International Journal of Surgery 70 (2019) 44–52

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Review

A prognostic role for non-thyroidal illness syndrome in chronic renal failure:a systematic review and meta-analysis

Huaiyu Xiong[a,b,c,1], Peijing Yan[b,d,1], Qiangru Huang[a,b,c], Tiankui Shuai[a,c], Jingjing Liu[a,c], Lei Zhu[a,c], Jiaju Lu[a,c], Xiue Shi[f], Kehu Yang[b,d,e,f,g,**], Jian Liu[a,c,*]

[a] Department of Intensive Care Unit, The First Hospital of Lanzhou University, Lanzhou, 730000, China
[b] Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou, 730000, China
[c] The First Clinical Medical College of the First Hospital of Lanzhou University, Lanzhou, 730000, China
[d] Institute of Clinical Research and Evidence Based Medicine, The Gansu Provincial Hospital, Lanzhou, 730000, China
[e] Evidence Based Social Science Research Center, Lanzhou University, Lanzhou, 730000, China
[f] Institute of Evidence Based Rehabilitation Medicine of Gansu Province, Lanzhou, 730000, China
[g] Key Laboratory of Evidence Based Medicine and Knowledge Translation of Gansu Province, Lanzhou, 730000, China

ARTICLE INFO

Keywords:
Non-thyroidal illness syndrome
Low T3 syndrome
Chronic renal failure
Chronic kidney disease
Meta-analysis

ABSTRACT

Background: Chronic renal failure (CRF) is a serious disease that has become a burden on global and local economics and public health. In addition, non-thyroidal illness syndrome (NTIS) has become increasingly more prevalent in CRF patients.

Materials and methods: A data search was conducted on the PubMed/Medline, Cochrane Library, Web of Science, Embase, and CBM databases to identify studies up to November 1st, 2018, that compared low T3 and normal T3 levels in patients with CRF. Data analysis was done by calculating the relative risks (RR) and 95% confidence intervals (95% CI) and continuous variables were described by weighted mean difference (WMD) and 95% CI. The efficacy outcomes included renal function and mortality. The Newcastle-Ottawa Scale and Agency for Healthcare Research and Quality scale were used to assess the quality of the cohort and cross-sectional studies, respectively. A funnel plot was used to identify publication bias.

Results: Seventeen studies with a total of 4593 patients were finally included in the analysis. Among the 17 studies, 11 reported the mortality of CRF patients with low T3 and normal T3 levels. Subgroups were assigned according to different follow-up times and different methods of treatment. The mortality rate in the low T3 group was much higher than in the normal T3 group. 11 studies reported creatinine (Cr) results in patients with low T3 and normal T3 levels and our analysis found no significant differences between the two groups (95%CI: 0.46–0.25; *P*-heterogeneity = 0.000; $P = 0.559$). Five studies reported uric acid results and we found no significant differences between the two groups (95%CI: 0.08–0.22; *P*-heterogeneity = 0.438; $P = 0.377$). Five studies reported the urea levels in the two groups and our analysis found no significant differences (95%CI: 1.60–1.23; $I^2 = 0.0\%$; *P*-heterogeneity = 0.498;$P = 0.798$).

Conclusion: Low T3 had a greater impact on the short-term prognosis of patients with CRF than on the long-term prognosis. NTIS did not cause substantial kidney damage.

1. Introduction

Chronic renal failure (CRF) is a serious disease that has become a global burden on both economics and public health [1]. The National Center for Health Statistics reported that CRF has risen among all causes of death [2]. Therefore, predicting the long-term outcomes of patients with CRF can help provide optimal care transition for patients and ultimately improve long-term outcomes [3,4].

Low levels of triiodothyronine (T3) (such as those in low T3 syndrome) are well-known, common complications of many serious diseases and T3 levels play a very essential role in the prognosis of critically-ill patients [5]. Non-thyroidal illness syndrome (NTIS) is defined

* Corresponding author. No.199 Donggang West Road, Chengguan District, Lanzhou City, Gansu Province, China.
** Corresponding author. No.199 Donggang West Road, Chengguan District, Lanzhou City, Gansu Province, China.
E-mail addresses: kehuyangebm2006@126.com (K. Yang), medecinliu@sina.com (J. Liu).
[1] Co-First Author: Huaiyu Xiong, Peijing Yan.

https://doi.org/10.1016/j.ijsu.2019.08.019
Received 25 February 2019; Received in revised form 24 July 2019; Accepted 16 August 2019
Available online 19 August 2019
1743-9191/

as decreased serum free T3 and/or free thyroxin (T4) concentrations, with increased reverse T3 (rT3) and normal concentrations of thyroid-stimulating hormone (TSH) [6].

A previous study reported a fast decrease in T3 and T4 levels in critically ill patients, with no concomitant rise in TSH levels, before their death [7]. Another study reported morbidity rates of up to 79% in dialysis patients with NTIS [8]. Furthermore, some investigators have suggested measuring T3 levels to assess the effects of thyroid dysfunction on the mortality of uremic patients [9–13].

A previous survey considered NTIS a protective co-morbidity in renal disease [14]' however, an increasing number of studies have shown that NTIS is a common complication in CRF patients, associated with poor prognosis and high mortality [15–26]. In addition, high-quality meta-analysis has been increasingly regarded as a key tool for validating evidence [27–29]. Here, we used original research reports to conduct a meta-analysis summarizing the relationship between NTIS and the prognosis of CRF patients to determine if NTIS substantially decreased renal function and to provide a foundation on which to base treatment decisions for NTIS in patients with CRF.

2. Research design and methods

All methods follow the PRISMA guidelines for conducting systematic reviews and meta-analyses [30]. This meta-analysis was conducted according to Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines and registered on PROSPERO International Prospective Register of systematic reviews (PROSPERO Identifier: CRD42019118428) [31].

2.1. Data sources and searches

Searches were conducted on the PubMed/Medline, Cochrane Library, Web of Science, Embase, and CBM databases [32] up to November 1, 2018, to identify studies that compared low T3 and normal T3 in patients with CRF. We also screened all relevant studies from references to supplement these databases. The keywords and Mesh terms were combined in the following search strategy: ("Euthyroid Sick Syndromes" [Mesh] OR "Non-Thyroidal Illness Syndrome" OR "Euthyroid Sick Syndrome")AND ("Kidney Failure, Chronic" [Mesh] OR "End-Stage Kidney Disease"). The detailed search strategy is shown in Appendix 1.

Eligible studies met the following inclusion criteria:

1. Observational studies that only included patients over the age of eighteen
2. Assessed the relationship between NTIS and CRF
3. Compared CRF patients with low T3 and normal T3
4. Study patients had no history of thyroid replacement therapy
5. Study patients had no history of renal transplant
6. The follow-up time was more than six months in studies that evaluated mortality

The following types of studies were excluded from the analysis:

1. Studies with research animals or cells
2. Studies that only provided an abstract
3. Reviews and meta-analyses

2.2. Data extraction and quality assessment

The data were extracted by two authors. For every study included, data on authors, location, publication year, study design, patient characteristics, numbers of patients with low T3 and normal T3, any use of thyroid medications or therapy, dialysis status, baseline concentration of FT3, and body mass index (BMI) were extracted. The Newcastle-Ottawa Scale (NOS), which contained 3 main concepts, selection, comparability, and outcome assessment, was used to assess the quality of 14 cohort studies. We defined scores ≥7 as low risk of bias, 5–7 as moderate risk, and < 5 as high risk. The Agency for Healthcare Research and Quality (AHRQ) scale, which included 11 terms, was used to assess the quality of 3 cross-sectional studies included in the analysis. AHRQ scores of 0–3 indicated low quality, 4–7 indicated moderate quality, and scores of 8–11 were classified as high quality. We used Engauge Digitizer (version 4.1) graphical data extraction software to extract data on mortality that were only provided by Kaplan-Meier curves (K-M survival curve) in several studies [33].

