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Reviews and Meta-analysis

The prognostic values of thyroid disorders in predicting COVID-19 composite poor outcomes: A systematic review and meta-analysis

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ABSTRACT

Background and aims: In this meta-analysis, we aimed to evaluate the prognostic properties of thyroid disorder during admission on poor prognosis and factors that may influence the relationship in patients with COVID-19.**Methods:** A systematic literature search of PubMed, EBSCO, and CENTRAL was conducted from inception to August 27, 2021. The main exposure was unspecified and specified thyroid disorders—hypothyroidism or hypothyroidism. The outcome of interest was the COVID-19 composite poor outcome that comprises of severity, mortality, ICU admission, and hospitalization.**Results:** There were 24,734 patients from 20 studies. Meta-analysis showed that thyroid disorder was associated with composite poor outcome (OR 2.87 (95% CI 2.04–4.04), $p < 0.001$; $I^2 = 62.4\%$, $p < 0.001$). Meta regression showed that age ($p = 0.047$) and hypertension ($p = 0.01$), but not gender ($p = 0.15$), DM ($p = 0.10$), CAD/CVD ($p = 0.38$), obesity ($p = 0.84$), and COPD ($p = 0.07$) affected the association. Sub-group analysis showed that thyroid disorder increased risk of severe COVID-19 (OR 5.13 (95% CI 3.22–8.17), $p < 0.05$; $I^2 = 0\%$, $p = 0.70$) and mortality (OR 2.78 (95% CI 1.31–5.90), $p < 0.05$; $I^2 = 80\%$, $p < 0.01$). Pooled diagnostic analysis of thyroid disorder yielded a sensitivity of 0.22 (0.13–0.35), specificity of 0.92 (0.87–0.95), and AUC of 0.72. The probability of poor outcome was 38% in patients with thyroid disorder and 15% in patients without thyroid abnormality.**Conclusion:** On-admission thyroid disorder was associated with poor prognosis in COVID-19 patients.

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1. Introduction

To date, millions of people worldwide have coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The evolving nature of virus subtype predisposes to the high prevalence followed by long incubation periods of the virus yields a long-lasting pandemic with an increasing number of cases across countries [1,2]. Multifaceted measures have been taken with various objectives—from prevention of viral transmission to prevent the complication of the disease.

The spectrum of clinical manifestation of COVID-19 is broad, ranging from asymptomatic patients to critically ill that requires hospitalization [1,3]. The disease progression has also been a concern due to its characteristics of wide-ranging and confounded by a multitude of factors. Early steps to mitigate disease progression by assessing risk stratification using a reliable predictive model are needed to prevent adverse outcomes. The relationship between comorbidities associated with metabolic disorders and COVID-19 outcomes has been extensively investigated. Utilizing patients' clinical history and markers especially those that are regularly assessed is paramount to assess risks and allocate resources

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efficiently [4,5]. Previous studies have been conducted to evaluate the association between thyroid disorder and COVID-19 poor outcome [6,7]. However, the prognostic properties of thyroid disorder and whether its value is influenced by other comorbidities that may be present in COVID-19 patients remain unknown. Thus, this present systematic review and meta-analyses were aimed to investigate the prognostic value of preexisting thyroid disorder during admission for various COVID-19 poor outcomes and factors that may affect its relationship.

2. Material and methods

This systematic review and meta-analysis were written following the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [8]. A detailed protocol has been previously registered in PROSPERO (CRD42021267278).

2.1. Eligibility criteria

The PECO (Population, Exposure, Comparison, Outcome) structure design was used to define the inclusion and exclusion criteria of exposure and outcomes. The inclusion criteria were research articles and letters that report COVID-19 patients with provided categorical data on thyroid disorder status during admission along with measurable outcomes—mortality, severity, ICU admission, and hospitalization.

Following types or articles were excluded: case report, non-research letter, editorial, invited commentary, review, abstract-only article, and preprint. Studies that included patients who have developed thyroid abnormalities secondary to the infection were excluded from further analysis. Also, studies reporting only continuous variables of thyroid serum level were excluded. There was no language restriction applied in this study.

2.2. Search strategy and study selection

A systematic search of PubMed, EBSCO, and Cochran Collaboration Central Register of Controlled Clinical Trials (CENTRAL) were initially performed from the inception to 27th of August 2021. An extended literature searching was then conducted by two independent investigators (NNMS and FAD) to pool articles until December 2nd, 2021. The following search terms were used: ("Thyroid Gland" [Mesh] OR "Thyroid (USP)" [Mesh] OR "Hyperthyroidism" [Mesh] OR "Hypothyroidism" [Mesh] OR "Thyroid Hormones" [Mesh] OR "thyroid disease" [tiab] OR "hyperthyroid" [tiab] OR "hypothyroid" [tiab] OR "thyroid" [tiab] OR thyroid OR "TSH" [tiab] OR "T3" [tiab] OR "T4" [tiab]) AND ("COVID-19" [Mesh] OR "SARS-CoV-2" [Mesh] OR COVID-19)) [7]. We used 'related articles' feature and hand searched the reference lists of the included articles to expand the search and obtain additional studies. Duplicate results were removed after the initial search.

