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Abnormal Liver Blood Tests in Patients with Hyperthyroidism: Systematic Review and Meta-Analysis

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Background: Abnormal liver blood tests (LBTs) in hyperthyroid patients are not uncommonly encountered. One major adverse event of antithyroid drug (ATD) therapy is drug-induced hepatotoxicity. Abnormal LBT in the hyperthyroidism scenario is a main diagnostic and therapeutic dilemma. We aimed to assess the prevalence and the response to ATD therapy of LBT abnormalities in newly diagnosed and uncomplicated hyperthyroidism through a systematic review and meta-analysis.

Methods: A literature search was performed reporting LBTs at presentation and after ATD therapy in hyperthyroid patients. A proportion meta-analysis was performed with random-effects model. Pooled data were presented with 95% confidence intervals (CI). I^2 statistic index was used to quantify the heterogeneity. Sensitivity analyses for prevalence of hyperthyroid patients with at least one abnormal LBT were performed. p-Value of <0.05 was regarded as significant.

Results: The literature search yielded 2286 studies, of which 25 were included for systematic review and meta-analysis. The prevalence of untreated hyperthyroid and Graves' disease patients with at least one abnormal LBT was 55% ([CI 46–63%], I^2 96%) and 60% ([CI 53–67%], I^2 92%), respectively. The prevalence of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total bilirubin (BIL), and γ-glutamyltransferase (GGT) abnormalities in hyperthyroid patients were 33% ([CI 24–44%], I^2 95%), 23% ([CI 17–29%], I^2 89%), 44% ([CI 35–52%], I^2 93%), 12% ([CI 7–20%], I^2 92%), and 24% ([CI 16–36%], I^2 95%), respectively. ATD therapy, along with euthyroidism restoration, was accompanied by normalization of LBT abnormalities in the following percentage of cases: ALT 83% ([CI 72–90%], I^2 46%), AST 87% ([CI 74–94%], I^2 2%), ALP 53% ([CI 32–73%], I^2 76%), BIL 50% (CI cannot be calculated), and GGT 70% ([CI 47–87%], I^2 74%). The sensitivity analyses showed similar results as those of the main analyses. The publication bias was not statistically significant for all outcomes, except for the prevalence of resolved BIL abnormalities that was not calculable.

Conclusions: LBT abnormalities are common in newly diagnosed and untreated hyperthyroidism setting. A high chance of safely normalizing elevated transaminases, up to fivefold above the upper limit of normal, accompanies the use of ATDs in the treatment of hyperthyroidism.

Keywords: hyperthyroidism, Graves' disease, liver abnormalities, liver dysfunction

Introduction

Thyroid hormones are fundamental for normal structure and metabolism of the hepatobiliary system (1–3). Anatomical findings of liver damage in uncomplicated thyrotoxicosis encompass varying degrees of alterations, which include: mild and not significant changes, inflammatory reactions with cholestasis and/or hepatocellular necrosis, steatosis, fibrosis, and cirrhosis (4–7).

Since severe and prolonged hyperthyroidism occurs only occasionally to date, severe hepatobiliary dysfunction associated with pure hyperthyroidism is rare (7,8). Conversely, it is not uncommon for clinicians to encounter abnormal liver blood test (LBT) results in newly diagnosed hyperthyroid patients when they check a liver profile before initiating antithyroid drugs (ATDs) (9).

ATD therapy is the most common Graves' disease (GD) treatment, which is associated with an overall good tolerance profile (10,11). However, one major adverse event that clinicians must consider is drug-induced hepatotoxicity (10). Interestingly, the American Thyroid Association (ATA) guidelines (9) recommend (Recommendation 15, weak

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recommendation with low-quality evidence) serious reconsideration of ATD therapy if baseline transaminase levels are more than five times the upper limit of normal. Therefore, finding abnormal LBTs in the hyperthyroidism scenario is a significant diagnostic and therapeutic dilemma.

In untreated and uncomplicated hyperthyroid patients, the prevalence of LBT abnormalities varies widely across studies, ranging from 11% to 78% (8,12,13). Moreover, while in some studies, serum alkaline phosphatase (ALP) elevation appears to be the most frequent blood abnormality (13–15), in others, alanine transaminase (ALT) or γ-glutamyltransferase (GGT) elevations are more prevalent (16,17). Thus, various types of hepatobiliary injuries (i.e., hepatocellular, cholestatic, and mixed patterns) could be part of untreated hyperthyroidism (4,7,18). These evidences need to be kept in mind to avoid unnecessary diagnostic investigations when searching for the etiology of LBT abnormalities (19).

Some studies have investigated the impact of ATDs in hyperthyroid patients with baseline abnormal LBTs and in the absence of factors potentially harmful to the liver (13,20,21). Substantial rates of normalization of LBTs together with the restoration of euthyroidism were found (13,20,21), providing some advantages and reassurance for the use of ATD therapy in this setting.

Considering the diagnostic and therapeutical implications of this topic, our aim was to assess the true prevalence and the response to ATD therapy of LBT abnormalities in the newly diagnosed and untreated (uncomplicated) hyperthyroidism setting through a systematic review and meta-analysis.

Methods

In this study, we used all the procedures consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (22). Human subjects or the public were not involved in any way in our study.

Search strategy

Two investigators (L.S. and G.B.) independently conducted a comprehensive literature in the online databases of MEDLINE (PubMed) and Scopus using the following search terms and their combinations: ''Hyperthyroidism'' (or ''Thyrotoxicosis''), ''liver'' (or ''liver dysfunction,'' or ''liver function,'' or ''liver abnormalities,'' or ''liver alterations,'' or ''hepatic dysfunction,'' or ''hepatic function''). A commencement date limit was not used, and the last search was carried on August 10, 2020. No language restrictions were imposed. The search strategy was refined to evaluate all references of the screened studies to identify additional relevant studies. The search was restricted to human studies.

