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ORIGINAL ARTICLE

Association of thyroid hormones and thyroid-stimulating hormone with mortality in adults admitted to the intensive care unit: A systematic review and meta-analysis

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Abstract

Background: Thyroid hormones (THs) and thyroid-stimulating hormone (TSH) seem to show high potential in predicting the clinical death outcome of patients admitted to the intensive care unit (ICU). However, diverse studies on this topic are conflicting.

Methods: A search was conducted by two investigators involved in this research in the PubMed, Embase, and Cochrane databases (all last launched on July 12, 2021). The quality of the included studies was evaluated using the Newcastle-Ottawa Quality Assessment Scale (NOS). Subgroup analyses were performed to determine the sources of heterogeneity. Sensitivity and publication bias analyses were also assessed.

Results: A total of 27 studies (4970 participants) were included based on the eligibility criteria. Compared with survivors, nonsurvivors were found to have lower levels of THs (T3, T4, fT3, and fT4), whereas no significant difference was found in TSH levels (13 studies for T3: standardized mean differences [SMD], −0.78; 95% CI, −1.36 to −0.20; I^2 = 96%; p = 0.008; 11 studies for T4: SMD = −0.79; 95% CI, −1.31 to −0.28; I^2 =95%; p = 0.0002; 14 studies for fT3: SMD = −0.76; 95% CI, −1.21 to −0.32; I^2 = 95%; p = 0.0008; 17 studies for fT4: SMD = −0.60; 95% CI, −0.99 to −0.22; I^2 = 95%; p = 0.002; 20 studies for TSH: SMD = 0.00; 93% CI, −0.29 to 0.29; I^2 = 93%; p = 0.98).

Conclusion: Nonsurvivors were associated with lower levels of THs (T3, T4, fT3, and fT4) than survivors. THs show great application potential in predicting ICU patients' death outcomes and improving already widely used prognostic scores in the ICU (ie, Acute Physiological and Chronic Health Evaluation [APACHE] II and Therapeutic Intervention Scoring System).

Keywords: Intensive care unit; Mortality; Thyroid hormones

1. INTRODUCTION

Since the patient population admitted to the intensive care unit (ICU) is severely ill, the ICU mortality rate is higher than that of any other unit in the hospital. The mean mortality rate ranges from 8% to 19% (≈500 000 deaths among 4 million ICU admissions per year).[1] It is vital for clinicians to accurately predict the outcome. Although several predictive tools have been widely used to predict death outcomes in ICU patients, such as the Acute Physiological and Chronic Health Evaluation (APACHE) II and the Sequential Organ Failure Assessment (SOFA), we still need an alternative predictive factor that is more accurate, easy to use, and readily available in patients with serious illnesses.[2,3]

Patients admitted to the ICU, who often suffer from critical illness, are always characterized by dysfunction of the hypothalamic-pituitary-thyroid (HPT) axis, and thyroid hormones(THs) and thyroid-stimulating hormone (TSH) beyond the normal range are frequently observed.[4,5] Some retrospective studies suggest that THs (T3, T4, fT3, and fT4) and TSH levels in nonsurvivors are lower than those in survivors. These studies highlight a significant correlation between THs and TSH levels and prognosis. As a result, THs and TSH can be considered a risk signal for death in ICU patients. However, this remains controversial, and we aimed to estimate the predictive efficacy of THs in ICU patients.

2. METHODS

This review was built on Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)

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CA9_V85N4_Text.indb 443 04-Apr-22 13:11:01

2015. We prospectively registered the protocol in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020139975). This review was exempt from institutional review board oversight because all collected data were open to the public, and none of the individual patient data was used.

2.1. Eligibility criteria, literature search, and study selection

Two investigators (R. M. and Z. Y.) in this study performed a systematic literature search in December 2020 to identify case-control studies involving adult patients (older than 18 years). Studies were considered eligible as long as they fulfilled the following eligibility criteria: (1) included patients had no limitation on age, race, ethnicity, and type of disease; (2) setting: ICU; (3) measured THs and TSH levels within 24 hours after admission, and the data can be extracted as mean ± SD according to their clinical outcomes; and (4) provided the mortality data of patients during admission or after discharge from the ICU or in the hospital. We excluded articles according to the following exclusion criteria: studies with patients younger than 18 years of age, reviews, case reports, editorials, letters, comments, animal studies, and duplicate studies. Disagreement between the 2 primary investigators was resolved by discussion with a third reviewer (P.W.) until a consensus was reached.

We searched trials using a comprehensive search strategy (shown in Supplementary Materials) developed based on the Peer Review of Electronic Search Strategies (PRESS) 2015 guidelines in the following databases: Cochrane, Embase, and PubMed. We also manually searched ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and the International Standard Randomized Controlled Trial Number Registry (ISRCTN) for all registered clinical trials. To avoid publication bias, language or race were not criteria for exclusion.

2.2. Outcomes

The previously defined outcome was mortality, which was recorded during admission or after discharge from the ICU or the hospital.

2.3. Data extraction and Newcastle-Ottawa Scale

R. M. and Z. Y. independently extracted individual trial data reported in the included studies and assessed trials for the risk of bias. We evaluated the quality of included studies using the Newcastle-Ottawa Scale (NOS) for case-control studies owing to the lack of cohort studies. This scale comprises 4 items that may be the source of bias as follows: participant selection, comparability of cases and controls, measurement devices, and outcome measurement. We scored each item on a scale from 0 to 9.

