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Meta-analysis of Risk Factors for Liver Damage in Newly Diagnosed Patients with Hyperthyroidism

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Abstract

Objective: To systematically evaluate the risk factors of liver damage in newly diagnosed patients with hyperthyroidism and provide a clinical basis for the diagnosis and treatment of liver injury in hyperthyroidism. **Methods:** Pubmed, Embase, The Cochrane Library, CNKI, VIP and other databases were searched to collect the risk factors of hepatic damage in newly diagnosed hyperthyroidism patients published up to May 2020. Library until May 2020. Two researchers independently screened the literature, extracted data, and evaluated the risk of bias in the included studies, and Meta-analysis was performed by RevMan 5.3 software. **Results:** A total of 18 documents were included, with a total of 2637 cases and 1884 controls. Meta-analysis results show: age, course of disease, thyroid weight, FT4, TRAb, TGAb, TPOAb are all risk factors for hepatic injury in newly diagnosed patients with hyperthyroidism. **Conclusion:** While age, course of disease, thyroid weight, FT4, TRAb, TGAb and TPOAb are risk factors for liver damage in newly diagnosed patients with hyperthyroidism, gender has nothing to do with them.

Keywords

Hyperthyroidism, liver damage, risk factors, Meta-analysis

Hyperthyroidism is a group of clinical syndrome [1]. Previous literature reported that the prevalence of hyperthyroidism combined with liver damage ranged from 37 to 77.9% [2]. Since the liver function status of patients is crucial to the treatment of newly diagnosed hyperthyroidism with anti-hyperthyroidism drugs and the prognosis evaluation, it is of great significance to analyze and evaluate the influencing factors of liver function damage of newly diagnosed hyperthyroidism patients for treatment and prognosis of hyperthyroidism. In this study, meta-analysis was used to systematically evaluate the risk factors of liver damage in newly diagnosed patients with hyperthyroidism, in order to provide evidence for the management of liver damage.

1. Data and methods

1.1 Source of data

Databases such as Pubmed, Embase, The Cochrane Library, CNKI and VIP were searched, and the search period was from the establishment of the database to May 2020. The search adopts the combination of subject words and free words. Searching terms include“hyperthyroidism”, “Graves' disease”, “hepatic injury”, etc.

1.2 Inclusion and exclusion criteria

Inclusion criteria: (1) Published literature on analytical studies of risk factors for liver damage in newly diagnosed patients with hyperthyroidism; (2) Parallel controlled studies with the same or similar purpose and design plan, divided into two groups: abnormal liver function and normal liver function; (3) Clear diagnosis of hyperthyroidism and liver damage; (4) All the patients with hyperthyroidism had the initial onset or stopped the drug for more than 1 month. Exclusion criteria: (1) Repeated publication of literature; (2) Literature with missing original data; (3) Case report, review, no control group literature, etc.

1.3 Literature screening and data extraction

Two researchers independently screened the literature, extracted the data and cross-checked them. According to the inclusion and exclusion criteria, they recorded in detail the basic information of the included studies for the documents that met the requirements.

1.4 Quality evaluation

Case-control studies and cohort studies were evaluated for quality using the New Castle-Ottawa scale (NOS). Cross-sectional studies were evaluated using quality evaluation criteria recommended by the Agency for Healthcare Research and Quality (AHRQ).

1.5 Statistical approach

RevMan5.3 was used for analysis. The odds raio (OR) and weighted mean difference (WMD) or standardized mean difference (SMD) were calculated for counting data. Each effect size provided its 95% confidence interval (CI) to plot the forest. $P < 0.05$ was considered statistically significant. Chi-squared test (alpha = 0.1) and I^2 was used to determine heterogeneity. If there was no statistical heterogeneity, the fixed effects model was used for statistics; otherwise, the random effects model was used. If necessary, subgroup analysis and sensitivity analysis were used to explore the sources of heterogeneity.

1.6 Publication bias

Draw a funnel plot. Generated by RevMan5.3. The symmetry of funnel plot indicates that publication bias is effectively controlled.

2. Results

2.1 Literature search results

A total of 884 literatures were obtained in the initial examination, and 18 were finally included after layer by layer screening, all of which were case-control studies. The literature screening process and results are shown in Figure 1.