Eligibility criteria and study selection

Records identified by our search strategy were screened using ''the report of LBTs in adult patients with newly diagnosed and untreated hyperthyroidism'' as the major criterion of inclusion. Eligible patient cohorts should not have concomitant liver disease (i.e., viral hepatitis, alcoholic liver disease, fatty liver, autoimmune hepatitis, liver cirrhosis, constitutional jaundice, cholangitis) or liver dysfunction due to other causes (i.e., heart failure, drugs potentially causing deleterious effects on the liver). Articles covering patients with thyroid storm (i.e., thyrotoxic crisis, acute thyrotoxicosis) or exogenous thyrotoxicosis were excluded. Only research articles were considered for inclusion (i.e., experimental studies, observational studies, and case series). Eligible studies examined two or more LBTs among the following: ALT, aspartate transaminase (AST), ALP, total bilirubin (BIL), GGT, prothrombin time (PT), lactate dehydrogenase (LDH), and albumin (ALB).

Excluded studies were: (i) case reports, reviews, editorials, letters, commentaries, and meeting abstracts; (ii) small studies with ≤10 patients; (iii) research articles only reporting the mean values of baseline LBTs. Two researchers (L.S. and G.B.), applying the above criteria, independently reviewed titles and abstracts of the screened articles. Then, all authors independently reviewed the main text of the eligible articles to define their inclusion. Disagreements were resolved by consensus among all the reviewers.

Data extraction

For the included studies, the following data were coded and extracted independently and in duplicate by two investigators (L.S. and G.B.), in a piloted form: (i) author, publication year, country, study design; (ii) number of patients with untreated hyperthyroidism, of which sex and age were reported; (iii) number of hyperthyroid patients with at least one abnormal LBT; (iv) number of patients with specific LBT abnormalities; (v) abnormal LBT values of hyperthyroid patients (i.e., mean values and/or the peak values expressed as times above the upper limit of the normal [ULN] of the reference ranges for serum ALT, AST, ALP, BIL, and GGT); (vi) number of liver abnormalities under therapy (ATDs, radioiodine [RAI], or surgery); (vii) figures of normalization of LBTs after euthyroidism restoration; (viii) occurrence of ATD-induced hepatotoxicity.

In the included studies, hyperthyroidism was documented by confirmatory thyroid function tests, thyroid scintigraphy, and/or thyrotropin receptor (TSHR) antibodies (TRAb). Underlying causes of hyperthyroidism were GD, toxic multinodular goiter, or toxic adenoma. An abnormal LBT was defined as being a value outside the study reference range. Serum APL levels expressed in catalytic activity (kat/L) by some older studies or BIL levels expressed in mol/L were converted into IU/L and mg/dL, respectively, using standard conversion factors (23). The collected details were cross-checked, and any discrepancies were fully reconciled by joint re-evaluations.

Risk of bias assessment

The risk of bias of the included studies was assessed independently by two investigators (L.S. and M.I.M.) through the National Heart, Lung, and Blood Institute Quality Assessment Tool (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

Study endpoints

The primary outcome was to define the prevalence and the most common profiles of abnormal LBTs in adult patients with newly diagnosed and untreated (uncomplicated) hyperthyroidism. The secondary outcome was to assess the percentages of resolution of LBT abnormalities after euthyroidism restoration by ATD therapy.

Statistical analyses

Outcomes were assessed on a patient basis for each study. A proportion meta-analysis was performed with the DerSimonian and Laird method (random-effects model) (24), where pooled data are weighted averages relative to the sample size of the single studies. Pooled data were presented with 95% confidence intervals (CI) and displayed in a forest plot. I^2 statistic index was used to quantify the between-study heterogeneity as follows: <25%, no heterogeneity; 25–50%, mild heterogeneity; 50–75%, moderate heterogeneity; and >75%, high heterogeneity. Sensitivity analyses for the prevalence of hyperthyroid patients with at least one abnormal LBT were performed by excluding the studies with high risk of bias on outcome measures (i.e., studies that did not mention heart failure as exclusion criterion). Trim and fill analysis and Egger's linear regression test were used to evaluate for publication bias. A two-sided p-value of <0.05 was regarded as significant for all analyses. Statistical analyses were performed using Prometa 3.0 (Internovi, Cesena FC, Italy).

Results

Study selection

The literature search using the above algorithm yielded 2286 studies. All the studies assessed and reasons for exclusion are shown in Figure 1. Among the studies finally excluded, there was one study on patients over the age of 60 years, two-thirds of whom had heart failure (25), and one other on hyperthyroidism in children (26). Twenty-five studies [23 English language studies, 1 with German (27), and 1 with Korean (14)] had appropriate data for systematic review and meta-analysis.

Qualitative analysis (systematic review)

Table 1 summarizes the general features of the 25 included studies. These studies were published between 1967 and 2019; 12 studies (48%) were published after 2007. Most studies were performed in Asia ($n=12$), Europe ($n=6$), or United States ($n=5$). They were single-center observational cohort studies, with a retrospective study design except for five which were prospective (13,20,28–30).

In accordance with the inclusion and exclusion criteria, we excluded specific patient cohorts. In particular, we excluded patients with other causes of thyrotoxicosis or with factors potentially skewing the baseline liver abnormalities: the 27 patients with painless thyroiditis in Kubota *et al.* (29); the 3 patients with amiodarone-induced thyrotoxicosis and the 6 patients with chronic hepatitis in Niculescu *et al.* (21); the 1073 patients who had been treated with ATDs before exploring liver function in Wang *et al.* (31); the 25 patients with underlying diseases in Ashkar *et al.* (12); the 19 patients with congestive heart failure and the 6 patients with concomitant liver diseases in Fong *et al.* (32).