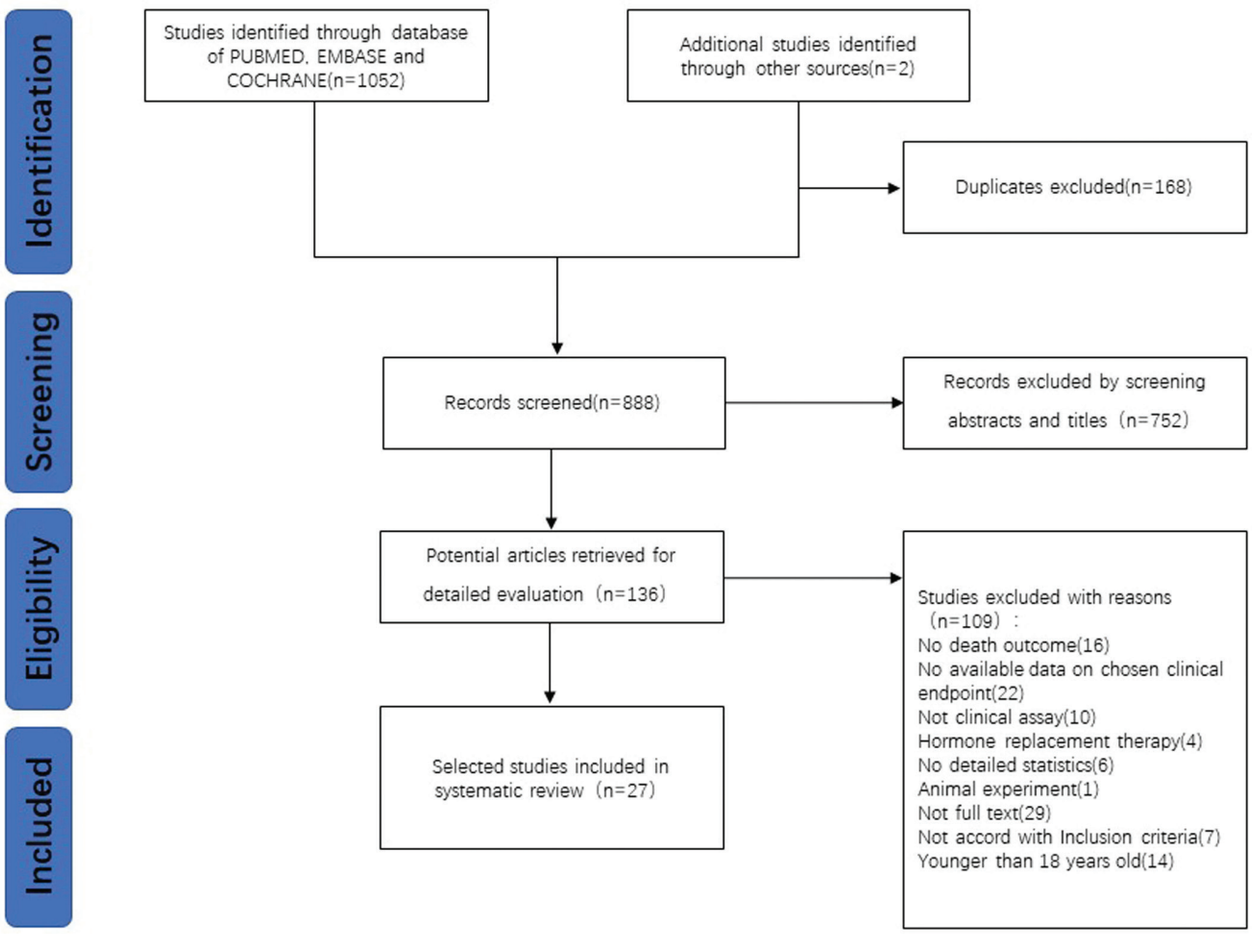

Fig. 1 Flow-chart of the systematic review.