2.3. Data analysis

We used Stata/SE 14.0 to analyze the data. Dichotomous outcomes between the two groups were compared by calculating the relative risks (RR) and 95% confidence interval (95% CI) and the continuous variables were described by weighted mean difference (WMD) and 95% CI. Heterogeneity was assessed by the I^2 statistic versus the P-value. A P-value ≤ 0.05 and $I^2 \geq 50\%$ were considered high heterogeneity and $I^2 \leq 50\%$ indicated heterogeneity in an acceptable range. At this time, a fixed effect model was selected for the data analysis. Otherwise, a random effect model was chosen. Sensitivity analysis and subgroup analysis were used to determine the source of the heterogeneity. Egger's Test and Begg's Test were used to assess publication bias. A funnel plot was also constructed [34]. $P < 0.05$ was considered statistically significant.

3. Results

We retrieved 265 studies from five databases and additional records identified through other sources. We excluded 248 studies based on the inclusion and exclusion criteria and 17 studies were finally included in our meta-analysis, 14 cohort studies and three cross-sectional studies (Fig. 1). A total of 4593 patients were included in the 17 studies and the data and information extracted are shown in Table 1. The sample size in each study varied from 27 to 835 patients and 1999 patients and 2594 patients had low T3 and normal T3 levels, respectively. The mean age ranged from 49 to 78.9 years in the low T3 group and 48–70.3 years in the normal T3 group. Differences in the baseline concentration of FT3 between the low T3 and normal T3 groups were significantly different. NOS scores ranged from 5 to 7 in the 14 cohort studies. Out of 14 cohort studies, six studies were at low risk of bias and eight studies were at moderate risk of bias. All three cross-sectional studies were at moderate risk of bias. Eleven studies reported the mortality of CRF patients with low T3 and normal T3 levels. Ten studies reported mortality for up to three years and one study reported only two years [23,35–44]. Of the 17 studies, 11 studies reported creatinine (Cr) test results [1,22,23,35–39,45–47], five studies reported uric acid test results [15,36,37,45,46], and five studies reported urea results [37,38,40,45,47].

3.1. Mortality

Eleven studies reported one-year data [23,35–44], 11 studies provided two-year follow-up [23,35–44], 10 reported data three years following discharge [23,35–39], eight reported four-year data [35,37–39,41–44], and seven studies collected mortality data every year until five years after discharge [35,37,38,41–44]. We compared each year to see if there was any correlation with years of follow-up. Relative risk (RR) was used to describe the mortality between two groups. The results showed that the mortality in the low T3 group was much higher than in the normal T3 group at each follow-up time (One year: RR: 3.030; 95%CI: 2.298–3.996; $I^2 = 0.00\%$; P-heterogeneity = 0.790; $P < 0.001$; 11 studies. Two years: RR: 2.374; 95%CI: 1.836–3.070; $I^2 = 42.9\%$; P-heterogeneity = 0.064; $P < 0.001$; 11 studies. Three years: RR: 1.928; 95%CI: 1.541–2.412; $I^2 = 58.9\%$; P-

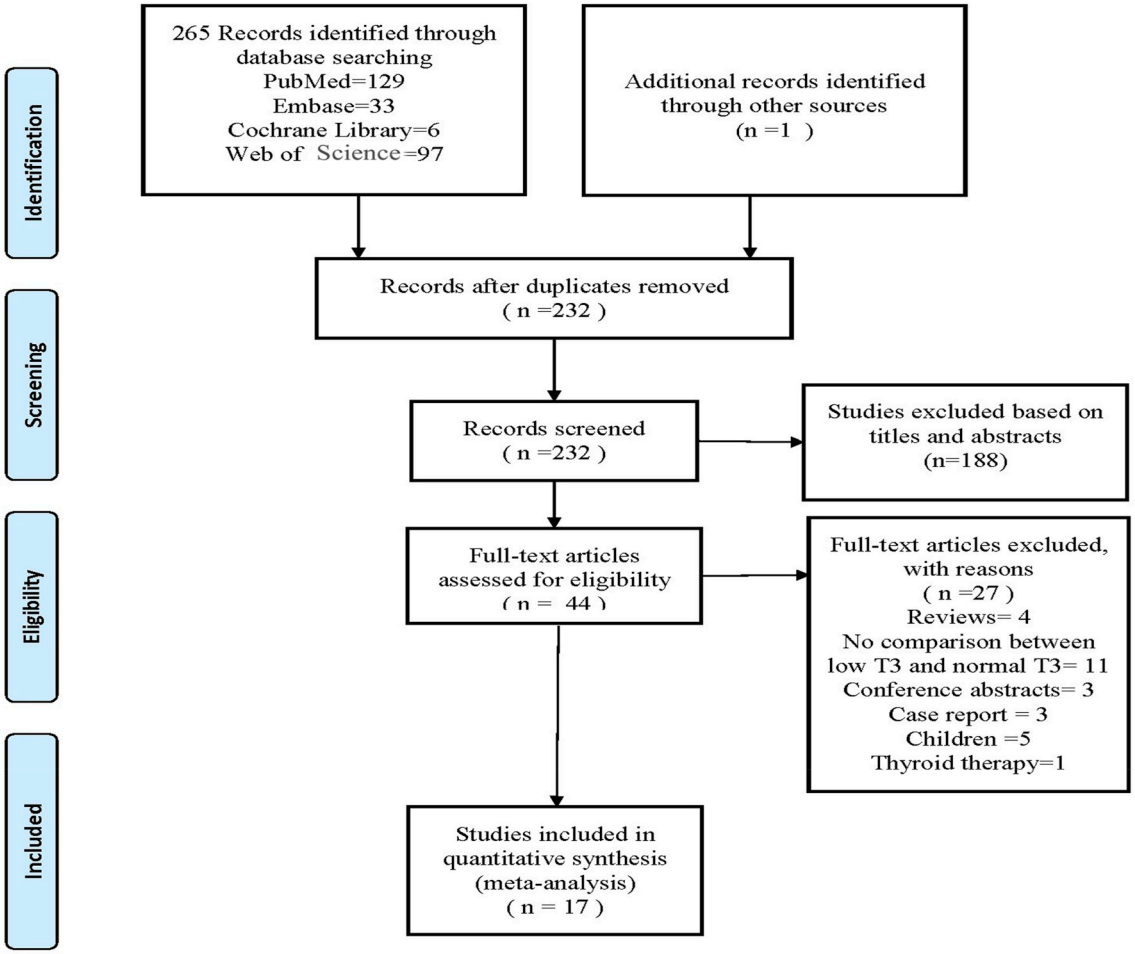

Fig. 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram and exclusion criteria.