2.2 The basic features of all included literatures

All included studies were case-control studies. There were 2637 cases of liver damage with hyperthyroidism (observation group), and 1884 cases without liver damage with hyperthyroidism (control group). The independent risk factors mentioned in previous studies and the influencing factors that are rarely studied were excluded. The risk factors included in this study were statistically analyzed, as shown in Table 1.

2.3 Meta analysis results

The results of meta-analysis (Table 2) and part of the forest maps (Figure 2, 3, 4, 5) showed that the age, course of disease (time from diagnosis of hyperthyroidism to treatment), thyroid weight, thyroid hormone (FT4) and thyroid-related antibody levels in the observation group were significantly higher than those in the control group ($P<0.01$); There was no significant correlation between the occurrence of newly diagnosed hyperthyroidism liver damage and the gender of the patient ($P>0.05$).

2.4 Analysis of sensitivity

The sensitivity analysis was carried out by replacing the analytical model. The effect size and 95%CI calculated by fixed effect model and random effect model were compared respectively, and the results showed that they were close, indicating that the combined results of this study were basically reliable, as shown in Table 3.

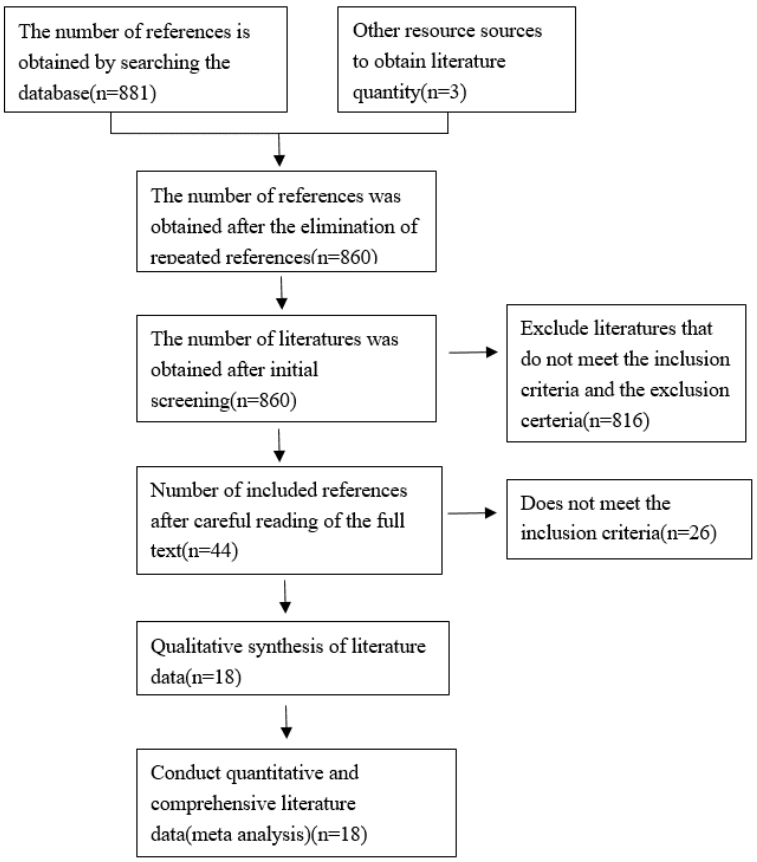

Figure 1. Literature screening flow chart.

Table 1. The basic characteristics of included studies

Authors	Year	Country	Experimental	Control	Risk factors	NOS score
C.Li	2014	China	709	361	①④⑥⑦⑧	6
He K	2014	China	184	52	③⑧	7
Zhang et al	2015	China	205	84	②④⑤⑥⑦	7
Ren et al	2011	China	86	74	①②③⑦	7
Ren et al	2012	China	54	122	②	6
Liu et al	2015	China	118	106	①⑤	7
Wu et al	2016	China	108	96	①②⑤⑥	7
Wu et al	2013	China	116	112	②	6
Zhang et al	2004	China	278	199	②	6
Zhang et al	2015	China	40	46	①②⑤⑥⑦⑧	7
Zhang et al	2013	China	146	58	②③④⑤⑥⑦	6
Dai et al	2009	China	51	84	⑤	7
Zhu et al	2017	China	159	95	④⑤⑥	7
Sidike et al	2011	China	141	137	②	6
Wang et al	2014	China	78	78	①②	6
Xiao et al	2012	China	24	24	②⑦⑧	7
Jiang et al	2015	China	32	65	①②③	5
Xiang et al	2010	China	108	91	②	6