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Table 1

Characteristics of included studies

Outcome		ICU mortality	ICU mortality	Hospital mortality	ICU mortality	ICU mortality	Hospital mortality	Hospital mortality	ICU mortality	ICU mortality	Hospital mortality	Hospital mortality	ICU mortality	ICU mortality
Measurement device		CIA	CIA	NR	CIA	ELISA	CIA	CIA	CIA	CIA	NR	ELISA	CIA	CIA
THs and TSH		fT3, fT4, TSH	T3, T4, fT3, fT4, TSH	fT3, fT4, TSH	fT3, fT4, TSH	fT3, fT4, TSH	T3, T4, fT3, fT4, TSH	fT3, fT4, TSH	fT3, fT4	T3, T4, fT3, fT4, TSH	T3, T4, TSH	TSH	T3, fT4	T3, fT4, TSH
Population	patients	Sepsis	Mixed	Mixed	Mixed	Sepsis	Mixed	Mixed	Cirrhosis	Mixed	Surgical sepsis	Mixed	Sepsis	Trauma
	Male(%)	63%	51.10%	55.50%	64.60%	75%	NR	52%	30.20%	59.79%	43%	73.70%	54.40%	88.30%
	Age, y	59.4 ± 14.1	38.99 ± 18.32	72.1 ± 15.5	53 ± 3	55.8 ± 17.0	67.65 ± 16.99	58.7 ± 16.9	55.5	71.71 ± 15.52	59 ± 3	66 ± 20	59 ± 16.7	35.8 ± 16.6
	No.	49	270	463	79	80	797	100	106	480	231	104	103	94
Country/publication year		Poland/2019	India/2018	China/2017	China/2016	Egypt/2015	China/2014	India/2013	Turkey/2012	China/2012	USA/2012	France/2011	Switzerland/2011	Greece/2007
Identification		Foks et al	Gutch et al	Ma et al	Quispe et al	Hosny et al	Chen et al	Kumar et al	Tas et al	Wang et al	Todd et al	Sharshar et al	Meyer et al	Ilias et al
Reference		[6]	[7]	[8]	[9]	[10]	[11]	[12]	[13]	[14]	[15]	[16]	[17]	[18]
Outcome		ICU mortality	ICU mortality	ICU mortality	Hospital mortality	ICU mortality	ICU 28-day mortality	ICU mortality	ICU mortality	ICU mortality	Hospital mortality	ICU mortality	Hospital mortality	ICU mortality
Measurement device		CIA	RIA	CIA	RIA	RIA	RIA	RIA	CIA	RIA	CIA	RIA	RIA	NR
THs and TSH		fT3, fT4, TSH	T3, T4, fT3, fT4, TSH	fT3	T3, T4, fT3, fT4, TSH	T3, T4, TSH	fT3, fT4, TSH	T3, T4	fT3, fT4, TSH	T3, T4, TSH	fT3, fT4, TSH	T3, T4, TSH	T3, T4, TSH	fT3, fT4, TSH
Population	Patients	ARDS	Mixed	Acute or acute-on-chronic respiratory failure	Mixed	Mixed	Mixed	NR	Mixed	Mixed	Mixed	Mechanically ventilated patients	Mixed	Mechanically ventilated patients
	Male, %	72.30%	38.50%	56%	75.6	62.30%	68.50%	NR	56.40%	54%	56.10%	NR	52.70%	60%
	Age, y	61.9 ± 13.4	59.3 ± 22.0	75.5 ± 11.75	Males: 17–77; females: 22–77	61.9 ± 13.4	55.3 ± 15.7	NR	Nonsurvivors 60.28 ± 11.52: Survivors 58.92 ± 11.20	Nonsurvivors: 56.8 ± 17: Survivors: 60.2 ± 15	70.1 ± 15.3	NR	59.6(range, 14–86) Survivors: 58.1 ± 15: Nonsurvivors: 61.3 ± 13	64.33 ± 5.96
	No.	206	123	32	41	61	305	42	417	200	157	49	260	40
Country/publication year		Turkey/2005	USA/2005	Italy/2004	Japan/1994	USA/1993	China/2020	Brasil/1997	Turkey/2012/	England/1993	Turkey /2016	USA /1996	UK /1995	Egypt /2015
Identification		Türe et al	Chinga-Alayo et al	Scoscia et al	Sumita et al	Jarek et al	Guo et al	Ward et al	Tas et al	Rothwell et al	Çuhacı et al	Arem et al	Rothwell et al	Abdel Naby et al
Reference		[19]	[20]	[21]	[22]	[23]	[24]	[25]	[26]	[27]	[28]	[29]	[30]	[31]

CIA = chemiluminescence immunoassay; ELISA = enzyme-linked immunosorbent assay; ICU = intensive care unit; NR = not reported; RIA = radioimmunoassay; TH = thyroid hormones; TSH = thyroid-stimulating hormone.

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2.4. Statistical analysis

The number of nonsurvivors and survivors and baseline values of THs and TSH in each study were extracted for use in the formal meta-analysis. We also extracted the following descriptive data: name of the first author, publication year and country, population number, mean age, male proportion, measurement devices, and clinical outcome.

To estimate the robustness of the association between THs and TSH and mortality, the standardized mean differences (SMD) were used for the survivor and nonsurvivor groups in a random-effects model. As the TH levels recorded in the included studies were measured with various measurement devices and reported with various units, we calculated the effect size by measuring SMD (95% CI), calculated using the following formula: ([nonsurvivor group mean level–survivor group mean level]/pooled standard deviation). The mean difference ± SD was based on the THs and TSH levels of the survivor and nonsurvivor groups. Between-study heterogeneity was quantified using the I^2 statistic, which estimates the percentage of variation across the included studies. Values of 25%, 50%, and 75% for the I^2 test were defined as low, moderate, and high heterogeneity, respectively.

We performed a subgroup analysis based on several subgroup variables for the exclusion criteria (ie, exclusion of thyroid diseases and drugs affecting TH levels, exclusion of thyroid diseases or drugs affecting TH levels, and the exclusion criteria not mentioned thyroid diseases and drugs affecting TH levels), ICU mortality and hospital mortality, and mortality rates (≥30% vs <30%). The 27 included studies were divided into different subgroups by the midpoint of the recorded rates or the value of each variable in the included 27 studies. Additional subgroup analysis (ie, NOS score (5-7 vs 8 vs 9) or measurement devices (radioimmunoassay [RIA] vs chemiluminescence immunoassay [CIA]) were also performed. Statistical significance was set at a p value less than 0.05.

Sensitivity analysis was performed by deleting individual studies step by step and tested publication bias using funnel plot and Egger test. The asymmetry of the funnel plot as well as p value < 0.05, using Egger test, suggested the existence of bias.

Statistical analysis was performed using Stata 15.1 (Stata, College Station, Texas, USA) and Review Manager V.5.4.1 2020 (The Cochrane Collaboration, Copenhagen, Denmark).