heterogeneity = 0.009; $P < 0.001$; 10 studies. Four years: RR: 1.757; 95%CI: 1.405–2.199; $I^2 = 71.3\%$; P-heterogeneity = 0.001; $P < 0.001$; eight studies. Five years: RR: 1.652; 95%CI: 1.355–2.015; $I^2 = 69.1\%$; P-heterogeneity = 0.003; $P < 0.001$; seven studies) (Fig. 2). The results of Egger's and Begg's tests showed that there was no publication bias in the studies included in our analysis (Egger's: $P = 0.162$; Begg's: $P = 0.213$; 11 studies) [48] (Supplementary S1). A funnel plot for mortality was constructed and is shown in Supplementary S2. We assigned subgroups by different therapy methods to construct a forest plot to compare mortality between the two groups. The results showed a significant difference between peritoneal dialysis (PD) group and Hemodialysis (HD) group (Not: RR: 1.57; 95%CI: 1.15–2.15; $P = 0.005$; one study. PD: RR: 1.72; 95%CI: 1.30–2.27; $I^2 = 56.9\%$; P-heterogeneity = 0.073; $P < 0.001$; four studies. HD: RR: 1.73; 95%CI: 1.47–2.03; $I^2 = 52.0\%$; P-heterogeneity = 0.034; $P < 0.001$; nine studies) (Fig. 3).

3.2. Renal failure severity

Renal failure severity was assessed by renal function tests, which included Cr, uric acid, and urea. Eleven studies reported Cr results in patients with low and normal T3 levels and our analysis found no significant difference between the two groups (WMD: 0.10; 95%CI: 0.46, −0.25; $I^2 = 77.7\%$; P-heterogeneity = 0.000; $P = 0.559$) (Fig. 4). Five studies reported uric acid results and no significant difference between the two groups was found (WMD: 0.07; 95%CI: 0.08, −0.22; $I^2 = 0.0\%$; P-heterogeneity = 0.438; $P = 0.377$) (Fig. 5). Five studies reported urea results and no significant difference was found between the two groups (WMD: 0.18; 95%CI: 1.60, −1.23; $I^2 = 0.0\%$; P-heterogeneity = 0.498; $P = 0.798$) (Fig. 6).

4. Discussion

This meta-analysis included 17 studies with a total of 4593 patients with CRF. The pooled data suggested that the all-cause mortality in the low T3 group was much higher than that in the normal T3 group. In order to explore the impact of T3 levels further, we conducted additional meta-analyses, which showed that NTIS did not have a significant effect on renal function in patients with CRF.

The meta-analysis of all-cause mortality demonstrated that the influence of low T3 in CRF patients was reduced each year of patient follow-up. The was a 3.030-fold relative risk at one-year follow-up and a 1.652-fold relative risk at five-year follow-up. The decrease from the one-year group to five-year group was statistically significant, indicating a negative correlation between the effect of low T3 on all-cause mortality and follow-up time. This result was consistent with a study by Christiane et al. [35] that reported an association of HD patients with NTIS and early mortality. Interestingly, Kanji tried to explore whether it is beneficial to treat CRF patients with NTIS and found no evidence indicating that treating NTIS patients accelerated their death [49]. The results of this meta-analysis highlighted the importance of early evaluation and detection of NTIS. Early diagnosis of NTIS and appropriate interventions will effectively reduce mortality in patients with CRF. This study also showed that early thyroid hormone replacement therapy had the potential to reduce the risk of mortality in CRF patients. In addition, there is an urgent need to explore the effect of NTIS on long-term mortality of CRF patients, as well as the deeper relationship between CRF and NTIS.

Table 1
Characteristics of studies we included in the meta-analysis.

Study	Year	Study Design	Country (period)	N	Dialysis	Outcome	AHRQ	NOS	Age (yrs)		Male (%)	FT3 (pg/ml)		BMI(Kg/m^2)	
									low	normal	low/normal	Low	Normal	low	normal
Shu-Lan Qin	2018	cohort	China (2015–2016)	120	Not	②③④	–	5	62.0 ± 12.4	61.0 ± 12.0	66.7/71.7	1.8 ± 0.4	2.6 ± 0.6	22.7 ± 2.0	23.3 ± 2.1
Baris Afsar	2017	cohort	Turkey (2010–2015)	183	Not	③	–	7	49 ± 10.7	48.8 ± 12.2	35.0/50.9	0.7 ± 0.815	2.9 ± 0.667	26.9 ± 2.5	26.3 ± 2.8
Jingxian Fan	2016	cross-sectional	China (2012–2013)	114	Not	②	6	–	78.9 ± 15.3	66.5 ± 13.8	57.9/65.8	2.25 ± 0.28	2.76 ± 0.24	NA	NA
Ismail Kocyigit	2014	cross-sectional	Turkey (2013–2013)	125	PD	②	7	–	54.7 ± 11.5	50.7 ± 13.8	54.3/63.3	NA	NA	29.5 ± 5.05	27.2 ± 4.4
Christiane Drechsler	2014	cohort	Germany (1998–2002)	835	HD	①②	–	6	66.3 ± 8.6	65.3 ± 8.5	31.0/57.0	1.56 ± 0.13	2.40 ± 0.45	25.1 ± 4.6	27.8 ± 5.1
Yee Yung Ng	2013	cohort	China (2009)	864	HD	②③	–	5	62.3 ± 13.0	59.2 ± 13.9	48.3/50.5	NA	NA	22.5 ± 3.5	22.6 ± 3.5
Christiaan L. Meuwese	2013	cohort	Sweden (2006–2009)	84	PD	①②	–	6	65.0 ± 13.0	62.0 ± 15.0	60.0/76.0	3.4 ± 0.3	4.5 ± 0.4	NA	NA
Jae Won Yang	2011	cohort	South Korea (2006–2009)	211	Not + PD + HD	①③④	–	6	62.2 ± 16.4	56.6 ± 15.1	57.5/53.3	NA	NA	NA	NA
Tae Ik Chang	2015	cohort	Korea (2000–2009)	297	PD	①④	–	7	60.8 ± 13.6	57.7 ± 14.9	53.6/47.3	NA	NA	22.3 ± 2.95	22.5 ± 3.79
Giuseppe Enia	2006	cohort	Italy (2008)	27	HD	①	–	7	57.0 ± 19.0	69.0 ± 14.0	86.0/54.0	3.11 ± 0.7	2.87 ± 0.83	NA	NA
M.J. Fernández-Reyes	2009	cross-sectional	Spain (2008)	32	HD + PD	②④	7	–	71.9 ± 9.8	70.3 ± 13.9	NA	NA	NA	23.9 ± 4.1	29 ± 4.2
Hyang Mo Koo	2013	cohort	Korea (2008–2012)	471	HD	①②③④	–	6	58.6 ± 14.9	55.2 ± 14.7	50.9/63.4	NA	NA	23.55 ± 3.43	22.71 ± 3.89
C Zoccali1	2006	cohort	Italy (2008)	132	HD	①	–	6	67.0 ± 12.0	60.0 ± 14.0	53.0/45.0	NA	NA	NA	NA
Stylianos Fragidis	2015	cohort	Grace (–)	114	HD	①③④	–	7	66.8 ± 13.1	59.9 ± 14.7	65.7/77.2	NA	NA	26.49 ± 4.02	25.65 ± 2.92
ezban Pinar Ozen	2011	cohort	Turky (2005)	669	HD	①②	–	6	56.0 ± 14.0	48.0 ± 14.0	51.0/52.0	1.28 ± 0.32	1.96 ± 0.24	24.1 ± 4.6	23.9 ± 4.77
Jianjun Gao	2017	cohort	China (2012–2012)	128	HD	①④	–	7	62.0 ± 14.0	59.0 ± 15.0	41.0/47.0	3.0 ± 0.6	4.4 ± 1.2	22.1 ± 3.6	23.2 ± 4.6
J. J. Carrero1	2007	cohort	Sweden (1994–2006)	187	HD + PD	①	–	7	55.0 ± 11.7	55.0 ± 12.7	69.0/59.0	NA	NA	24.8 ± 4.1	23.9 ± 4.3

Outcome:①Mortality; ② Creatine (Cr); ③Uric acid; ④Urea; BMI:Body Mass Index; NOS: Newcastle-Ottawa Scale; AHRQ: Agency for Healthcare Research and Quality; N:Number of samples.
Abbreviations: HD: Hemodialysis; PD: Peritoneal dialysis; Not: Not dialysis; NR: Not Reported.