The total number of newly diagnosed and untreated hyperthyroid patients without apparent concomitant diseases or drugs potentially interfering with liver function was 6345, and 3629 of whom had GD. The age of patients ranged from 19 to 77 years and

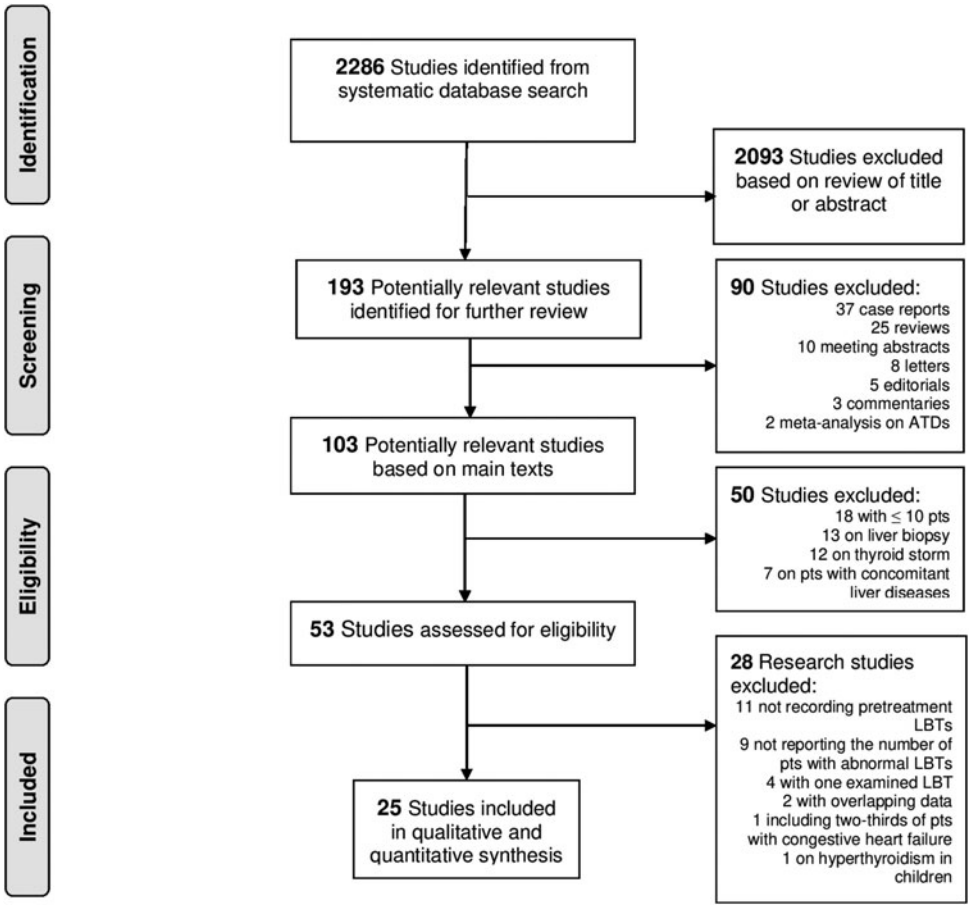

FIG. 1. Flowchart of the study selection process. ATDs, antithyroid drugs; LBTs, liver blood tests; pts, (hyperthyroid) patients.

Table 1. General Features of the 25 Included Studies

Authors	*Year*	*Country*	*Study design*	*Hyperthyroid* (n)	*GD* (n)	*Age (years)*	*Female/ male*	*LBTs*	*Patients with at least one abnormal LBT* (n)
Dooner *et al.* (36)	1967	Chile	R	15		40 ± 13	11/4	ALP, BIL, PT	9
Weber (27)	1968	Germany	R	14	11	46 ± 9	10/4	ALT, AST, BIL	6
Ashkar *et al.* (12)	1971	United States	R	545				AST, ALP, BIL	60
Thompson *et al.* (33)	1978	United States	R	85				ALT, AST, ALP, BIL, LDH	65
Azizi (34)	1982	Iran	R	16				ALP,GGT	10
Benvenga *et al.* (40)	1985	Italy	R	27	27	39.5 ± 3	21/6	ALP,GGT	15
Beckett *et al.* (7)	1985	United Kingdom	R	14		19–75	14/0	AST, ALP, GGT	8
Fong *et al.* (32)	1992	United States	R	18		36	13/5	ALT, BIL, ALB	12
Huang *et al.* (13)	1994	Taiwan	P	95	95	34 ± 2	69/26	ALT, AST, ALP, BIL, GGT	72
Gurlek *et al.* (20)	1996	Turkey	P	43	33	19–77	36/7	ALT, AST, ALP, BIL, GGT	26
Biscoveanu and Biscoveanu (39)	2000	United States	R	30	30	40 ± 8	27/3	ALT, AST, ALP, BIL, GGT	11
Aydemir *et al.* (28)	2005	Turkey	P	64	12	48 ± 14	45/19	ALT, AST, ALP, BIL, GGT	30
Chae *et al.* (14)	2007	Korea	R	378		47 ± 13		ALT, AST, ALP, BIL, GGT	272
Kubota *et al.* (29)	2008	Japan	P	30	30	40 ± 14	25/5	ALT, AST, ALP, GGT	23
Khan *et al.* (41)	2010	Pakistan	R	50	50	41 ± 6	40/10	ALT, AST	38
Sarinnapakorn *et al.* (30)	2011	Thailand	P	112	112		103/9	ALT, AST, ALP, BIL, GGT, ALB	28
He *et al.* (38)	2014	China	R	236	236	45 ± 1	147/89	ALT, AST, ALP, BIL, GGT	184
Madani *et al.* (35)	2014	Iran	R	50		45 ± 17		ALT, AST, ALP, BIL	19
Li *et al.* (42)	2014	China	R	1070	1070	42 ± 14	869/201	ALT, AST, BIL	709
Zhang *et al.* (16)	2015	China	R	289	289	41 ± 12	195/94	ALT, AST, ALP, BIL, GGT	205
Niculescu *et al.* (21)	2016	Romania	R	70	54	52	60/10	ALT, AST	18
Wang *et al.* (31)	2017	China	R	1312	1312	43 ± 13		ALT, AST, ALP, BIL, GGT	821
Lin *et al.* (15)	2017	United States	R	1514		60 ± 19	1166/348	ALT, AST, ALP, BIL, GGT	590
Xiao *et al.* (37)	2018	China	R	122	122	34 ± 10	90/32	ALT, AST	52
Hsieh *et al.* (17)	2019	Australia	R	146	146	35 ± 11	120/26	ALT, AST, ALP, GGT	69
Total, *n*				6345	3629		3061/898		3352