3. RESULTS

3.1. Literature search and characteristics of included studies

The search strategy identified 1054 records and 27 eligible records (4970 participants; range, 32-488 participants) were selected (Fig. 1). The information and characteristics of the

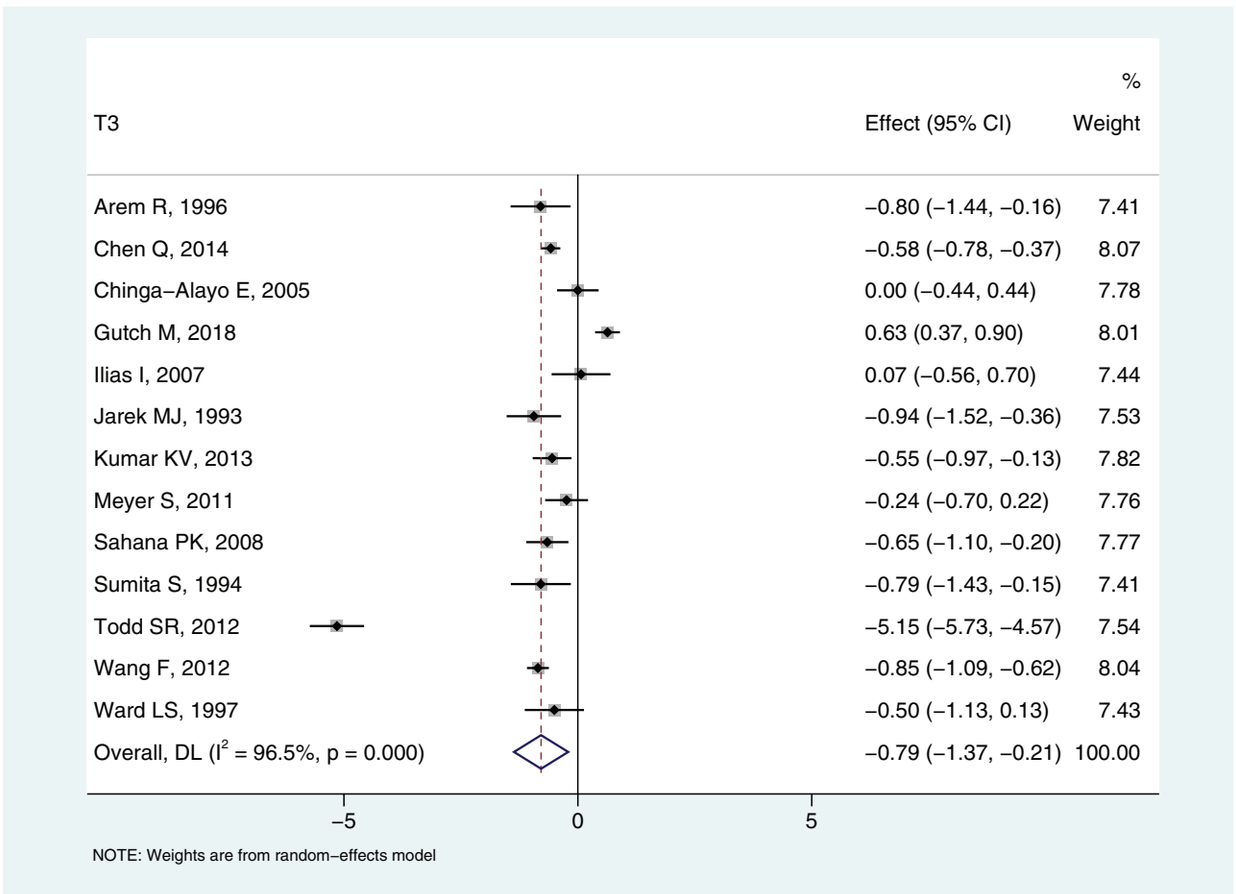

Fig. 2 Forest plots of clinical outcome in intensive care unit (ICU) patients is associated with thyroid hormones and thyroid stimulating hormone. A, Funnel plot of the T3 level between nonsurvivors and survivors in adults admitted to the ICU. B, Funnel plot of the T4 level between nonsurvivors and survivors in adults admitted to the ICU. C, Funnel plot of the fT3 level between nonsurvivors and survivors in adults admitted to the ICU. D, Funnel plot of the fT4 level between nonsurvivors and survivors in adults admitted to the ICU. E, Funnel plot of the TSH level between nonsurvivors and survivors in adults admitted to the ICU.