A large number of previous research has shown that NTIS could predict an adverse prognosis in patients with CRF [15–26]. Moreover, this meta-analysis, which showed that low T3 affected the mortality of patients with CRF, agreed with the findings of those previous studies. However, the mechanism of its influence was not clear from our analysis. Thus, we hypothesized that the effect of low T3 on mortality was by caused by damage to renal function. We collected renal function results, including creatinine, urea, and uric acid, in the studies we included and analyzed them in relation to T3 levels. The analyses found no statistical differences between the renal function test results in the low T3 group and the normal T3 group, which indicated that the presence of low T3 did not substantially damage renal function. Low T3 was only an acute reaction that occurred after CRF and further illustrates that low T3 synthesis was not the cause of chronic renal failure.

A previous study suggested that low T3 levels in patients with CRF were due to dysregulated thyroid hormone metabolism in the peripheral and central [50], that may be due to a variety of reasons including, increased mitogenic cytokines, changes in thyroid hormone and binding protein levels, and metabolic changes associated with free fatty acid and bilirubin levels [50]. Several works in the past have investigated the mechanism of low T3 in patients and concluded it to be endogenous reactions caused by CRF [51–53]. During CRF inflammation, an increase in IL-6 levels may result in an increase in C-reactive protein and suppression of the hypothalamic-pituitary axis (HPA), subsequently preventing stimulation of thyroid hormones and inhibiting peripheral thyroxine-triiodothyronine (T4-T3) conversion [51–53].

Heterogeneity in the mortality results increased as the follow-up time increased. Possible reasons for this phenomenon are: First, over time, patients could develop other kinds of diseases that might cause death. Christiane et al. [35] only found an association between CRF and NTIS in blood samples taken within one year and the association completely diminished after three years. Second, the CRF patients in the original studies could suffer from different types of disorders. The study by Christiaan et al. [17], for example, included patients with diabetes mellitus, renovascular disease, glomerulonephritis, and immunoglobulin A nephropathy. Different disorders and outcomes in these patients may cause heterogeneity in mortality.

High heterogeneity was seen in creatinine levels. Heterogeneity may result from the use of different T3 value cutoffs, different blood specimen collection times, and different laboratory methods. For example, several studies we included used total T3 instead of free T3 to describe NTIS [1,37,41,46]. Possible additional reasons include varying lengths of study follow-up, adjustment of sample size, and other confounding factors. Moreover, patient characteristics (e.g., racial differences, different mean age) can also lead to heterogeneity. Carrerol et al. [44], only included patients in stage 5, who likely were more seriously ill than the patients included in other studies.

The studies included in this analysis were assessed to have a low-moderate risk of bias. Over half of the included studies were at moderate risk of bias and this might cause our results to be less representative of all studies. Further studies are needed to test our conclusion. There was no publication bias for mortality, which means it was less likely we missed studies that might have influenced the results.

There were several limitations to this study. First, this meta-analysis was limited by the types of studies included. We only searched for observational studies and not randomized controlled trials. We evaluated a massive amount of literature to find high-quality evidence, however, because of a lack of articles in this area, the small number of studies we retrieved is a limitation of the study. Second, we cannot rule out selection bias by excluding studies that did not group low T3 and normal T3 patients separately. Third, information bias was inevitable because of the limited original data. From the eleven studies reporting mortality [23,35–44], the data we obtained were all extracted from K-M curves by using Engauge Digitizer software (version 4.1), which may be the main cause of the moderate heterogeneity in mortality in the

