to show the association between COVID-19 severity and thyroid hormone level itself. Thirdly, since several unpublished articles and abstracts were not available in this study, potential publication bias might arise. Additionally, due to the language criteria, only studies published in English or Chinese were included; this language restriction might also lead to bias risk and affect the results. Despite all the above limitations, our study confirmed that there is a correlation between thyroid disease and severe COVID-19 infection. Nowadays, the research on the relationship between thyroid disease and COVID-19 begins to show a

trend of data explosion, and this paper provides some theoretical support for this study. However, considering the limitation of this meta-analysis, the results of this study should be interpreted with caution and more work need to be done in the future to validate our findings.

Conclusion

There is a correlation between thyroid disease and severe COVID-19 infection.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships.

Data availability

Data and any supplementary material related to this article can be obtained from the corresponding author on request.

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