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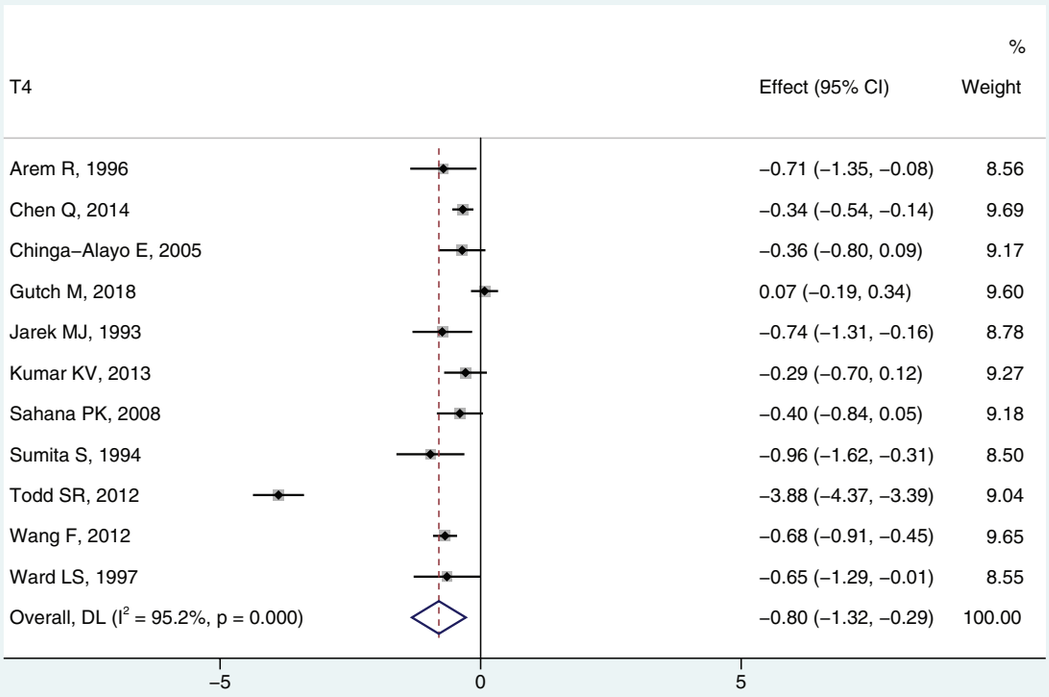

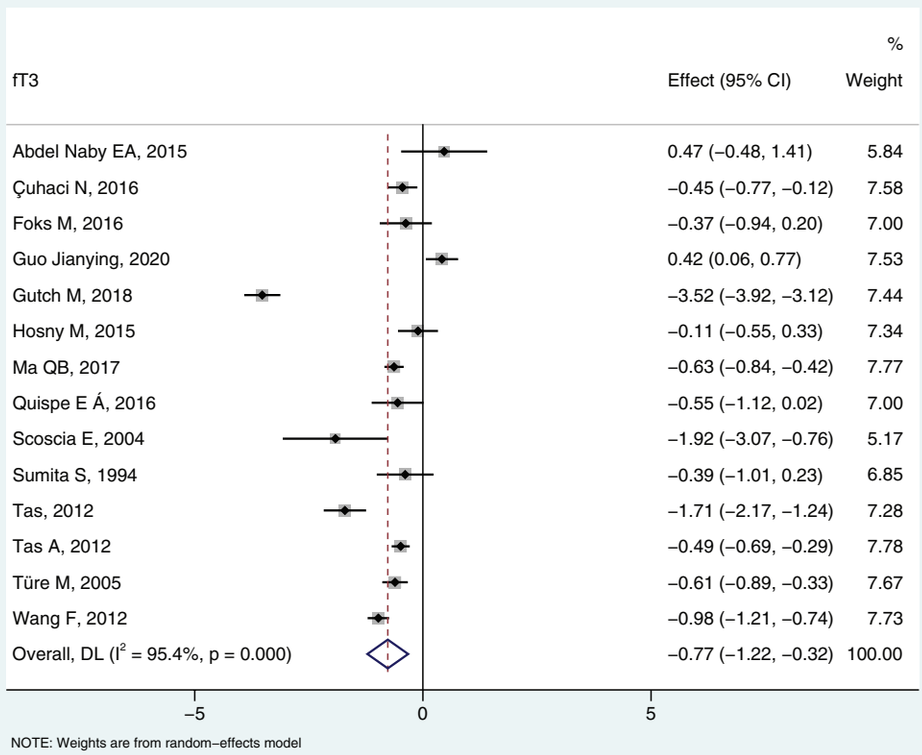

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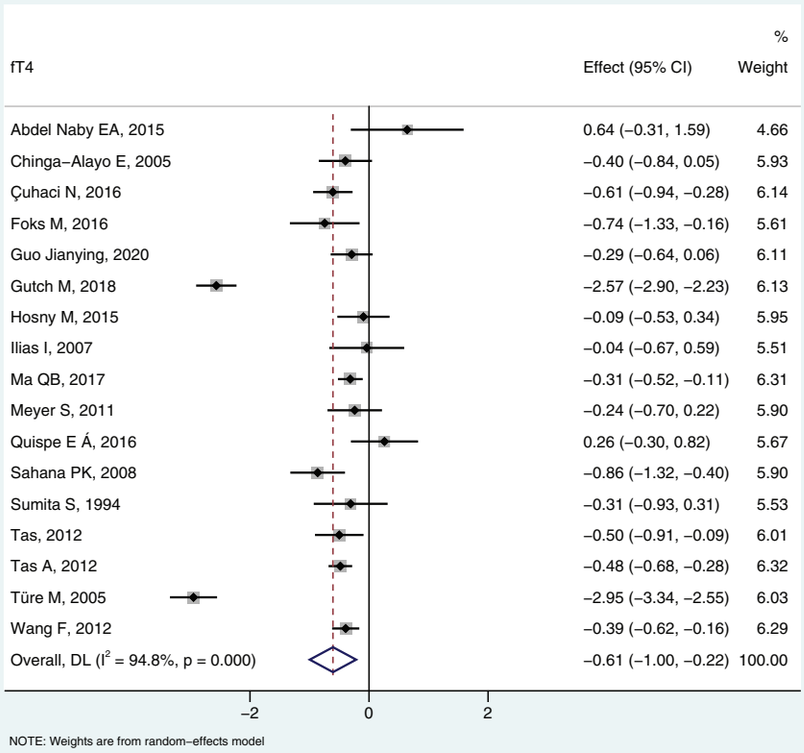