2.3. Data extraction

Data extraction was conducted independently by two authors (NNMS and FAD). Included studies were summarized in a standardized form that comprised of the author, year of publication, study design, sample size, age, gender, and reported comorbidities—hypertension (HT), coronary artery disease/cerebrovascular disease (CAD/CVD), Diabetes mellitus (DM), obesity, and chronic pulmonary obstructive disease (COPD). Different opinions in extracting data or eliminating possible duplicates were resolved through discussion and consensus.

The primary exposure was preexisting thyroid disease from baseline characteristics or a group of patients with lower- or

higher-than-normal measured thyroid hormone levels during admission. The type of thyroid measurement during admission to categorize the patient's type of thyroid level abnormality was thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), or free thyroxine (fT4). The patient was considered hypothyroidism if the level of thyroid hormone was lower than normal reference according to the specified cut-off defined by each study. Conversely, the patient was considered hypothyroidism if the level of measured thyroid hormone was higher than the normal range. Furthermore, we also performed subgroup analyses on each type of thyroid abnormalities—undefined, hypothyroidism, and hypothyroidism. The primary measured outcome of interest in this present study was the composite poor outcome that comprised of COVID-19 mortality, severity, ICU admission, and hospitalization.

We used Newcastle-Ottawa Scale (NOS) to assess the quality of included studies. The following aspects were taken into consideration in the assessment: cohort selection, the comparability of the cohort based on the design or analysis, the way exposure is determined, and the way of outcomes of interest are evaluated. Discrepancies of perception were resolved by discussion.

2.4. Statistical analysis

All statistical analysis was performed using R (version 4.0.4, The R Foundation, Vienna, Austria). The incidence of poor composite outcome and thyroid disorder was pooled using meta-analysis of proportion. Also, the diagnostic odds ratio (DOR) was calculated using DerSimonian and Laird method random-effects model. The inconsistency index (I^2) and subgroup analysis using the Chi-square test was used to explore potential sources of heterogeneity. An I^2 of more than 50% and a p-value of less than 0.05 were considered significant for heterogeneity [9]. Random-effects model was used regardless of the heterogeneity value. Sensitivity analysis was conducted by using leave-one-out analysis to detect studies that significantly influence the pooled estimate. Meta-regression was also conducted with restricted-maximum likelihood random-effects with age, gender, and comorbidities (hypertension, DM, CAD/CVD, obesity, and COPD).

Diagnostic meta-analysis was done by calculating pooled sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR). Pooled sensitivity and specificity were displayed using a forest plot and summary receiver operating characteristics (SROC) curve [10]. Fagan's nomogram was also used to present the prediction of post-test probability from pre-test probability. We also performed Deek's funnel plot asymmetry test to identify publication bias and used Egger's test to ascertain the findings [11].

3. Results

3.1. Study selection

The selection to obtain included studies in the systematic review is shown in (Fig. 1). The initial search yielded 672 articles from PubMed, EBSCO, and CENTRAL.

Among 672 studies, two articles were removed automatically due to duplication, yielding the remaining 670 articles that were eligible to be screened and sought for retrieval. From all 670 screened articles, 631 irrelevant studies were excluded, resulting in the remaining 39 studies to be assessed for each eligibility. From 39 studies, a total of 19 full-text articles were excluded from further analysis in which the studies did not present the outcome of interest and did not categorize patients into different thyroid statuses, the reported thyroid disorder was continuous data, and no comparator was reported. Thereby, 20 studies were included in the systematic review and meta-analysis [12–31].