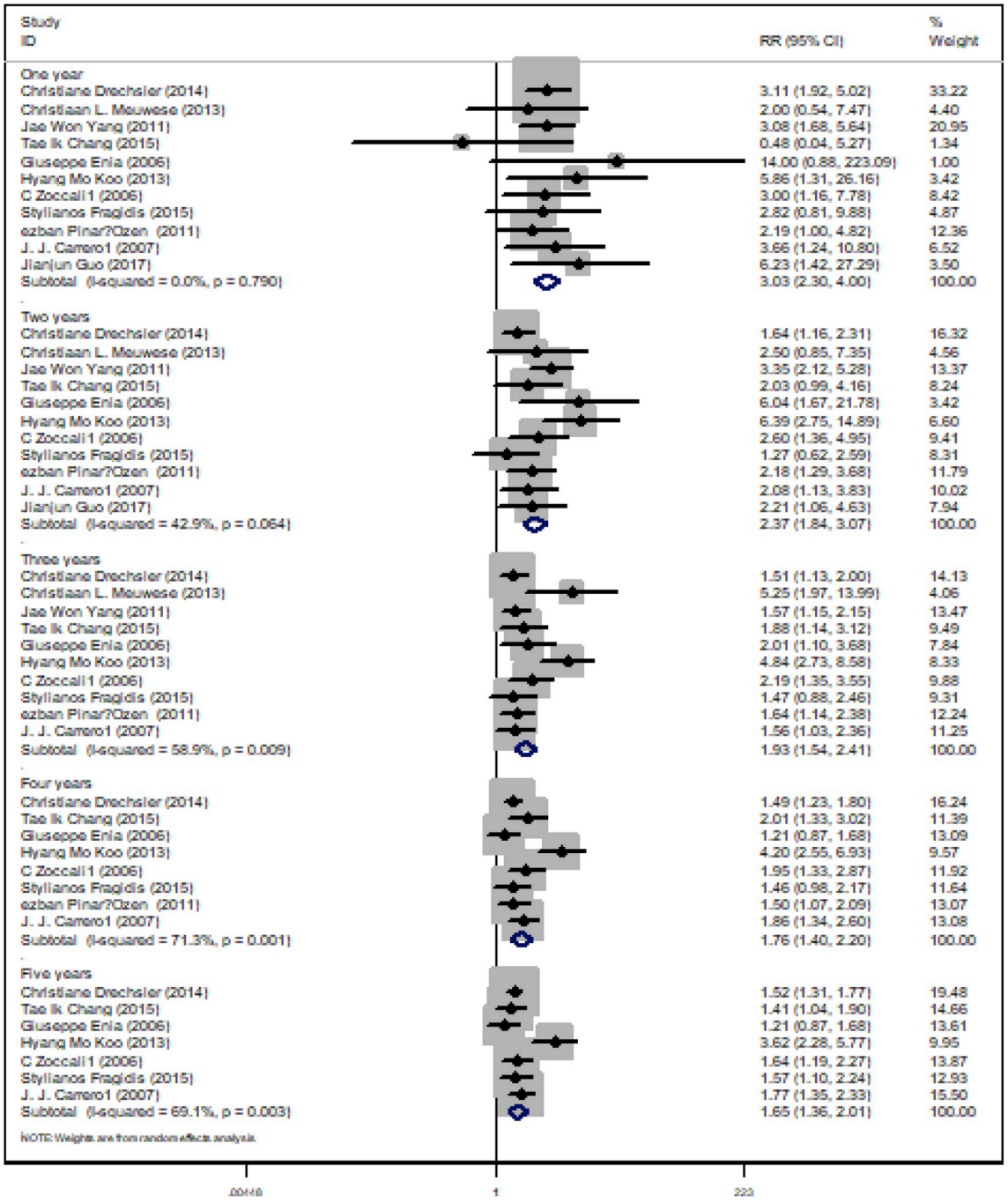

Fig. 2. Forest plot of mortality in CRF patients with or without NTIS according to different length of follow-up time.

groups. And several articles we included used the mean (quartile) or the mean (upper and lower) to describe the outcome indicators we needed. However, although we conducted an exhaustive search to identify as many articles as possible, the number of articles eventually included was still small and the sample size was insufficient, which may reduce the generalizability of our meta-analysis results.

Despite these limitations, our study had some strengths. This meta-analysis provides guidance for the treatment of CRF patients with low T3 levels. Because of the small number of included studies, more research is needed to determine if low T3 influences the 10- or even 20-year prognosis of CRF patients.

5. Conclusion

Low T3 had a greater impact on the short-term prognosis of patients with CRF than on the long-term prognosis. NTIS did not cause substantial reductions in kidney function.

Ethical approval

Not Applicable.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

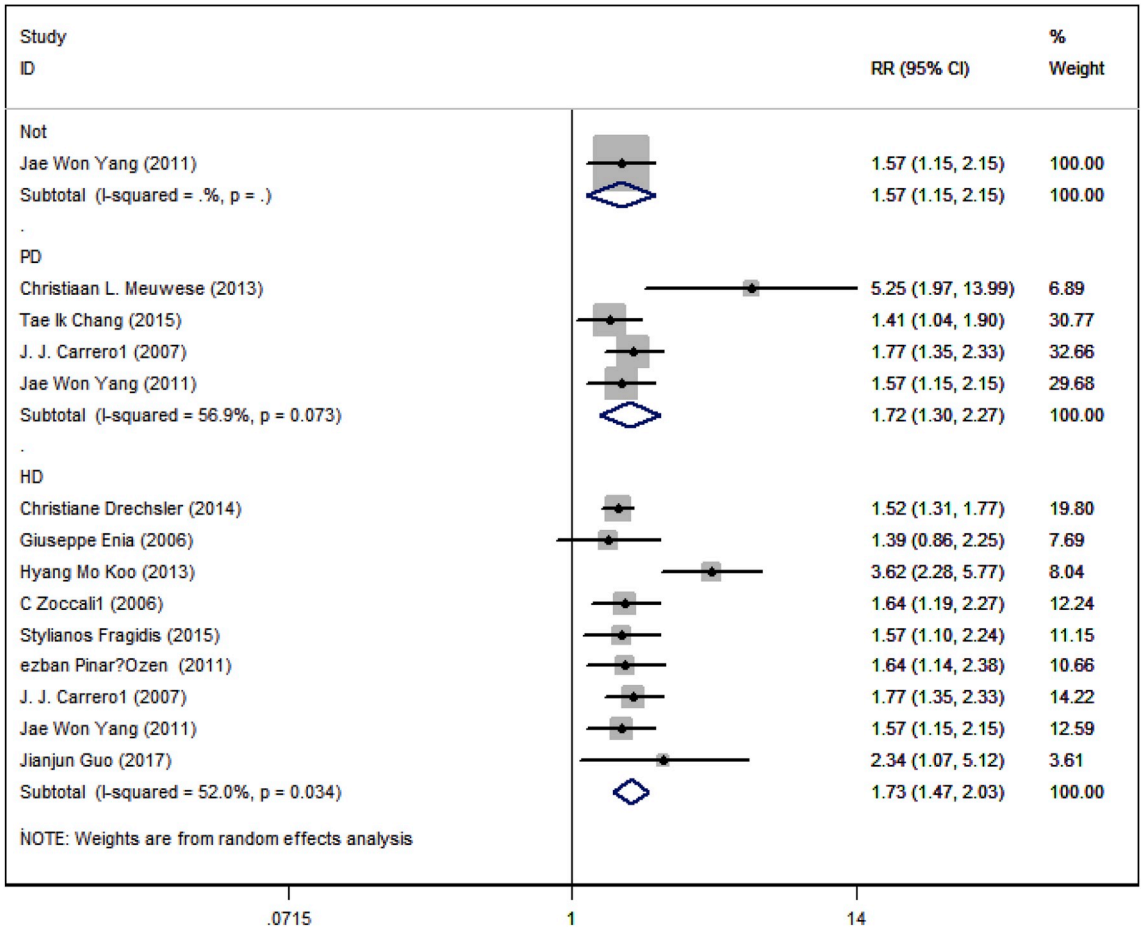

Fig. 3. Forest plot of mortality in CRF patients with or without NTIS according to different type of therapy methods.