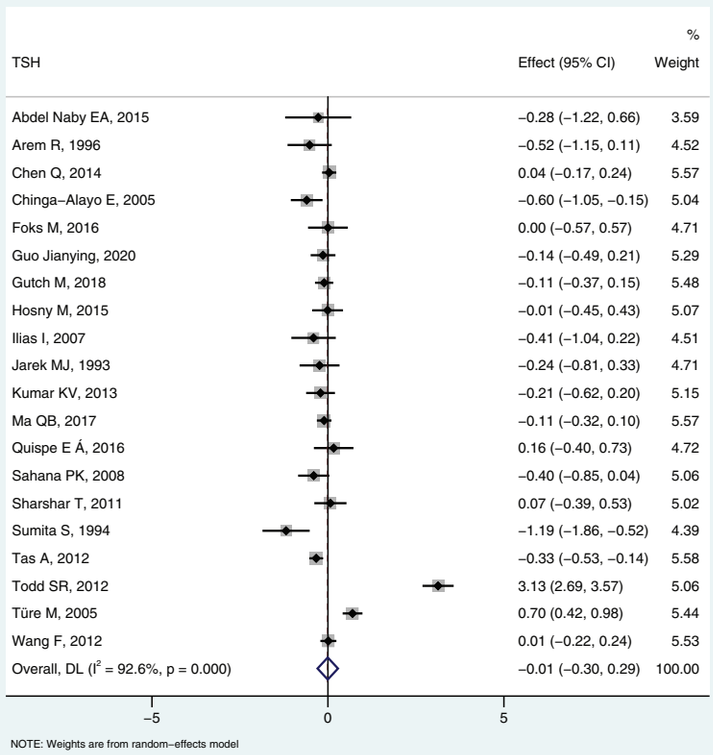

Fig. 2 Continued.

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included studies are summarized in Table 1. The mean age ranged from 35.8 to 75.5 years. Sepsis was the most common diagnosis in 4 trials (15%). Nearly half of the included studies (13) reported an overall mortality rate higher than 40%.

3.2. Association of THs and TSH with mortality

We present data on the association between serum thyroid levels and clinical outcomes in ICU patients (Fig. 2). Overall, nonsurvivors had lower levels of THs (T3, T4, fT3, and fT4) than survivors, while no significant difference was found in TSH levels.

3.3. Quality of included studies

In accordance with the Newcastle-Ottawa Quality Assessment Scale for case-control studies (9 is the total maximum score), the leading factors determining the study quality are the following: the comparability of nonsurvivors and survivors with the study design or analysis/ascertainment of exposure as well as the same method of ascertainment for cases and controls. The detailed results of the NOS are presented in Table 2.

Table 2

The Newcastle-Ottawa Quality Assessment Scale for the included studies

First author	Year	Selection[a]	Comparability[b]	Exposure[c]	Overall quality score
Abdel Naby et al[31]	2015	4	2	3	9
Arem et al[29]	1996	4	1	3	8
Chen et al[11]	2014	4	0	3	7
Chinga-Alayo et al[20]	2005	4	2	3	9
Çuhacı et al[28]	2016	4	2	3	9
Foks et al[6]	2016	4	1	3	8
Guo et al[24]	2020	4	2	3	9
Gutch et al[7]	2018	4	2	3	9
Hosny et al[10]	2015	4	2	3	9
Ilias et al[18]	2007	4	2	3	9
Jarek et al[23]	1993	4	0	3	7
Kumar et al[12]	2013	4	2	3	9
Ma et al[8]	2017	4	0	1	5
Meyer et al[17]	2011	4	0	3	7
Quispe et al[9]	2016	4	2	3	9
Rothwell et al[27]	1993	4	0	3	7
Rothwell et al[30]	1995	4	1	3	8
Sahana et al[32]	2008	4	2	3	9
Scoscia et al[21]	2004	4	2	3	9
Sharshar et al[16]	2011	4	0	3	7
Sumita et al[22]	1994	4	1	3	8
Tas et al[26]	2012	4	2	3	9
Taş et al[13]	2012	4	1	3	8
Türe et al[19]	2005	4	1	3	8
Todd et al[15]	2012	4	0	1	5
Wang et al[14]	2012	4	2	3	9
Ward et al[25]	1997	4	2	3	9

[a]Selection: (1) Is the case definition adequate? (a) yes, with independent validation; (b) yes, for example, record linkage or based on self-reports; (c) no description. () Representativeness of the cases: (a) consecutive or obviously representative series of cases; (b) potential for selection biases or not stated. (3) Selection of controls: (a) community controls; (b) hospital controls; (c) no description. (4) Definition of controls: (a) no history of disease (endpoint); (b) no description of source.

[b]Comparability: Comparability of cases and controls on the basis of the design or analysis: (a) study controls for thyroid diseases and drugs affecting thyroid hormone levels; (b) study controls for thyroid diseases or drugs affecting thyroid hormone levels.

[c]Exposure: (1) Ascertainment of exposure: (a) secure record (eg, surgical records); (b) structured interview blinded to case/control status; (c) interview not blinded to case/control status; (d) written self-report or medical record only; (e) no description. (2) Same method of ascertainment for cases and controls: (a) yes; (b) no. (3) Nonresponse rate: (a) same rate for both groups; (b) non respondents described; (c) rate different and no designation.