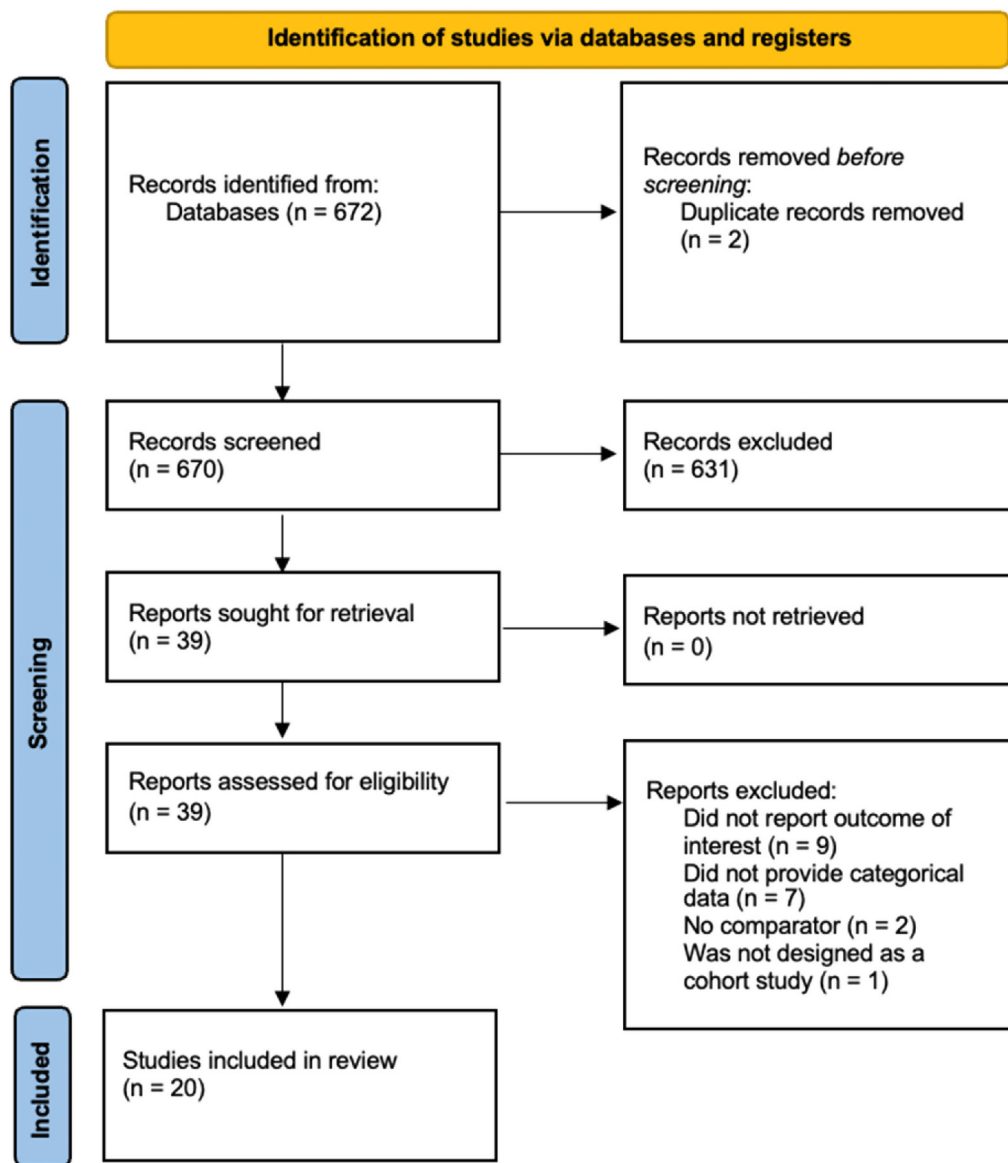


Fig. 1. PRISMA literature search flowchart.

3.2. Characteristics of included studies

The characteristics of the included studies are available in Table 1. There are 24,734 patients from 20 studies included in this present systematic review and meta-analysis. All patients were adult confirmed COVID-19 cases. There was a variability of cut-offs used within studies in which patients were grouped as hypothyroidism or hypothyroidism. However, the amount of study using each of the different cut-offs was inadequate to perform diagnostic meta-analysis with different cut points to generate optimal cut-off value. In addition, we extracted the number of comorbidities reported in the included studies cumulatively.

3.3. Thyroid disorders and poor outcomes

The preexisting of thyroid disorder was associated with higher odds of COVID-19 composite poor outcome (OR 2.87 (95% CI 2.04–4.04), $p < 0.001$; $I^2 = 62.4\%$, $p < 0.001$). Subgroup analysis showed that thyroid disorder was associated with higher risks of increased COVID-19 severity (OR 5.13 (95% CI 3.22–8.17), $p < 0.05$;

$I^2 = 0\%$, $p = 0.70$), ICU admission (OR 2.14 (95%CI 0.87–15.30), $p > 0.05$; $I^2 = 53\%$, $p = 0.07$), mortality (OR 2.78 (95%CI 1.31–5.90), $p < 0.05$; $I^2 = 80\%$, $p < 0.01$), and hospitalization (OR 1.84 (95%CI 1.40–2.40), $p < 0.05$; $I^2 = 0\%$, $p = 0.61$) (Fig. 2). Publication bias was evaluated qualitatively and quantitatively using funnel-plot analysis and Egger's test, respectively indicating a small study effect demonstrated in an asymmetrical shape ($p < 0.001$). Trim and fill analysis with imputation of 5 studies yielded an OR of (2.24 (95% CI 1.57–3.18) for poor outcomes. Sensitivity analysis by omitting individual study did not affect pooled estimate significantly. Meta regression showed that the incidence was vary by age ($p = 0.047$) and hypertension ($p = 0.014$), but not gender ($p = 0.148$), DM ($p = 0.102$), CAD/CVD ($p = 0.383$), obesity ($p = 0.835$), and COPD ($p = 0.069$). The incidence of composite poor outcome was 17%.

3.4. Diagnostic meta-analysis

Thyroid disorder had a sensitivity of 0.22 (0.13–0.35), specificity of 0.93 (0.88–0.96), DOR of 2.87 (2.04–4.04), and Area under curve (AUC) of 0.72 in predicting COVID-19 poor outcomes. Pooled

Table 1
Characteristics of thyroid disorders and COVID-19 outcomes related studies.