Notes: ①age; ②gender; ③duration; ④thyroid weight; ⑤FT4; ⑥TRAb; ⑦TGAb; ⑧TPOAb

Table 2. Results of Meta-analysis of risk factors for liver damage in newly diagnosed hyperthyroidism

Risk factors	The literature number	heterogeneity test		model	Combined effect value	
		I^2（%）	*P*		*WMD/SMD/OR*（*95%CI*）	*P*
age	7	22	0.26	fixed-effect	3.59[2.49,4.68]	<0.001
duration	4	14	0.32	fixed-effect	1.06[0.93,1.19]	<0.001
gender	14	0	0.60	fixed-effect	1.12[0.96,1.30]	0.140
thyroid weight	4	30	0.23	fixed-effect	2.63[0.71,4.54]	0.007
FT4	7	35	0.16	fixed-effect	13.27[12.51,14.02]	<0.001
TRAb	6	19	0.29	fixed-effect	2.48[2.15,2.80]	<0.001
TGAb	6	0	0.97	fixed-effect	16.70[14.16,19.24]	<0.001
TPOAb	4	77	0.005	random effect	71.54[39.31,103.77]	<0.00001

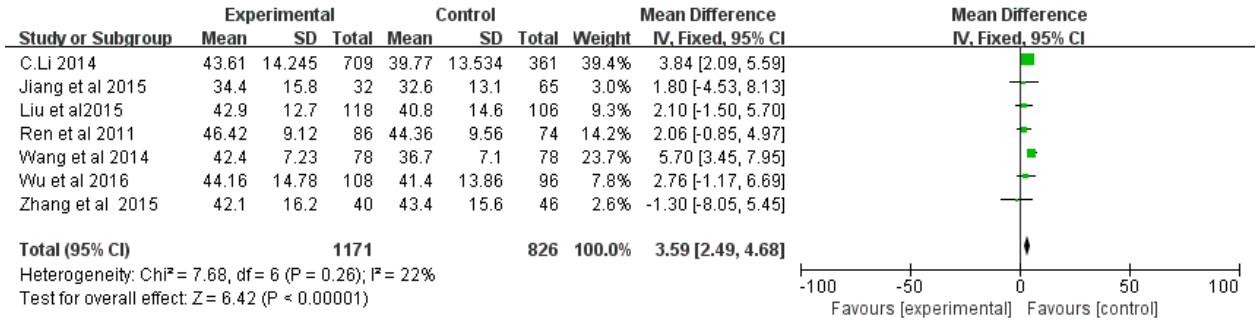

Figure 2. Forest map of age was compared between observation group and control group.

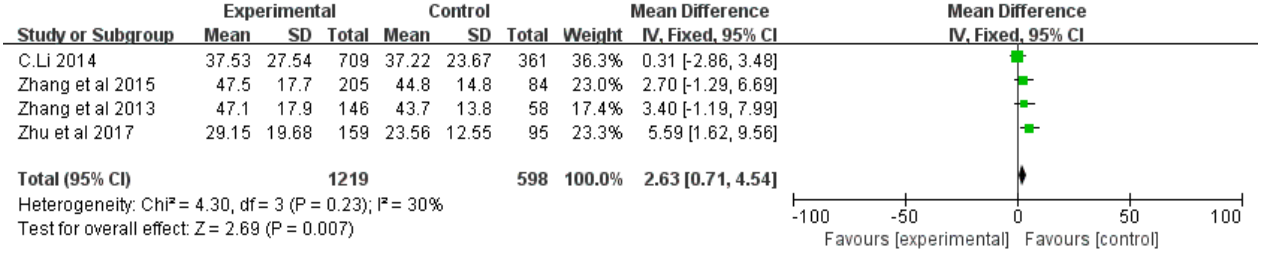

Figure 3. Forest map of thyroid weight was compared between observation group and control group.