Age is expressed in years as mean ± SD, or median, or wide range.

Blank cells indicate the unavailability of data.

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BIL, total bilirubin; GGT, γ-glutamyltransferase; GD, Graves' disease (GD cohort as a subgroup of the respective hyperthyroid cohort); LBTs, liver blood tests; LDH, lactate dehydrogenase; P, prospective; PT, prothrombin time; R, retrospective.

the female-to-male ratio was ~3.5:1. Four (12,30,33,34) and six (12,14,31,33–35) studies did not report age and sex details, respectively. All included studies assessed two or more LBTs, but PT, LDH, and ALB were rarely measured [i.e., PT in one study (36), LDH in one study (33), ALB in two studies (30,32)].

As shown in Supplementary Table S1, most of the included studies recorded high figures of LBT abnormalities. Peak serum levels of LBTs varied widely. Ten studies (13,14,17,20,21,27–30,37) reported details about the effects of ATD therapy on LBT abnormalities, and high rates of resolved LBT abnormalities were reported after restoration to euthyroidism. In the cases when abnormal LBTs did not achieve normal ranges, they remained almost unchanged or slightly decreased, although euthyroidism was achieved. ALT and GGT levels significantly increased after propylthiouracil (PTU) therapy only in 12 and 5 cases, respectively (13). One case of symptomatic PTU-induced hepatic injury was recorded among hyperthyroid patients with abnormal baseline ALT (13). Further significant increases in abnormally elevated ALP levels were reported in two patients after RAI therapy by Azizi (34).

Quantitative analysis (meta-analysis)

Table 2 shows all pooled results. The prevalence of untreated hyperthyroid patients with at least one abnormal LBT was 55% ([CI 46–63%], I^2 96%, of 6345 patients) (Fig. 2). Sensitivity analysis, among 20 studies with low risk of bias on outcome measures, showed that hyperthyroid patients with at least one abnormal LBT were 58% ([CI 49–67%], I^2 96%, of 4529 patients). When excluding ALP elevations, the prevalence of at least one abnormal LBT was 54% ([CI 37–69%], I^2 92%, of 1344 patients).

When analyzing the 12 studies enrolling only patients with GD, the prevalence of hyperthyroid patients with at least one abnormal LBT was 60% ([CI 53–67%], I^2 92%, of 3519 patients). Sensitivity analysis, including nine studies on GD patients, showed at least one LBT abnormality among 67% of GD patients ([CI 62–73%], I^2 87%, of 3231 patients) (Fig. 3). The prevalence of at least one abnormal LBT in patients with GD was 63% ([CI 47–76%], I^2 89%, of 1260 patients) if excluding ALP elevations.

Five studies (7,16,27,33,38) (i.e., collectively 468 patients) separated patients into groups based on the number of abnormal LBTs (ALT, AST, ALP, BIL, and GGT): 41% ([CI 34–49%], I^2 50%) had one LBT abnormality (Group I); 31% ([CI 26–35%], I^2 8%) had two LBT abnormalities (Group II); and 28% ([CI 19–39%], I^2 74%) had three or more LBT abnormalities (Group III). The prevalence of ALT, AST, ALP, BIL, and GGT abnormalities in hyperthyroid patients were 33% ([CI 24–44%], I^2 95%, of 757 patients) (Fig. 4),

Table 2. Results of the Meta-Analysis

Outcome	*Studies included* (n)	*Patients* (n)	*Pooled prevalence [CI]*	*Heterogeneity (%)*	*Publication bias* (p-*value*)
Hyperthyroid patients with at least one abnormal LBT	25	6345	55 [46–63]	96	0.9
Hyperthyroid patients with at least one abnormal LBT (sensitivity analysis)	20	4529	58 [49–67]	96	0.5
Group I	5	468	41 [34–49]	50	0.4
Group II	5	468	31 [26–35]	8	0.9
Group III	5	468	28 [19–39]	74	0.5
Hyperthyroid patients with at least one abnormal LBT[a]	6	1344	54 [37–69]	92	0.5
GD patients with at least one abnormal LBT	12	3519	60 [53–67]	92	0.4
GD patients with at least one abnormal LBT (sensitivity analysis)	9	3231	67 [62–73]	87	0.6
GD patients with at least one abnormal LBT[a]	4	1260	63 [47–76]	89	0.6
Abnormal LBTs in hyperthyroid patients					
ALT	17	757	33 [24–44]	95	0.2
AST	18	595	23 [17–29]	89	0.2
ALP	17	1140	44 [35–52]	93	0.1
BIL	14	341	12 [7–20]	92	0.8
GGT	14	432	24 [16–36]	95	0.9
Resolved LBT abnormalities after ATDs in hyperthyroid patients		*LBTs* (n)			
ALT	9	200	83 [72–90]	46	0.7
AST	7	97	87 [74–94]	2	0.8
ALP	5	149	53 [32–73]	76	0.6
BIL	2	9	50[b]	NC[b]	NC[b]
GGT	5	105	70 [47–87]	74	0.8