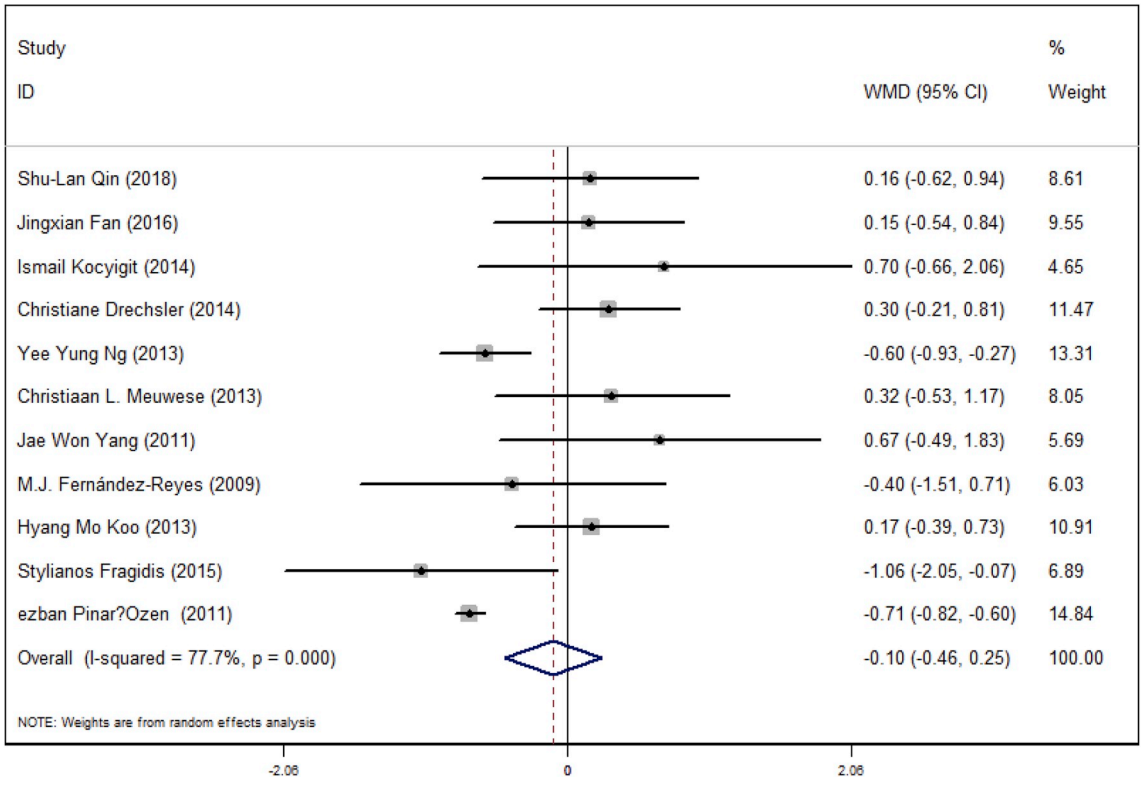

Fig. 4. Forest plot of Cr in both low T3 and normal T3 group.

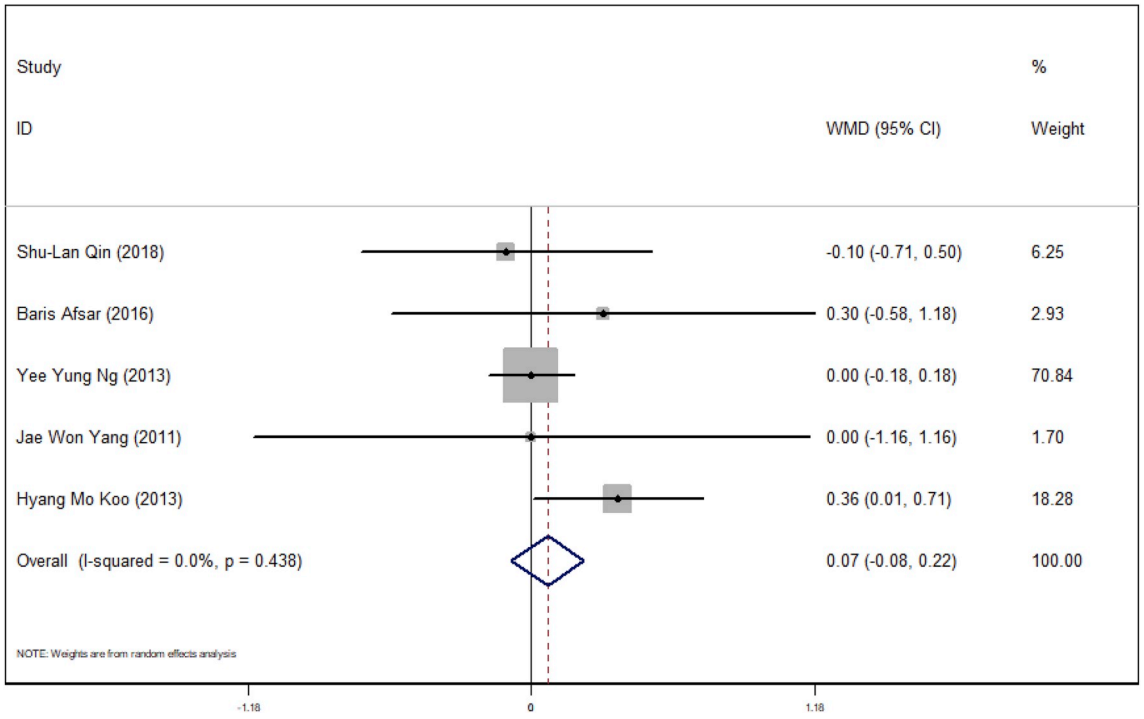

Fig. 5. Forest plot of uric acid in CRF patients with or without NTIS.

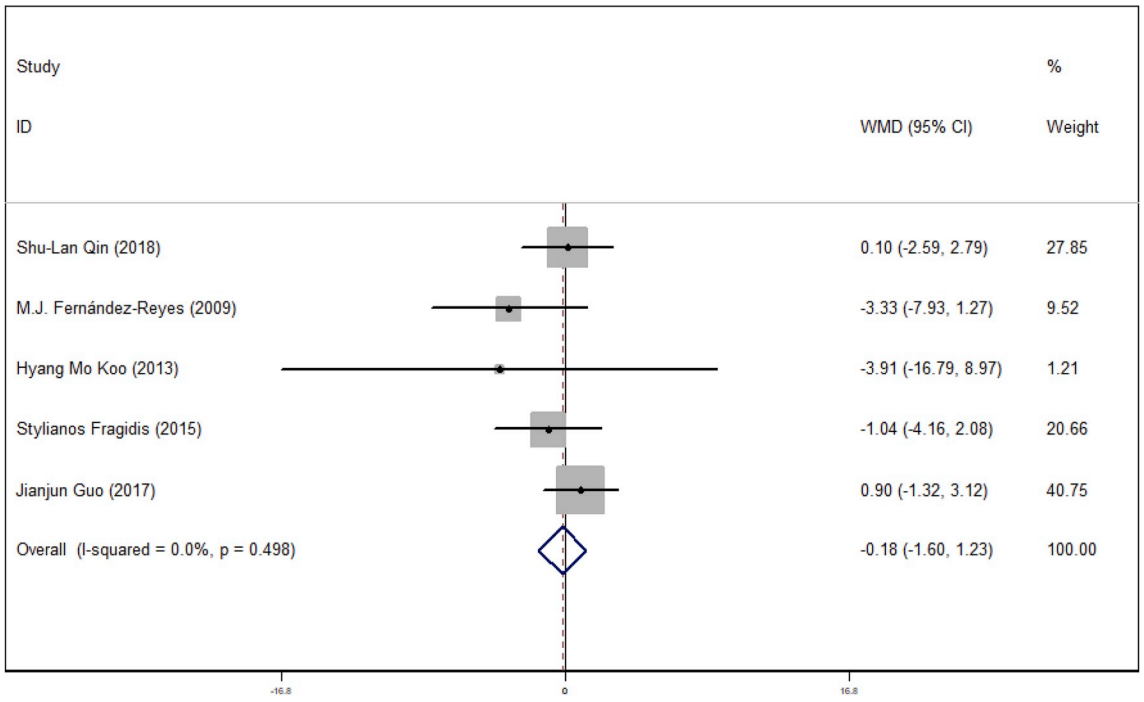

Fig. 6. Forest plot of Urea in CRF patients with or without NTIS.

Unique identifying number (UIN)

PROSPERO Identifier: CRD42019118428.
https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=118428.

Author contribution

Specific author contributions: Kehu Yang and Jian Liu provided experimental design; Jiaju Lu and Lei Zhu extracted studies; Tiankui Shuai, Qiangru Huang and Jingjing Liu collected and analyzed the data; Huaiyu Xiong and Peijing Yan drafted the manuscript; Kehu Yang and Jian Liu contributed to revision the manuscript;

All authors commented on drafts of the paper and final approval of the manuscript.

Conflicts of interest

Not Applicable.

Guarantor

Huaiyu Xiong.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Acknowledgements

Not applicable.