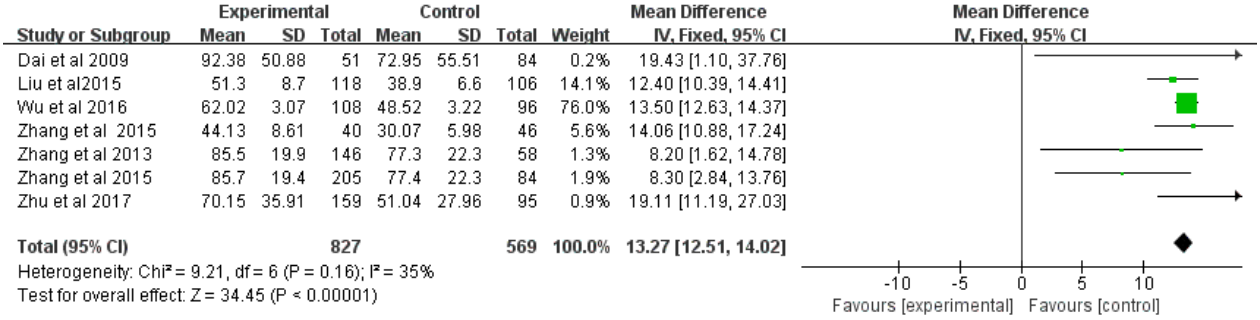

Figure 4. Forest map of FT4 was compared between observation group and control group.

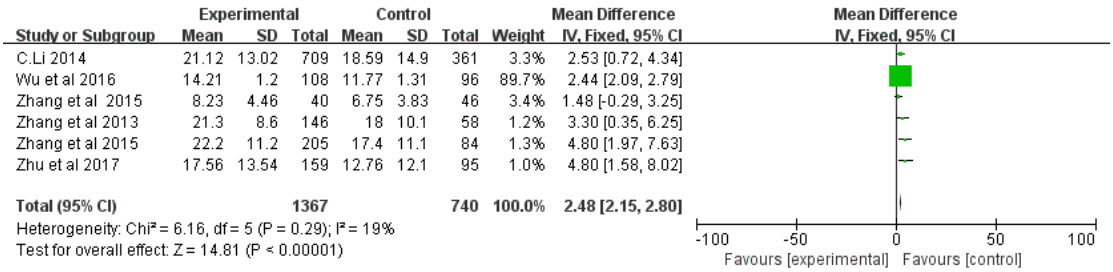

Figure 5. Forest map of TRAb was compared between observation group and control group.

Table 3. Calculation results of fixed effect model and random effect model

factors	Results by fixed effects model	Results by random effect model
age	3.59 [2.49, 4.68]	3.40 [2.06, 4.74]
duration	1.06 [0.93, 1.19]	1.15 [0.51, 1.78]
thyroid weight	2.63 [0.71, 4.54]	2.76 [0.44, 5.08]
FT4	13.27 [12.51, 14.02]	12.93 [11.42, 14.44]
TRAb	2.48 [2.15, 2.80]	2.60 [1.92, 3.29]
TGAb	16.70 [14.16, 19.24]	16.70 [14.16, 19.24]
TPOAb	69.29 [57.63, 80.95]	71.54 [39.31, 103.77]

2.5 Publication bias

The funnel plot with thyroid weight as an example showed that the effect points of each study were basically symmetrical. However, due to the limited number of included studies, no significant publication bias could be found from the funnel plot, as shown in Figure 6.

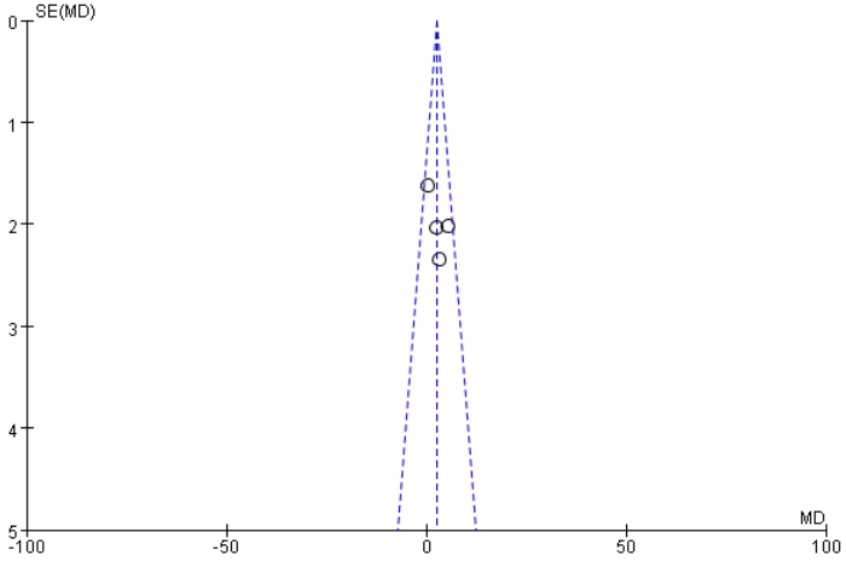

Figure 6. Funnel plot of studies with thyroid weight as a risk factor.