Group I: patients with one LBT abnormality.
Group II: patients with two LBT abnormalities.
Group III: patients with three or more LBT abnormalities.
[a]One abnormal LBT (among ALT, AST, BIL) without the inclusion of ALP elevation, which is an enzyme potentially derived from nonliver sources.
p-Value at Egger's test. [b]CI, heterogeneity, and *p*-value were not calculated due to few strata.
Heterogeneity and publication bias were defined in the Methods section.
ATDs, antithyroid drugs; CI, 95% confidence interval.

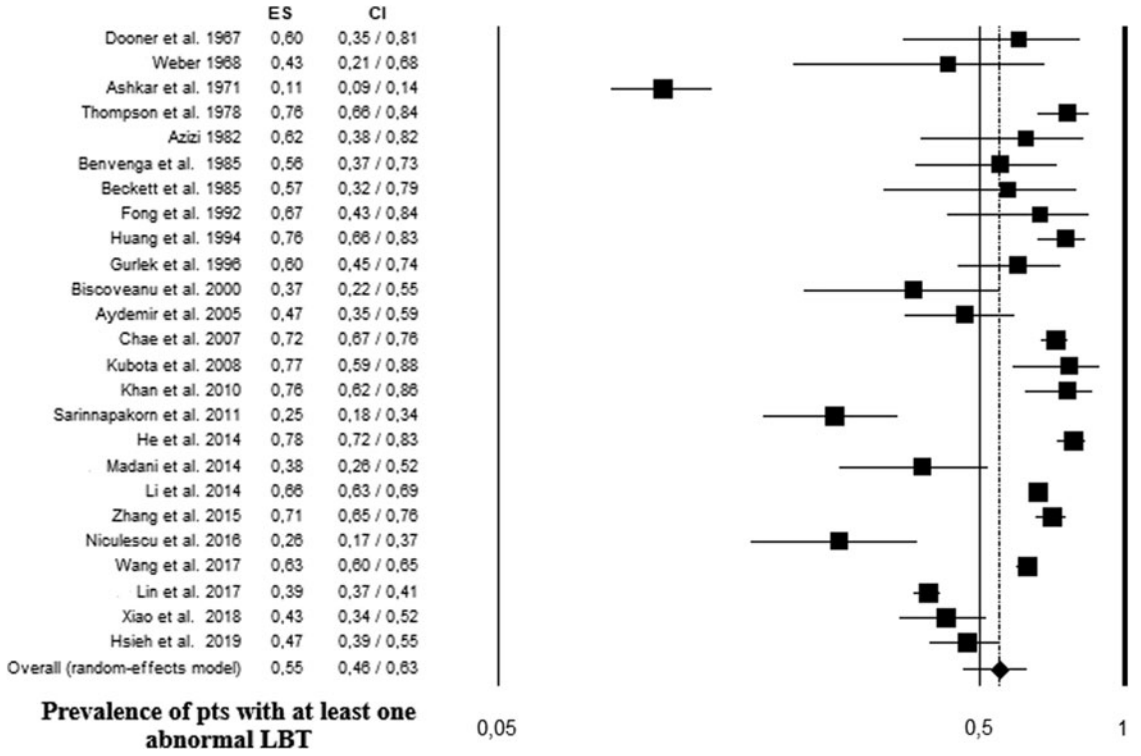

FIG. 2. Forest plot of pooled prevalence of hyperthyroid patients with at least one abnormal LBT in untreated patients with hyperthyroidism, including CI. The size of the squares indicates the weight of each study. ES corresponds to the prevalence of at least one abnormal LBT. CI, 95% confidence interval; ES, effect size.

23% ([CI 17–29%], I^2 89%, of 595 patients), 44% ([CI 35–52%], I^2 93%, of 1140 patients) (Fig. 5), 12% ([CI 7–20%], I^2 92%, of 341 patients) (Fig. 6), and 24% ([CI 16–36%], I^2 95%, of 432 patients), respectively.

ATD therapy, along with euthyroidism restoration, was associated with the normalization of LBT abnormalities in the following percentage of cases: ALT 83% ([CI 72–90%], I^2 46%, of 200 patients), AST 87% ([CI 74–94%], I^2 2%, of 97 patients), ALP 53% ([CI 32–73%], I^2 76%, of 149 patients), BIL 50% (CI and heterogeneity were not calculated due to few available data, of 9 patients), and GGT 70% ([CI 47–87%], I^2 74%, of 105 patients). The publication bias was not statistically significant for all outcomes, except for the prevalence of resolved BIL abnormalities that was not calculated because of few data.

Study quality assessment

Supplementary Table S2 summarizes the quality assessment of the 25 included studies. The risk of bias for each study could be judged as low in 11 of 14 items. By contrast, all studies did not report anything about power or sample size justification. Participation rate of eligible persons was not mentioned in any of the included studies. In five studies (7,15,17,30,39), where heart failure was not mentioned among the exclusion criteria, the risk of bias on outcome measures was regarded as high and sensitivity analyses were *ad hoc* performed.