Abbreviations

AHRQ	agency for health care research and quality
BMI	body mass index
CKD	chronic kidney disease
CRF	chronic renal failure
Cr	creatinine
HD	hemodialysis
HPA	hypothalamic-pituitary axis
K-M curve	Kaplan-Meier curve
NOS	newcastle-ottawa scale
NTIS	non-thyroidal illness syndrome
PD	peritoneal dialysis
PRISMA	preferred reporting items for systematic reviews and meta-analyses
rT3	reverse triiodothyronine
T3	triiodothyronine
T4	thyroxine.
TSH	thyroid-stimulating hormone

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.08.019.

References

[1] J. Fan, P. Yan, Y. Wang, B. Shen, F. Ding, Y. Liu, Prevalence and clinical significance of low T3 syndrome in non-dialysis patients with chronic kidney disease, Med. Sci. Monit. 22 (2016) 1171–1179.

[2] National Center for Health Statistics, Mortality Multiple Cause Micro-data Files, 2013: Public-Use Data File and Documentation: NHLBI Tabulations, (2015).

[3] B. Wang, S. Liu, L. Li, Q. Yao, R. Song, X. Shao, et al., Non-thyroidal illness syndrome in patients with cardiovascular diseases: a systematic review and meta-analysis, Int. J. Cardiol. 226 (2017) 1–10.

[4] J. Hofmeijer, L.J. Kappelle, A. Algra, G.J. Amelink, J. van Gijn, H.B. van der Worp, Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy after Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial, Lancet Neurol. 8 (4) (2009) 326–333.

[5] E. Cole, D. Naimark, M. Aprile, J. Wade, R. Bear, An analysis of predictors of long-term cadaveric renal allograft survival, Clin. Transplant. 9 (4) (1995) 282–288.

[6] G. Xu, W. Yan, J. Li, An update for the controversies and hypotheses of regulating non thyroidal illness syndrome in chronic kidney diseases, Clin. Exp. Nephrol. 18 (6) (2014) 837–843.

[7] D.G. McLarty, W.A. Ratcliffe, K. McColl, D. Stone, J.G. Ratcliffe, Letter: thyroid-hormone levels and prognosis in patients with serious non-thyroidal illness, Lancet 2 (7928) (1975) 275–276.

[8] S.H. Song, I.S. Kwak, D.W. Lee, Y.H. Kang, E.Y. Seong, J.S. Park, The prevalence of low triiodothyronine according to the stage of chronic kidney disease in subjects with a normal thyroid-stimulating hormone, Nephrol. Dial. Transplant. 24 (5) (2009) 1534–1538.

[9] C.L. Meuwese, O.M. Dekkers, P. Stenvinkel, F.W. Dekker, J.J. Carrero, Nonthyroidal illness and the cardio renal syndrome, Nat. Rev. Nephrol. 9 (10) (2013) 599–609.

[10] C.M. Rhee, G.A. Brent, C.P. Kovesdy, O.P. Soldin, D. Nguyen, M.J. Budoff, et al., Thyroid functional disease: an under-recognized cardiovascular risk factor in kidney disease patients, Nephrol. Dial. Transplant. 30 (5) (2015) 724–737 official publication of the European Dialysis and Transplant Association - European Renal Association.

[11] C.M. Rhee, Low-T3 syndrome in peritoneal dialysis: metabolic adaptation, marker of illness, or mortality mediator? Clin. J. Am. Soc. Nephrol. : CJASN 10 (6) (2015) 917–919.

[12] C. Zoccali, F. Mallamaci, Thyroid function and clinical outcomes in kidney failure, Clin. J. Am. Soc. Nephrol. : CJASN. 7 (1) (2012) 12–14.

[13] W. Reinhardt, S. Dolff, S. Benson, M. Broecker-Preuss, S. Behrendt, A. Hog, et al., Chronic kidney disease distinctly affects relationship between selenoprotein P status and serum thyroid hormone parameters, Thyroid 25 (10) (2015) 1091–1096.

[14] E.M. Kaptein, Thyroid hormone metabolism and thyroid diseases in chronic renal failure, Endocr. Rev. 17 (1) (1996) 45–63.

[15] B. Afsar, M.I. Yilmaz, D. Siriopol, H.U. Unal, M. Saglam, M. Karaman, et al., Thyroid function and cardiovascular events in chronic kidney disease patients, J. Nephrol. 30 (2) (2017) 235–242.

[16] P. Mangieri, K. Suzuki, M. Ferreira, L. Domingues, L.A. Casulari, Evaluation of pituitary and thyroid hormones in patients with subarachnoid hemorrhage due to ruptured intracranial aneurysm, Arquivos de neuro-psiquiatria 61 (1) (2003) 14–19.

[17] C.L. Meuwese, J.J. Carrero, I. Cabezas-Rodriguez, O. Heimburger, P. Barany, B. Lindholm, et al., Nonthyroidal illness: a risk factor for coronary calcification and arterial stiffness in patients undergoing peritoneal dialysis? J. Intern. Med. 274 (6) (2013) 584–593.

[18] E. Tatar, F. Kircelli, G. Asci, J.J. Carrero, O. Gungor, M.S. Demirci, et al., Associations of triiodothyronine levels with carotid atherosclerosis and arterial stiffness in hemodialysis patients, Clin. J. Am. Soc. Nephrol. : CJASN. 6 (9) (2011) 2240–2246.

[19] E. Tatar, M. Sezis Demirci, F. Kircelli, O. Gungor, M. Yaprak, G. Asci, et al., The association between thyroid hormones and arterial stiffness in peritoneal dialysis patients, Int. Urol. Nephrol. 44 (2) (2012) 601–606.

[20] C. Zoccali, F. Benedetto, F. Mallamaci, G. Tripepi, S. Cutrupi, P. Pizzini, et al., Low triiodothyronine and cardiomyopathy in patients with end-stage renal disease, J. Hypertens. 24 (10) (2006) 2039–2046.

[21] E.W. Kang, J.Y. Nam, T.H. Yoo, S.K. Shin, S.W. Kang, D.S. Han, et al., Clinical implications of subclinical hypothyroidism in continuous ambulatory peritoneal dialysis patients, Am. J. Nephrol. 28 (6) (2008) 908–913.

[22] I. Kocyigit, O. Gungor, A. Unal, M. Yasan, O. Orscelik, O. Tunca, et al., A low serum free triiodothyronine level is associated with epicardial adipose tissue in peritoneal dialysis patients, J. Atheroscler. Thromb. 21 (10) (2014) 1066–1074.

[23] C.L. Meuwese, H. Olauson, A.R. Qureshi, J. Ripsweden, P. Barany, C. Vermeer, et al., Associations between thyroid hormones, calcification inhibitor levels and vascular calcification in end-stage renal disease, PLoS One 10 (7) (2015) e0132353.

[24] M.M. Fraczek, K. Lacka, Thyroid hormone and the cardiovascular system, Pol. Merkur. Lek. : organ Polskiego Towarzystwa Lekarskiego 37 (219) (2014) 170–174.

[25] G. Iervasi, G. Nicolini, Thyroid hormone and cardiovascular system: from basic concepts to clinical application, Int. Emerg. Med. 8 (Suppl 1) (2013) S71–S74.

[26] M.I. Yilmaz, A. Sonmez, M. Karaman, S.A. Ay, M. Saglam, H. Yaman, et al., Low triiodothyronine alters flow-mediated vasodilatation in advanced nondiabetic kidney disease, Am. J. Nephrol. 33 (1) (2011) 25–32.