Authors	Study Design	Samples	Male (%)	Age (years)	Hypertension (%)	CAD/CVD (%)	DM (%)	Obesity (%)	COPD (%)	Outcome	NOS
Alqahtani et al., 2020 (12)	Retrospective cohort	458	86.9	N/A	10.94	1.97	13.6	57.1	N/A	Severity	8
Almazeedi et al., 2020 (13)	Retrospective cohort	1096	81	41	16.1	4.3	14.1	21.8	0.5	Severity	6
Baldelli et al., 2021 (14)	Retrospective cohort	46	69.5	59.6	N/A	N/A	N/A	N/A	N/A	ICU	7
Brix et al., 2021 (15)	Retrospective cohort	16,502	45.6	57.3	26.73	17.35	11.96	10.9	5.8	Mortality	7
Cao et al., 2020 (16)	Retrospective cohort	198	51	50.1	21.2	6	7.6	N/A	N/A	ICU	7
Daraei et al., 2020 (17)	Retrospective cohort	390	67.7	58.1	N/A	N/A	N/A	N/A	N/A	Mortality	6
Gao et al., 2020 (18)	Retrospective cohort	100	52	62.3	N/A	N/A	N/A	N/A	N/A	Severity and Mortality	9
Gong et al., 2021 (19)	Retrospective cohort	150	54	69.8	N/A	11.33	N/A	N/A	N/A	Mortality	9
Güven et al., 2021 (20)	Prospective cohort	250	63	68	N/A	N/A	N/A	N/A	N/A	ICU	8
Khoo et al., 2020 (21)	Prospective cohort	334	60.8	66.1	48.5	23.7	39.5	N/A	17.4	Mortality and ICU	9
Lang et al., 2021 (22)	Retrospective cohort	127	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Mortality	7
Lui et al., 2020 (23)	Prospective cohort	191	51.8	53.5	27.2	6.3	13.1	N/A	3.1	Severity	8
Muller et al., 2020 (24)	Prospective cohort	145	61.3	66.9	N/A	N/A	N/A	N/A	N/A	ICU	6
Sen et al., 2021 (25)	Prospective cohort	60	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Severity	6
Shabrawishi et al., 2020 (26)	Retrospective cohort	150	60	46.1	28.8	8	26	N/A	0.7	Severity	6
Sisó-Almirall et al., 2020 (27)	Retrospective cohort	322	50	56.7	33.9	7.8	14.3	14.3	5.9	Hospitalization	7
van Gerwen et al., 2020 (28)	Retrospective cohort	3703	55.3	56.9	N/A	N/A	N/A	57.4	N/A	Hospitalization	8
Wang et al., 2020 (29)	Retrospective cohort	84	63.1	57.3	N/A	N/A	N/A	N/A	N/A	Severity	9
Zhang et al., 2020 (30)	Retrospective cohort	140	50.7	56.3	30	7.1	12.1	N/A	1.4	Severity	7
Zhang et al., 2020 (31)	Retrospective cohort	71	56.3	62.7	28.2	21.1	18.3	N/A	N/A	Severity and Mortality	7

CAD/CVD: Coronary artery disease/cardiovascular disease; COPD: Chronic Obstructive Pulmonary Disease; DM: Diabetes Mellitus; HTN: Hypertension; N/A: Not applicable; NOS: Newcastle-Ottawa Scale.

sensitivity and specificity to predict poor outcomes are shown in Fig. 4. A subgroup analysis of sensitivity showed the sensitivity of thyroid disorder to predict severe COVID-19 was 0.20 (95% CI 0.10–0.37), ICU admission was 0.18 (95% CI 0.05–0.46), mortality was 0.40 (95% CI 0.13–0.75), and hospitalization was 0.08 (0.07–0.10). Subsequently, subgroup analyses of the specificity of thyroid disorder to predict severe COVID-19 was 0.96 (95% CI 0.91–0.98), ICU admission was 0.90 (95% CI 0.73–0.97), mortality was 0.85 (95% CI 0.72–0.93), and hospitalization was 0.95 (0.94–0.96). Also, a summary receiver operating characteristics curve to predict composite poor outcome was conducted (Fig. 3).

Fagan’s nomogram showed that the post-test probability of poor outcome was 38% in patients with a thyroid disorder and the post-test probability of a poor outcome in a group with normal thyroid was 15% (Fig. 4). The positive likelihood ratio (PLR) was 3 and the negative likelihood ratio (NLR) was 0.85. Deek’s funnel plot showed asymmetry with respect to the regression line and the asymmetry test showed significant results ($p = 0.01$).

4. Discussion

The presence of thyroid disorder was associated with an almost three-fold increase in composite poor outcomes compared to patients with a sensitivity of 22% and specificity of 93%. To date, this is the first study to exhibit pooled analyses from the existing evidence to describe the prognostic properties of thyroid disorder to the outcome of COVID-19.

Meta-regression analyses indicated that the association

between thyroid disorder and poor COVID-19 outcomes vary by age and hypertension. It is postulated that physiological responses have deteriorated in the elderly population and this will further also lead to decreased levels of TSH and thyroxine [32–35]. The iodine nutritional status of the populations may also result in different thyroid function patterns during aging [33,34]. Previous studies also found the association between hypertension and poor COVID-19 outcomes [7,36]. In addition, it is also found that both types of thyroid disorders—hypothyroidism and hyperthyroidism can lead to hypertension. Although these disorders influenced the cardiovascular system through distinct mechanisms, these relationships may explain the influence of hypertension on the findings [37,38]. Furthermore, our results showed that the association between thyroid disorders and poor outcomes did not vary with other comorbidities—gender, DM, CAD/CVD, Obesity, and COPD.

Thyroid disorder has 93% of specificity with a 38% of positive probability of poor outcome and 17% of pre-test poor outcome probability. The sensitivity of thyroid disorder was relatively low (21%) and therefore, thyroid disorder in COVID-19 is better to be implemented to rule in the risk of poor outcomes rather than ruling it out. Among different types of poor outcomes defined in this study, a relatively stronger association was found between thyroid disorder and disease severity. The diagnostic analysis also showed that the sensitivity of thyroid disorder and death outcome was found comparably higher than other poor outcomes, although the finding posed a relatively higher heterogeneity.