Discussion

In hyperthyroidism, LBT abnormalities can be the expression of thyrotoxicosis itself, or they more rarely indicate

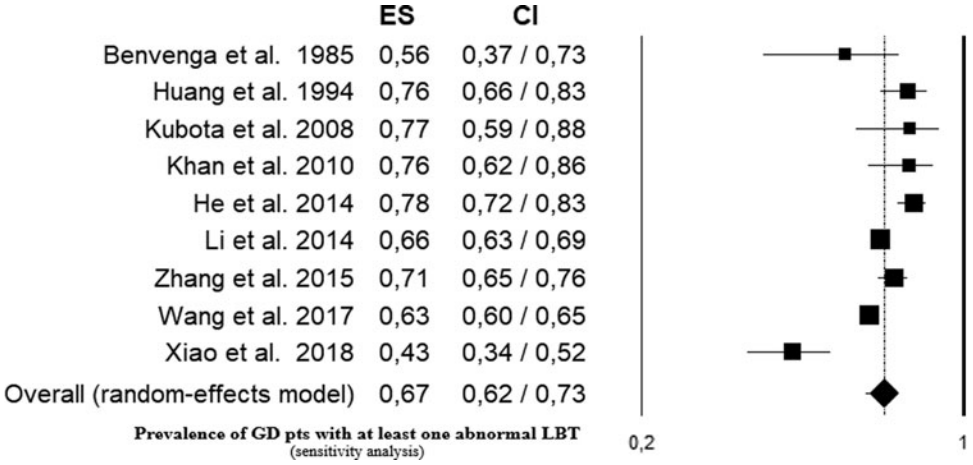

FIG. 3. Forest plot of pooled prevalence of hyperthyroid patients with at least one abnormal LBT in untreated patients with GD, including CI (sensitivity analysis). The size of the squares indicates the weight of each study. ES corresponds to the prevalence of at least one abnormal LBT. GD, Graves' disease.

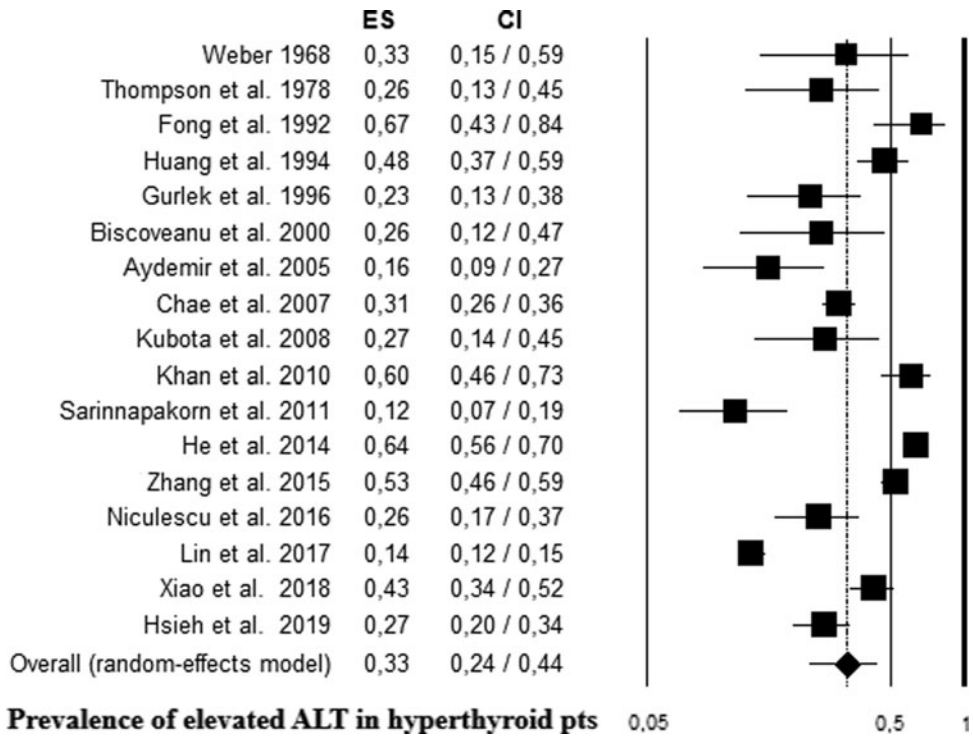

FIG. 4. Forest plot of pooled prevalence of elevated ALT in untreated hyperthyroid patients, including CI. The size of the squares indicates the weight of each study. ES corresponds to the prevalence of elevated ALT. ALT, alanine transaminase.

ADT-induced liver injury (10,43) or the coexistence of an independent liver disease (8,19,44). Thus, the correct interpretation of LBT abnormalities should be based on prior results, medical history, and current clinical context (19,44). The present article is the first meta-analysis exploring the biochemistry of liver disease related to pure endogenous hyperthyroidism. We summarized liver details from a large cohort of adult patients with newly diagnosed and untreated hyperthyroidism with no additional factors potentially capable of producing LBT abnormalities.

The results of this meta-analysis indicate that in untreated conditions one in two hyperthyroid patients has at least one LBT abnormality (among ALP, ALT, AST, GGT, and BIL) either when including or excluding ALP elevations. The prevalence is higher when considering only GD subpopulation (about two-thirds of GD patients). Overall, two principal mechanisms could underpin the liver abnormalities: hepatic hypoxia due to increased oxygen extraction in the face of normal splanchnic blood flow (45); the direct toxic effects on hepatobiliary system of thyroid hormone excess, which