3.4. Subgroup analysis and sources of heterogeneity

We performed subgroup analysis to evaluate the association between THs and TSH levels and mortality, and to identify potential sources of heterogeneity. As we can see in the Supplementary Table S1–5, the most probable sources of heterogeneity were measurement devices, NOS scores, and exclusion criteria. Moreover, the clinical outcomes and mortality rates may contribute to heterogeneity.

3.5. Sensitivity analysis

Sensitivity analyses were conducted to evaluate the strength of the association, and we found three outlier studies (Todd et al,[15] Gutch et al,[7] Türe et al[19]) that showed evident heterogeneities (shown in the Supplementary Fig. S1–5). After omitting the record accordingly, significantly lower heterogeneity levels in TSH and T4 were evident, whereas heterogeneities barely decreased in fT3, fT4, and T3 (TSH: SMD, –0.14, 95% CI, –0.29 to 0.02, I^2 =70%, p=0.08; T3: SMD, –0.78, 95% CI, –1.39 to –0.17, I^2 =97%, p = 0.01; T4: SMD, –0.44, 95% CI, –0.64 to –0.24, I^2 =63%, p <0.0001; fT3: SMD, –0.53, 95% CI, –0.80 to –0.27, I^2 = 85%, p <0.0001; fT4: SMD, –0.23, 95% CI, –0.38 to –0.08, I^2 =74%, p = 0.003). Todd et al[15] contributed significantly to the heterogeneities of TSH and T4. A possible explanation is that the quality of this trial is quite low, as its NOS score is 5, which is the lowest score of the included studies. Although we excluded the Todd et al[15] records, there was no statistically significant difference in TSH values between the two groups (p = 0.08).

3.6. Publication bias

The forest plots did not show an asymmetrical appearance (Supplementary Fig. S7–10). As shown in Supplementary Table S7, we did not find any significant bias statistically calculated using Egger's regression test (T3, p = 0.391; T4, p = 0.275; fT3, p = 0.770; fT4, p = 0.961; TSH, p = 0.938).

4. DISCUSSION

This is the first time that a systematic review and meta-analysis have been utilized to calculate the prognostic value of THs and TSH in adults admitted to the ICU. This study showed that nonsurvivors were associated with lower THs levels compared with survivors, while the difference in TSH was not significant. As a result, THs can provide important information as risk signals permitting the early identification of patients in danger of dying. These risk signals enable doctors to initiate appropriate organ support rapidly, such as mechanical ventilation for dyspnea, blood transfusion for shortage of red blood cells, and extracorporeal membrane oxygenation (ECMO) for heart and lung failure.[33] Timely interventions can significantly improve patient outcomes.

The results are consistent with 2 published meta-analyses focusing on sepsis, which showed that nonsurvivors were associated with decreased THs levels.[34,35] However, one of the systematic reviews included studies primarily targeting neonates and children.[34] Moreover, the number of included studies was less than 9. Based on a larger study population (27 trials, 4970 participants), our study further confirmed the same conclusion. As the inclusion criteria were not limited to sepsis, our results may be generalizable to a broader population.

ICU patients are always characterized by low levels of plasma T3 and T4 and lower or normal TSH levels. This phenomenon is defined as nonthyroidal illness syndrome (NTIS).[36] As for ICU patients with different conditions, the reasons for NTIS vary

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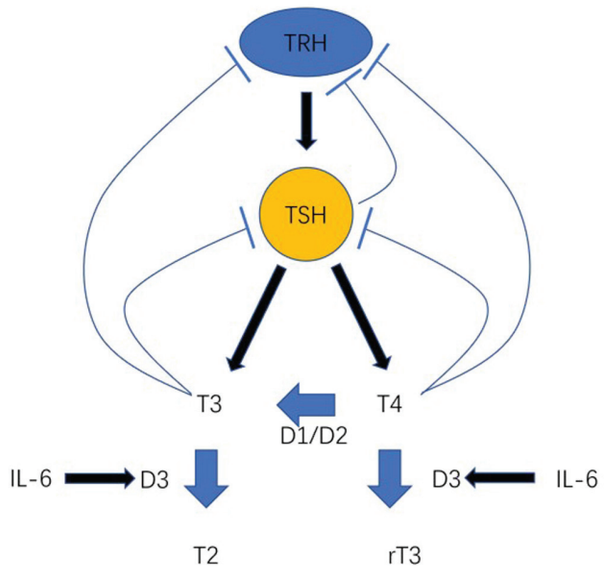

Fig. 3 Hypothalamic-pituitary-thyroid axis. D = deiodinase; IL = interleukin; rT3 = reverse T3; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

considerably. Regarding brain injury, secretory THs of HPT axis and end products of them are reduced owing to loss of intracerebral blood circulation.[37] Regarding sepsis, inflammatory cytokines (like IL [interleukin]-6) may play an important role in decreasing the levels of THs;[38] IL-6 upregulates type-3 deiodinase (D3, which converts T4 to rT3, metabolically inactive form, shown in Fig. 3) activity.[39] For fasting patients (large proportion of ICU patients), increased levels of type-2 iodothyronine (D2, which converts T4 to T3, metabolically active form) in the mediobasal hypothalamus was supposed to promote local T3 production, which inhibits the expression of thyrotropin-releasing hormone (TRH) and secretion of TSH.[40] And type-3 deiodinase (D3, which converts T4 to rT3 or T3 to T2) activity is increased as a result of fasting and decreases T4 concentrations.[41] For patients with severe illness, serum T3 concentration tends to decrease with the increase in severity.[42] Similar to humans, the same phenomenon has been found in animals.[43,44] All these studies further confirmed the predictive value of THs for the outcome of critical ill patients.