Overall, our results showed a moderate level of heterogeneity. It is likely due to unspecified types of thyroid disorders included in

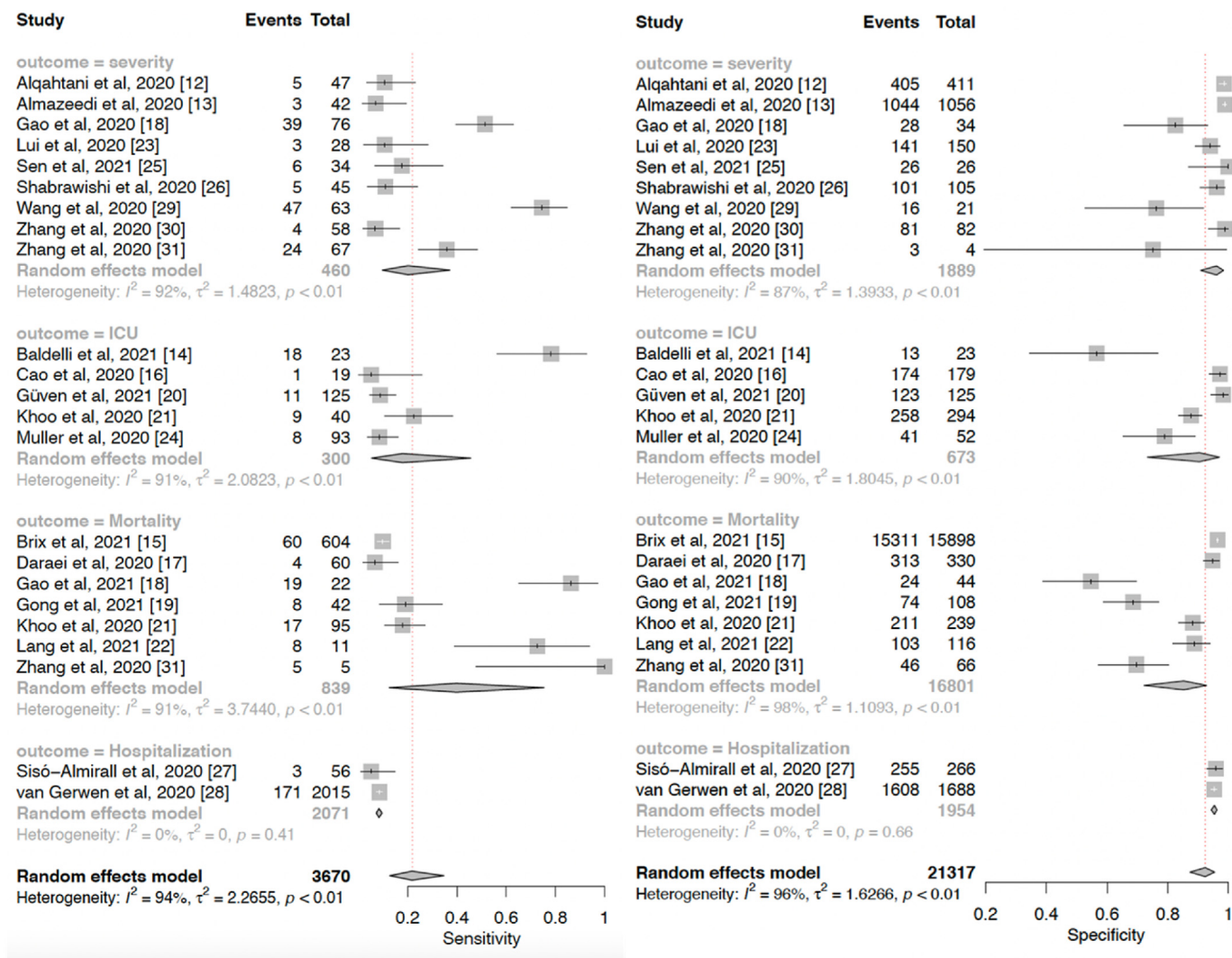


Fig. 2. Pooled sensitivity and specificity of thyroid disorders for COVID-19 poor outcomes.

the analysis. In addition, studies that included hypothyroidism or hypothyroidism populations potentially used different cut-off

points, diagnostic tools, and quantification methods used among studies that further explain the relatively high heterogeneity of the results [39]. However, sensitivity analysis through leave-one-out analyses indicated that retracting a single study did not significantly alter the effect estimate and heterogeneity of the association between thyroid disorders and poor outcomes. Subsequently, publication bias was also noted in this study as the funnel plot showed a slightly asymmetrical. Trim-and-fill analysis was performed, and it showed a reduced effect estimate without altering its significance after five imputed studies were included. Therefore, the prognostic performance will not be affected by the inclusion of additional studies.