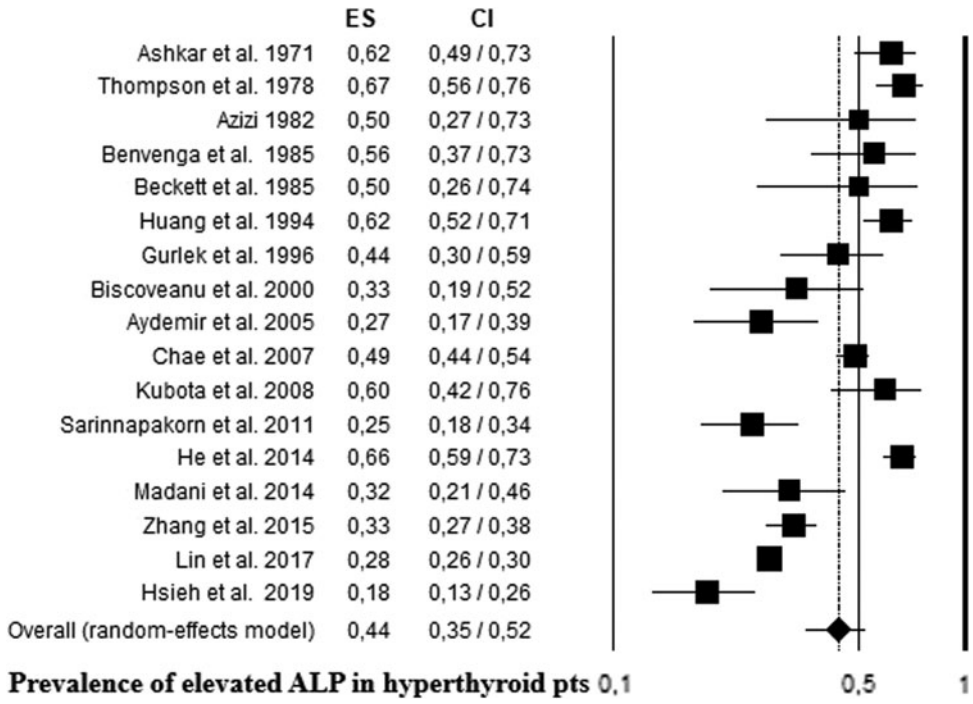

FIG. 5. Forest plot of pooled prevalence of elevated ALP in untreated hyperthyroid patients, including CI. The size of the squares indicates the weight of each study. ES corresponds to the prevalence of elevated ALP. ALP, alkaline phosphatase.

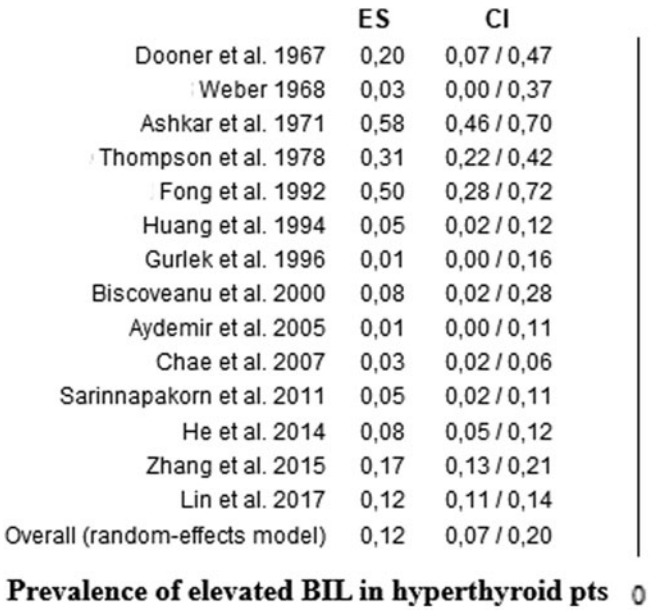

FIG. 6. Forest plot of pooled prevalence of elevated BIL in untreated hyperthyroid patients, including CI. The size of the squares indicates the weight of each study. ES corresponds to the prevalence of elevated BIL. BIL, total bilirubin.

induces cellular apoptosis and oxidative stress (46–48). Additionally, in GD hyperthyroidism, TRAb could result in an inflammatory injury to hepatocytes (37,38), since it is assumed that TRAb efficiently stimulate the TSHR of human hepatocytes (49,50). Therefore, GD hyperthyroidism could have an intrinsic higher propensity to liver insult compared with the other causes of hyperthyroidism.

ALP elevation was the most common LBT abnormality, but it could also come from bone (19). Although ALP results were not examined by electrophoresis, in line with the study by Cooper *et al.* (51), we can assume that both liver and bone isoenzymes contributed to ALP elevations. ALT elevation was the second most common LBT abnormality since it occurred in about one in three patients. ALT and AST are released into the blood stream in response to hepatocyte injury or death (hepatitis), and ALT is considered to be more liver-specific than AST (19). AST and GGT elevations were observed in about one in four patients. Since GGT is abundant in the liver but not in bone, it can be useful in confirming that an elevated ALP is of liver origin (19). BIL elevation was more rarely found and maybe a consequence of the rare hepatobiliary dysfunction in the uncomplicated hyperthyroidism scenario.

Our results also showed that the occurrence of only one LBT abnormality is slightly more frequent than two or more LBT abnormalities. There is insufficient evidence to clearly affirm that hepatic pattern (i.e., predominantly raised ALT and AST compared with the ALP level) was the most common presentation. However, in uncomplicated hyperthyroid patients, cholestatic pattern (i.e., disproportionate elevation in ALP level compared with ALT and AST levels) and isolated hyperbilirubinemia are mainly reported as case reports (52–54).

Regarding the degree of elevation of LBTs (i.e., ALP, ALT, AST, GGT, BIL), it was on average borderline (<2 × ULN) or mild (2–5 × ULN). Nevertheless, as shown in Supplementary Table S1, individual peak values of LBTs could have moderate (5–15 × ULN) or even severe (>15 × ULN) elevations.