3. Discussion

Hyperthyroidism not only causes abnormal thyroid function, but also can cause multiple organ system damage, among which the incidence of hyperthyroidism liver damage is high, great influence on the treatment of patients, and has attracted much attention from clinicians. In this study, a meta-analysis was used to include 4521 newly diagnosed patients with hyperthyroidism, excluding drug-induced liver damage, viral hepatitis, autoimmune hepatitis, etc. The results showed that age, disease course, thyroid weight, FT4, TRAb, TGAb and TPOAb were all risk

factors for liver damage in newly diagnosed patients with hyperthyroidism, and there was no significant correlation between gender and liver damage.

Excessive secretion of thyroid hormone is the main factor causing liver damage [3, 4]: hypermetabolism caused by hyperthyroidism increases the burden of thyroid hormone degradation in the liver, and there is the possibility of hepatocyte degeneration and cholestasis in severe cases. At the same time, excessive thyroid hormone can cause different degrees of liver damage through oxidative stress reaction [5]. In addition, hyperthyroidism can keep the liver in a state of relative hypoxia for a long time [6]. The results of this study suggest that serum FT4 level is significantly increased in newly diagnosed patients with hyperthyroidism complicated with liver damage, and it is considered that the increased thyroid hormone has a certain influence on the occurrence of liver damage.

Studies [7-9] showed that TRAb, TGAb, TPOAb, IgA, IgG, circulating immune complex (CIC) and globulin (GLO) in patients with hyperthyroidism and liver damage were significantly higher than those in patients with simple hyperthyroidism. The mechanism is not well understood. In this study, it was found that the levels of thyroid-related antibodies in the experimental group were higher than those in the control group, which confirmed the possibility of immune factors participating in the occurrence of hyperthyroidism liver damage.

The results of this study also suggest that age, course of disease, thyroid weight and other general factors are also risk factors for liver damage in newly diagnosed patients with hyperthyroidism. It may be related to the aggravation of liver relative hypoxia with the increase of age and the prolongation of disease course, and the decrease of liver tolerance to relative hypoxia and repair ability. This is different from the results of previous studies, and it is considered that the difference in results may be related to the inconsistency of the inclusion criteria between studies and the disease course of the subjects. In addition, this study suggests that thyroid weight is a risk factor for liver damage in newly diagnosed hyperthyroidism patients, which may be related to the increase of thyroid hormone synthesis enzymes during hyperthyroidism. Studies [10] suggest that female hyperthyroidism is more prone to liver damage, which is presumed to be related to estrogen, sex chromosome and microchimerism. However, the literature included in this study did not find a correlation between liver damage and sex at first diagnosis of hyperthyroidism.

Individual studies have also reported the effects of other factors on liver function in patients with hyperthyroidism: Such as BMR, 24 h iodine uptake rate, complement C3, C4, the C allele of PTPN22 rs 3789604, the C allele of GPR174 rs 3827440 and the G allele of RNASET2 rs 9355610 [11]. It is believed that more mechanisms and influencing factors will be discovered with the development of high-quality studies, which will provide better directions for the prevention and clinical diagnosis and treatment of hyperthyroidism liver damage.

Limitations of this study: the included literatures were case-control studies, univariate analysis, and confounding factors were not considered. The literature sources of risk factors included were not identical, and there was some heterogeneity between studies. The sample size of the included studies was uneven, and the risk factors of each study focused on were different.

In conclusion, age, disease course, thyroid weight, FT4 and thyroid-related antibodies (TRAb, TGAb, TPOAb) are all risk factors for liver damage in newly diagnosed hyperthyroidism patients. Clinicians should identify the risk groups for hyperthyroidism as early as possible and make individualized treatment plans.

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