Thyroid hormones are known to have bidirectional interaction between hormonal regulation and immune response. Studies have investigated these interactions in both pathological and physiological settings. Thyroid hormones influence both innate and adaptive immune responses [40,41]. Both are affected through cytokine release that is modulated by intracellular signaling as the response of thyroid hormone bindings [42,43]. Several studies have shown that in the acute phase of critically ill patients, the concentration of T3 was markedly decreased [12,13,18]. Hence, in the presence of thyroid disorder, the robustness of the immune response may be reduced as the regulation of hormonal release has

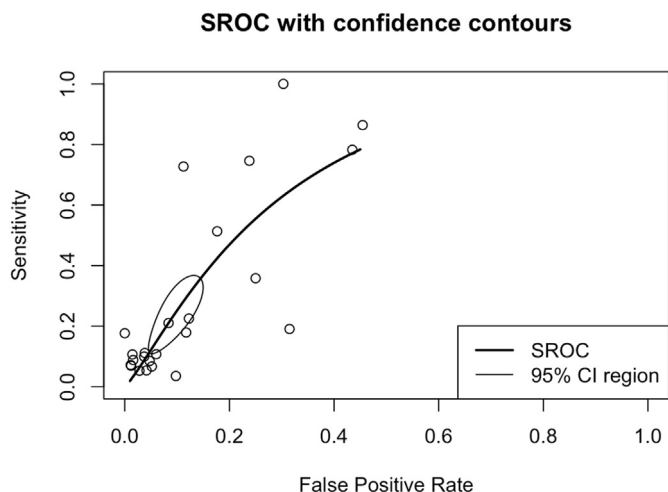


Fig. 3. Summary receiver operating characteristics (SROC) of thyroid disorders for COVID-19 composite poor outcome.

Fagan's nomogram

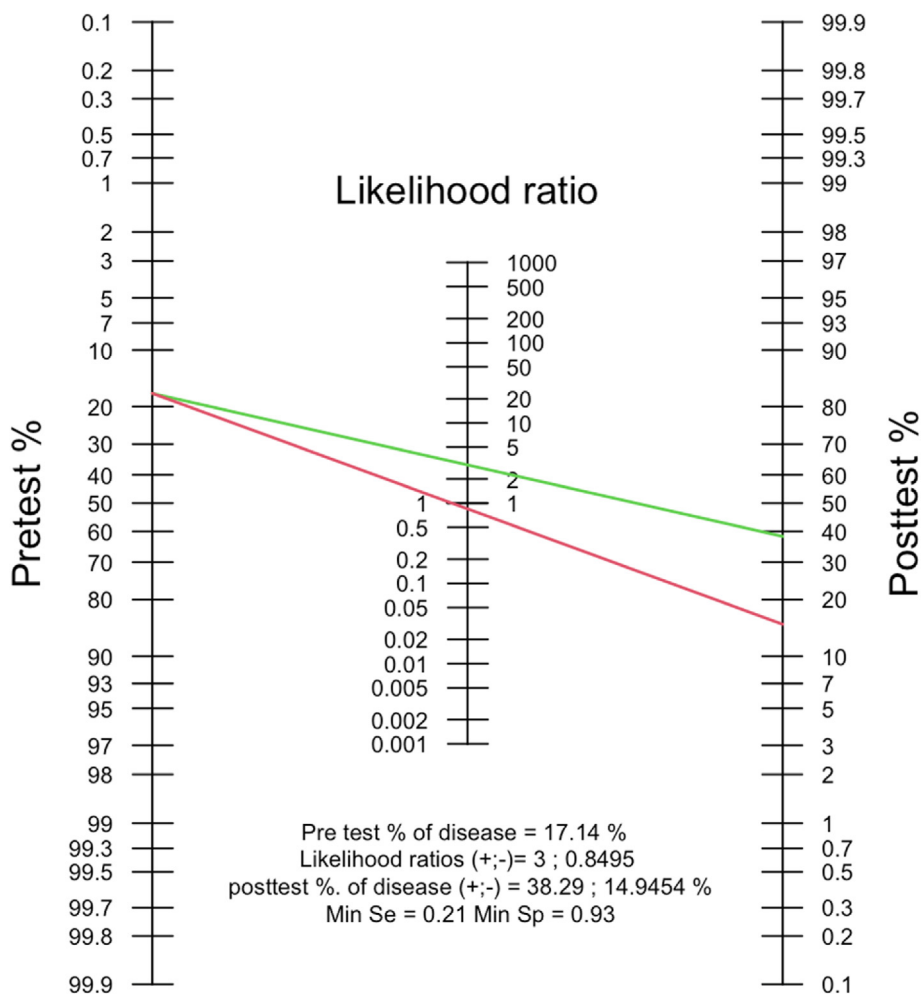


Fig. 4. Fagan's nomogram analysis elucidating the post-test probability of the presence of thyroid disorders in predicting COVID-19 poor outcomes.

obliterated. Another mechanism that could contribute to the worsening of the outcomes is the impairment of renin-angiotensinogen system (RAS) regulation [44,45]. Patients with thyroid abnormalities are potent to have an increased angiotensin-converting enzyme 2 (ACE2) expression [46]. This may increase a greater risk of severe infection as ACE2 plays an essential role in SARS-CoV-2 infection as the key receptor of the virus to enter the host [47–50]. Taken together, the presence of thyroid disorder may worsen COVID-19 infection through immune response dysregulation or viral entry modulation that both increase the risk of poor outcomes.

The main limitation of this present study is due to retrospective studies that have a higher risk of bias. In addition, this study involved all baseline thyroid disorders that may contribute to a greater rate of heterogeneity of the results. Importantly, the paucity of reported data of other comorbidities on each study makes further study with complete information on baseline characteristics to reassure the relationship of contributing factors is still required.

5. Conclusion

This study shows that on-admission thyroid disorders were

associated with poor outcomes in patients with COVID-19 and was vary with age and hypertension, but not gender, DM, CAD/CVD, obesity, and COPD. Pooled diagnostic analysis indicates the sensitivity of 22% and specificity of 92%.