Less data were evaluable in hyperthyroid patients with baseline LBT abnormalities who underwent ATD therapy. This was to be expected since clinicians would not feel confident adopting ATD therapy in the presence of abnormal LBTs. However, our results indicate that there is a high chance for increased LBTs to normalize after euthyroidism restoration through ATD therapy. In particular, we found that ALT, AST, and GGT elevations normalized in 7/8 of 10 cases, and normalization time varied from 6 weeks (20) to 12 months (28). Conversely, elevated ALP values reached the normal range only in about 50% of cases and maybe as a consequence of the heightened osteoblastic activity under ATDs (51,55). For BIL elevations, we found a similar low normalization percentage (50%) compared with ALP, but this result is based on limited data. Of note in patients who received ATD therapy, peak levels of abnormal LBTs were consistent with borderline (<2 × ULN) or mild (2–5 × ULN) elevations. However, in different case reports, ATDs were shown to be safe and successful in treating both severe elevations of transaminases (>15 ULN) (56,57) or BIL (58) and hyperthyroidism.

Only one study (13) recorded mild further increase of ALT levels during ATD therapy in 12 patients, but in 10 of them, high ALT levels returned to normal within 6 months after PTU dose reduction. These mild increases of LBTs are not likely to be induced by ATDs but were likely due to changes in thyroid function (29). Moreover, two studies (20,21) proved that the presence of baseline abnormal LBTs did not increase the risk of ATD-induced liver disease. A single case of severe increase of ALT and BIL levels after PTU was documented, which resolved after discontinuation of the drug (13).

A major strength of this study is that this is the first study performing a systematic review and meta-analysis on abnormal LBTs in patients with hyperthyroidism. Compared with narrative reviews (8,59,60), our study provides a more accurate estimation of the percentage of liver biochemical abnormalities in pure hyperthyroidism setting. Of note, we excluded patient cohorts potentially confounding our

analysis such as patients with amiodarone-induced thyrotoxicosis (since amiodarone possesses a significant side effect profile that includes hepatotoxicity) and patients with painless thyroiditis.

Our results were supported by the sensitivity analyses, which yielded similar results as those of the main analyses. Thus, the weight of heart failure in the results of the main analyses would be marginal since it is known that heart failure rarely characterizes the onset of hyperthyroidism (61,62) and we excluded cohorts with congestive heart failure (25,32). A further important strength and finding of the current study is our comprehensive approach by which we were able to provide a better understanding of what is known and unknown on this topic. We demonstrated lack of data about the impact of ATD therapy when baseline transaminases are moderately (5–15 × ULN) or severely (>15 ULN) elevated and limited data on hyperbilirubinemia. In addition, we show the high chance of safely normalizing borderline (<2 × ULN) and mild (2–5 × ULN) transaminase elevations accompanied the restoration of euthyroidism through ATDs, consequently providing evidence of the reliability of the ATA suggested cutoff of ''5 × ULN'' for the initiation of ATD therapy (9). Finally, publication bias was not relevant for all outcomes.

Our study does have some limitations. Higher degrees of heterogeneity affected the robustness of results regarding the prevalence of abnormal LBTs, while the absence and mild degree of heterogeneity was associated with the normalization of AST and ALT abnormalities after ATDs, respectively. Several factors could affect the reported outcomes. For example, the body mass index is known to have a linear relationship with ALT levels (44), but hyperthyroid patients often are normal-weight patients as reported in three studies included in our analysis (16,21,37). Moreover, different assay technologies and cutoffs for the measurement of LBTs could impair the consistency of our percentages. However, the laboratory measurements of ALT, AST, and ALP are deemed to be highly reproducible, and interlaboratory differences for ALT levels are not significant (44). Sex and older age could be other factors of heterogeneity. Nevertheless, similar ratios of females/males and average ages were reported by most of the included studies. Moreover, the different severity and duration of hyperthyroidism could be one main cause of the heterogeneity. However, the impact of the severity of hyperthyroidism on the development of LBT abnormalities is controversial since positive correlation between thyroid hormones and abnormal LBTs was found only in some studies (16,17,21,28,33,38,42). In any of the included studies, malnutrition, bone diseases (i.e., hyperparathyroidism, Paget's disease, metastases), and vitamin D deficiency were not assessed as causes of elevated ALP.

The different times to reach the euthyroid status and the duration of follow-up could represent two main sources of heterogeneity regarding the percentages of normalization of LBT abnormalities after ATDs (13,29). A causal relationship between ATD therapy and normalization of LBT abnormalities cannot be demonstrated since the data were from observational studies. However, in the setting of new-onset and uncomplicated hyperthyroidism, we could have few or none confounding factors in the reversal of LBT abnormalities. Thus, our results could be regarded as the first proof of an association between restoration of euthyroidism through ATDs and normalization of elevated transaminases, up to fivefold above the ULN, as there are currently no data from randomized controlled trials.

The knowledge of the relationship between liver injury and hyperthyroidism is of paramount importance for diagnostic and therapeutic choices. Based on the results of this meta-analysis, LBT abnormalities are common in newly diagnosed and untreated hyperthyroidism setting. Additionally, there is a high chance of safely normalizing elevated transaminases up to fivefold above the ULN with the use of ATDs in the treatment of hyperthyroidism. Our findings support the guideline recommendations of the ATA. Future studies should be carried out to address unsolved questions such as whether higher transaminase elevations (>5 × ULN) are a risk factor for ATD-induced hepatotoxicity and if it truly represents a contraindication to adopt ATD therapy. Data on the effects of ATD therapy on hyperbilirubinemia also need further investigations.

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Authors' Contributions

L.S. conceived the study. L.S., G.B., and K.E. participated in the design and coordination of the study. L.S., M.I.M., G.B., and K.E. undertook the statistical analysis and drafted the article. All the authors read and approved the final article.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2

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