The coexistence of normal or low TSH and low TH levels (T3, T4, fT3, fT4) affects the setpoint of the HPT axis. The uneven distribution of T3 plays a critical role in the process. The critical ill state is associated with the increased expression of D2 and decreased expression of D3 in the mediobasal hypothalamus. Elevated D2 and reduced D3 both contributed to the inhibition of TRH neurons, which led to lower expression of TRH. As a result, TSH activity was downregulated.[36,45] The changes in hypothalamic D3 were mediated by the inflammatory pathways nuclear factor κB (NF-κB) and activator protein-1, whereas D2 was mediated by NF-kB.[45,46] When the levels of circulating THs are low, high levels of local T3 in hypothalamic cells inhibit the expression of TRH and downregulate TSH activity directly.[47,48]

Although a decrease in THs may be an adaptive response to critical illness, like fasting,[36] low levels of THs have been demonstrated to be associated with high mortality. Researchers have tried to give patients T3, LT4, TRH, GH-releasing peptide-2, and growth hormone-releasing hormone as TH replacement. Only a few trials (Table 3) analyzed the relationship between TH replacement and mortality. Some clinical trials have shown beneficial effects (improving cardiac function, decreasing the vasopressor score, synchronizing pituitary secretion of growth hormone and prolactin, etc), and most T3 and LT4 trials failed to show benefits.[36] Furthermore, trials focused on the clinical outcome of mortality did not demonstrate positive effects of TH replacement therapy. As for the failure of T3 and LT4 (L-thyroxine) therapy in reducing mortality, a logical assumption is that high doses of LT4 or T3 will further suppress TSH release and aggravate HPT dysfunction.[51,52] In this regard, neuropeptides like TRH may be a better solution to normalize thyroid function.[53]

There are other prognostic markers already widely used for predicting ICU outcomes (ie, APACHE II and Therapeutic Intervention Scoring System [TISS]). Although these widely approved ICU mortality prediction scores are more accurate, they are more time-consuming and require measurement of multiple parameters by well-trained personnel. Concomitant THs measurement can be more helpful to assess severity and to predict clinical outcomes.[19,29] A recent study showed that the combination of THs with APACHE II score may prove to be a better indicator of ICU morbidity and mortality than APACHE II alone in ICU patients with sepsis.[54] Taking the THs index into account, APACHE II will be a more accurate illness scoring system.

This systematic review had a level of heterogeneity. First, this meta-analysis was based on the premise that the included studies enrolled populations without limits to specific diseases. However, most included studies were limited to a single ICU (ie, medical ICU, emergency ICU, or surgical ICU), for which the patients were limited to certain diseases. Second, there is a fine distinction of the endpoint of the clinical outcomes among the included studies. The clinical outcomes included ICU mortality, hospital mortality, and 28-day mortality. The differences in outcomes contribute to a stronger confounding effect. Third, the measurement devices in the included studies in the analysis were different to a great extent. Therefore, the THs levels are distributed over a vast range. We had to calculate the statistics with SMD rather than MD, which resulted in greater statistical errors. Fourth, the measurement of THs differed with time in a day/night. Thyroid hormones and TSH show day-night variations,

Table 3

The clinical trials using mortality or death as clinical outcomes

Diagnosis	Design of clinical trials	Intervention	Outcomes
Coronary artery bypass grafting with a preoperative LVEF < 30% (n = 80)[48]	Prospective, randomized trial	T3 (125 μg/d) orally (7 d preoperative until discharge)	No difference
Acute renal failure (n = 59)[49]	Prospective, randomized, placebo-controlled, double-blind trial	LT4 infusion, 150 μg/20 mL every 12 h for 48 h	Higher mortality in the thyroxine group than the control group (43% vs 13%)
Patients in the ICU with low T4 concentrations (n = 23)[50]	Randomized prospective trial	1.5 μg/kg bodyweight LT4 IV for 2 weeks	Higher mortality in the LT4 group without statistical difference.

ICU = intensive care unit; IV = intravenous; LT4 = levothyroxine; LVEF = left ventricular ejection fraction.

CA9_V85N4_Text.indb 450 04-Apr-22 13:11:04

TSH and T3 reach maximal levels during the early part of the night.[55] Partial uncertainty was contributed by unfixed measure time, the measurement taken in a day/night. In addition, metabolic or endocrine diseases and drugs known to affect the endocrine axis (glucocorticoids, estrogens, etc) may alter TH levels, but a minority of the included trials took this point into account. All these heterogeneities cannot be adequately explained, and thus undermine the credibility of the results.

In addition, there are few randomized control trials and prospective trials evaluating the prognostic value of this risk assessment method. Besides, as the accurate concentrations of THs cannot be obtained, this study cannot further evaluate the cutoff values of THs to improve current widely used predictive tools, such as APACHE II and SOFA. Thus, the prognostic value of THs remains unclear.

In conclusion, nonsurvivors were associated with lower levels of THs (T3, T4, fT3, fT4) than survivors in patients admitted to the ICU. THs show high potential in improving the already widely used prognostic scores in the ICU (ie, APACHE II and TISS). Further research is needed to confirm the association between the clinical outcomes and THs.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A129.

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CA9_V85N4_Text.indb 452 04-Apr-22 13:11:05