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None.

Declaration of competing interest

The authors declare that there is no conflict of interest.

References

- [1] Gao Z, Xu Y, Sun C, Wang X, Guo Y, Qiu S, et al. A systematic review of asymptomatic infections with COVID-19. *J Microbiol Immunol Infect* 2021;54(1):12–6.
- [2] Chung JY, Thone MN, Kwon YJ. COVID-19 vaccines: the status and perspectives in delivery points of view. *Adv Drug Deliv Rev* 2021;170:1–25.
- [3] Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* 2021;19(3):141–54.
- [4] Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. *BMJ Evid Based Med* 2020.

- [5] Soetedjo NNM, Iryaningrum MR, Damara FA, Permadhi I, Sutanto LB, Hartono H, et al. Prognostic properties of hypoalbuminemia in COVID-19 patients: a systematic review and diagnostic meta-analysis. *Clinical Nutrition ESPEN*; 2021.
- [6] Hariyanto TI, Kurniawan A. Thyroid disease is associated with severe coronavirus disease 2019 (COVID-19) infection. *Diabetes Metab Syndr* 2020;14(5):1429–30.
- [7] Damara FA, Muchamad GR, Ikhsani R, Hendro, Syafiyah AH, Bashari MH. Thyroid disease and hypothyroidism are associated with poor COVID-19 outcomes: a systematic review, meta-analysis, and meta-regression. *Diabetes & Metabolic Syndrome: Clin Res Rev* 2021;15(6):102312.
- [8] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339.
- [9] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557–60.
- [10] Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. *Stat Med* 1993;12(14):1293–316.
- [11] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50(4):1088–101.
- [12] Alqahtani AM, AlMalki ZS, Alalweat RM, Almazrou SH, Alanazi AS, Alanazi MA, et al. Assessing the severity of illness in patients with coronavirus disease in Saudi Arabia: a retrospective descriptive cross-sectional study. *Front Public Health* 2020;8:593256.
- [13] Almazeedi S, Al-Youha S, Jamal MH, Al-Haddad M, Al-Muhaini A, Al-Ghimlas F, et al. Characteristics, risk factors and outcomes among the first consecutive 1096 patients diagnosed with COVID-19 in Kuwait. *EClinicalMedicine* 2020;24:100448.
- [14] Baldelli R, Nicastri E, Petrosillo N, Marchioni L, Gubbio A, Sperduti I, et al. Thyroid dysfunction in COVID-19 patients. *J Endocrinol Invest* 2021;1–5.
- [15] Brix TH, Hegedüs L, Hallas J, Lund LC. Risk and course of SARS-CoV-2 infection in patients treated for hypothyroidism and hyperthyroidism. *Lancet Diabetes Endocrinol* 2021;9(4):197–9.
- [16] Cao M, Zhang D, Wang Y, Lu Y, Zhu X, Li Y, et al. Clinical features of patients infected with the 2019 novel coronavirus (COVID-19) in Shanghai, China. *medRxiv*. 2020.
- [17] Daraei M, Hasibi M, Abdollahi H, Mirabdolhagh Hazaveh M, Zebaradst J, Hajinoori M, et al. Possible role of hypothyroidism in the prognosis of COVID-19. *Intern Med J* 2020;50(11):1410–2.
- [18] Gao W, Guo W, Guo Y, Shi M, Dong G, Wang G, et al. Thyroid hormone concentrations in severely or critically ill patients with COVID-19. *J Endocrinol Invest* 2021;44(5):1031–40.
- [19] Gong J, Wang DK, Dong H, Xia QS, Huang ZY, Zhao Y, et al. Prognostic significance of low TSH concentration in patients with COVID-19 presenting with non-thyroidal illness syndrome. *BMC Endocr Disord* 2021;21(1):111.
- [20] Güven M, Gültekin H. The prognostic impact of thyroid disorders on the clinical severity of COVID-19: results of single-centre pandemic hospital. *Int J Clin Pract* 2021;75(6):e14129.
- [21] Khoo B, Tan T, Clarke SA, Mills EG, Patel B, Modi M, et al. Thyroid function before, during, and after COVID-19. *J Clin Endocrinol Metab* 2021;106(2):e803–11.
- [22] Lang S, Liu Y, Qu X, Lu R, Fu W, Zhang W, et al. Association between thyroid function and prognosis of COVID-19: a retrospective observational study. *Endocr Res* 2021;1–8.
- [23] Lui DTW, Lee CH, Chow WS, Lee ACH, Tam AR, Fong CHY, et al. Thyroid dysfunction in relation to immune profile, disease status, and outcome in 191 patients with COVID-19. *J Clin Endocrinol Metab* 2021;106(2):e926–35.
- [24] Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, et al. SARS-CoV-2-related atypical thyroiditis. *Lancet Diabetes Endocrinol* 2020;8(9):739–41.
- [25] Sen K, Sinha A, Sen S, Chakraborty S, Alam MS. Thyroid function test in COVID-19 patients: a cross-sectional study in a tertiary care hospital. *Indian J Endocrinol Metab* 2020;24(6):532–6.