[27] J. Tian, J. Zhang, L. Ge, K. Yang, F. Song, The methodological and reporting quality of systematic reviews from China and the USA are similar, J. Clin. Epidemiol. 85 (2017) 50–58.

[28] L. Yao, R. Sun, Y.L. Chen, Q. Wang, D. Wei, X. Wang, et al., The quality of evidence in Chinese meta-analyses needs to be improved, J. Clin. Epidemiol. 74 (2016) 73–79.

[29] P. Yan, L. Yao, H. Li, M. Zhang, Y. Xun, M. Li, et al., The methodological quality of robotic surgical meta-analyses needed to be improved: a cross-sectional study, J. Clin. Epidemiol. 109 (2019) 20–29.

[30] L. Ge, J.H. Tian, Y.N. Li, J.X. Pan, G. Li, D. Wei, et al., Association between prospective registration and overall reporting and methodological quality of systematic reviews: a meta-epidemiological study, J. Clin. Epidemiol. 93 (2018) 45–55.

[31] X. Wang, Y. Chen, L. Yao, Q. Zhou, Q. Wu, J. Estill, et al., Reporting of declarations and conflicts of interest in WHO guidelines can be further improved, J. Clin. Epidemiol. 98 (2018) 1–8.

[32] L. Li, J. Tian, H. Tian, D. Moher, F. Liang, T. Jiang, et al., Network meta-analyses could be improved by searching more sources and by involving a librarian, J. Clin. Epidemiol. 67 (9) (2014) 1001–1007.

[33] J.J. Lu, H. Guo, B. Gao, Y. Zhang, Q.L. Lin, J. Shi, et al., Prognostic value of urokinase plasminogen activator system in non-small cell lung cancer: a systematic review and meta-analysis, Mol. Clin. Oncol. 8 (1) (2018) 127–132.

[34] J. Lau, J.P. Ioannidis, N. Terrin, C.H. Schmid, I. Olkin, The case of the misleading funnel plot, BMJ (Clin. Res. Ed.) 333 (7568) (2006) 597–600.

[35] C. Drechsler, A. Schneider, L. Gutjahr-Lengsfeld, M. Kroiss, J.J. Carrero, V. Krane, et al., Thyroid function, cardiovascular events, and mortality in diabetic hemodialysis patients, Am. J. Kidney Dis. : Off. J. Nat. Kidney Found. 63 (6) (2014) 988–996.

[36] J.W. Yang, S.T. Han, S.H. Song, M.K. Kim, J.S. Kim, S.O. Choi, et al., Serum T3 level can predict cardiovascular events and all-cause mortality rates in CKD patients with proteinuria, Ren. Fail. 34 (3) (2012) 364–372.

[37] H.M. Koo, C.H. Kim, F.M. Doh, M.J. Lee, E.J. Kim, J.H. Han, et al., The impact of

low triiodothyronine levels on mortality is mediated by malnutrition and cardiac dysfunction in incident hemodialysis patients, Eur. J. Endocrinol. 169 (4) (2013) 409–419.
[38] S. Fragidis, K. Sombolos, E. Thodis, S. Panagoutsos, E. Mourvati, M. Pikilidou, et al., Low T3 syndrome and long-term mortality in chronic hemodialysis patients, World J. Nephrol. 4 (3) (2015) 415–422.
[39] K.P. Ozen, G. Asci, O. Gungor, J.J. Carrero, F. Kircelli, E. Tatar, et al., Nutritional state alters the association between free triiodothyronine levels and mortality in hemodialysis patients, Am. J. Nephrol. 33 (4) (2011) 305–312.
[40] J. Gao, Y. Xu, D. Kong, L. Zhou, H. Jia, B. Liang, et al., Association of triiodothyronine levels with left ventricular function, cardiovascular events, and mortality in hemodialysis patients, Int. J. Artif. Organs 40 (2) (2017) 60–66.
[41] T.I. Chang, J.Y. Nam, S.K. Shin, E.W. Kang, Low triiodothyronine syndrome and long-term cardiovascular outcome in incident peritoneal dialysis patients, Clin. J. Am. Soc. Nephrol. : CJASN 10 (6) (2015) 975–982.
[42] G. Enia, V. Panuccio, S. Cutrupi, P. Pizzini, G. Tripepi, F. Mallamaci, et al., Subclinical hypothyroidism is linked to micro-inflammation and predicts death in continuous ambulatory peritoneal dialysis, Nephrol. Dial. Transplant. 22 (2) (2007) 538–544 official publication of the European Dialysis and Transplant Association - European Renal Association.
[43] C. Zoccali, F. Mallamaci, G. Tripepi, S. Cutrupi, P. Pizzini, Low triiodothyronine and survival in end-stage renal disease, Kidney Int. 70 (3) (2006) 523–528.
[44] J.J. Carrero, A.R. Qureshi, J. Axelsson, M.I. Yilmaz, S. Rehnmark, M.R. Witt, et al., Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease, J. Intern. Med. 262 (6) (2007) 690–701.
[45] S.L. Qin, Q. He, L. Hu, C.Y. He, L.C. Gao, C.A. Young, et al., The relationship between inflammatory factors, oxidative stress and DIO-1 concentration in patients with chronic renal failure accompanied with or without euthyroid sick syndrome, J. Int. Med. Res. 46 (10) (2018) 4061–4070.
[46] Y.Y. Ng, H.D. Lin, S.C. Wu, C.Y. Yang, W.C. Yang, H.H. Liou, et al., Impact of thyroid dysfunction on erythropoietin dosage in hemodialysis patients, Thyroid 23 (5) (2013) 552–561.
[47] M.J. Fernandez-Reyes, R. Sanchez, M. Heras, P. Tajada, P. Iglesias, L. Garcia, et al., Can FT3 levels facilitate the detection of inflammation or catabolism and malnutrition in dialysis patients? Nefrologia 29 (4) (2009) 304–310.
[48] M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, BMJ (Clin. Res. Ed.) 315 (7109) (1997) 629–634.
[49] S. Kanji, J. Neilipovitz, B. Neilipovitz, J. Kim, W.M.R. Haddara, M. Pittman, et al., Triiodothyronine replacement in critically ill adults with non-thyroidal illness syndrome, Can. J. Anaesth. = Journal canadien d'anesthesie. 65 (10) (2018) 1147–1153.
[50] E.M. de Vries, E. Fliers, A. Boelen, The molecular basis of the non-thyroidal illness syndrome, J. Endocrinol. 225 (3) (2015) R67–R81.
[51] A. Bunevicius, T. Smith, E.R. Laws, Low tri-iodothyronine syndrome in neurosurgical patients: a systematic review of literature, World Neurosurg. 95 (2016) 197–207.
[52] A. Bunevicius, G. Iervasi, R. Bunevicius, Neuroprotective actions of thyroid hormones and low-T3 syndrome as a biomarker in acute cerebrovascular disorders, Expert Rev. Neurother. 15 (3) (2015) 315–326.
[53] M. Alevizaki, M. Synetou, K. Xynos, T. Pappa, K.N. Vemmos, Low triiodothyronine: a strong predictor of outcome in acute stroke patients, Eur. J. Clin. Investig. 37 (8) (2007) 651–657.