- [26] Shabrawishi M, Al-Gethamy MM, Naser AY, Ghazawi MA, Alsharif GF, Obaid EF, et al. Clinical, radiological and therapeutic characteristics of patients with COVID-19 in Saudi Arabia. *PLoS One* 2020;15(8):e0237130.
- [27] Siso-Almirall A, Kostov B, Mas-Heredia M, Vilanova-Rotllan S, Sequeira-Aymar E, Sans-Corrales M, et al. Prognostic factors in Spanish COVID-19 patients: a case series from Barcelona. *PLoS One* 2020;15(8):e0237960.
- [28] van Gerwen M, Alsen M, Little C, Barlow J, Naymagon L, Tremblay D, et al. Outcomes of patients with hypothyroidism and COVID-19: a retrospective cohort study. *Front Endocrinol (Lausanne)*. 2020;11:565.
- [29] Wang W, Su X, Ding Y, Fan W, Zhou W, Su J, et al. Thyroid function abnormalities in COVID-19 patients. *Front Endocrinol (Lausanne)* 2020;11:623792.
- [30] Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020;75(7):1730–41.
- [31] Zhang Y, Lin F, Tu W, Zhang J, Choudhry AA, Ahmed O, et al. Thyroid dysfunction may be associated with poor outcomes in patients with COVID-19. *Mol Cell Endocrinol* 2021;521:111097.
- [32] Aggarwal N, Razvi S. Thyroid and aging or the aging thyroid? An evidence-based analysis of the literature. *J Thyroid Res* 2013;2013:481287.
- [33] Barbesino G. Thyroid function changes in the elderly and their relationship to cardiovascular health: a mini-review. *Gerontology* 2019;65(1):1–8.
- [34] Bremner AP, Feddema P, Leedman PJ, Brown SJ, Beilby JP, Lim EM, et al. Age-related changes in thyroid function: a longitudinal study of a community-based cohort. *J Clin Endocrinol Metab* 2012;97(5):1554–62.
- [35] Li X, Marmar T, Xu Q, Tu J, Yin Y, Tao Q, et al. Predictive indicators of severe COVID-19 independent of comorbidities and advanced age: a nested case-control study. *Epidemiol Infect* 2020;148:e255.
- [36] Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. *J Renin-Angiotensin-Aldosterone Syst JRAAS* 2020;21(2). 1470320320926899.
- [37] Berta E, Lengyel I, Halmi S, Zrinyi M, Erdei A, Harangi M, et al. Hypertension in thyroid disorders. *Front Endocrinol (Lausanne)* 2019;10:482.
- [38] Saito I, Saruta T. Hypertension in thyroid disorders. *Endocrinol Metab Clin N Am* 1994;23(2):379–86.
- [39] Infusino I, Panteghini M. Serum albumin: accuracy and clinical use. *Clin Chim Acta* 2013;419:15–8.
- [40] Kumari K, Gbn Chainy, Subudhi U. Prospective role of thyroid disorders in monitoring COVID-19 pandemic. *Heliyon* 2020;6(12):e05712.
- [41] Rubingh J, van der Spek A, Fliers E, Boelen A. The role of thyroid hormone in the innate and adaptive immune response during infection. *Compr Physiol* 2020;10(4):1277–87.
- [42] Montesinos MDM, Pellizas CG. Thyroid hormone action on innate immunity. *Front Endocrinol (Lausanne)*. 2019;10:350.
- [43] De Luca R, Davis PJ, Lin HY, Gionfra F, Percario ZA, Affabris E, et al. Thyroid hormones interaction with immune response, inflammation and non-thyroidal illness syndrome. *Front Cell Dev Biol* 2020;8:614030.
- [44] Park CW, Shin YS, Ahn SJ, Kim SY, Choi EJ, Chang YS, et al. Thyroxine treatment induces upregulation of renin-angiotensin-aldosterone system due to decreasing effective plasma volume in patients with primary myxoedema. *Nephrol Dial Transplant* 2001;16(9):1799–806.
- [45] Vargas F, Rodriguez-Gomez I, Vargas-Tendero P, Jimenez E, Montiel M. The renin-angiotensin system in thyroid disorders and its role in cardiovascular and renal manifestations. *J Endocrinol* 2012;213(1):25–36.
- [46] Diniz GP, Senger N, Carneiro-Ramos MS, Santos RA, Barreto-Chaves ML. Cardiac ACE2/angiotensin 1-7/Mas receptor axis is activated in thyroid hormone-induced cardiac hypertrophy. *Ther Adv Cardiovasc Dis* 2016;10(4):192–202.
- [47] Vieira C, Nery L, Martins L, Jabour L, Dias R, Simoes ESAC. Downregulation of membrane-bound angiotensin converting enzyme 2 (ACE2) receptor has a pivotal role in COVID-19 immunopathology. *Curr Drug Targets* 2021;22(3):254–81.
- [48] Aleksova A, Ferro F, Gagno G, Cappelletto C, Santon D, Rossi M, et al. COVID-19 and renin-angiotensin system inhibition: role of angiotensin converting enzyme 2 (ACE2) - is there any scientific evidence for controversy? *J Intern Med* 2020;288(4):410–21.
- [49] Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care* 2020;24(1):422.
- [50] Kragstrup TW, Singh HS, Grundberg I, Nielsen AL, Rivellesse F, Mehta A, et al. Plasma ACE2 predicts outcome of COVID-19 in hospitalized patients. *PLoS One* 2021;16(6):e0252799.