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ORIGINAL ARTICLE

Thyroid dysfunction incidence and risk factors in Chinese chronic hepatitis B patients treated with pegylated interferon alpha: A long-term follow-up study

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Abstract

The long-term impact, incidence and risk factors of thyroid dysfunction in chronic hepatitis B (CHB) patients receiving pegylated interferon (IFN) alpha (PegIFN-alpha) therapy remain unclear. We aim to investigate the long-term safety of thyroid dysfunction in CHB patients receiving PegIFN-alpha. A retrospective observational study of 425 CHB patients with normal baseline thyroid function was carried out. Patients were followed up over 10 years to assess thyroid function after receiving IFN. At the end of the IFN therapy, 67 patients (15.8%) had developed thyroid dysfunction, 31 patients (46.3%) had hyperthyroidism and 64.4% presented with subclinical thyroid dysfunction. In follow-up of thyroid dysfunction patients, 37 patients (74.0%) spontaneously regained normal thyroid function. Pretreatment thyroid-stimulating hormone (TSH) level, thyroid peroxidase antibody (TPOAb) positivity and free thyroxine (FT4) were independent risk factors associated with thyroid dysfunction incidence. High TSH level (OR = 9.866, 95%CI, 3.245–29.998) was associated with a greater likelihood of hypothyroidism. High FT4 levels (OR = 0.464, 95%CI, 0.248–0.868) indicate a low likelihood of thyroid dysfunction. Thyroid dysfunction is a common but acceptable side effect of IFN therapy for CHB. Most thyroid dysfunction is reversible. Pretreatment TSH level and TPOAb positivity are risk factors for thyroid dysfunction development during IFN therapy. A high TSH level predicts an increased incidence of hypothyroidism. Moreover, FT4 may be a protective factor for thyroid dysfunction.

KEYWORDS

chronic hepatitis B, long-term follow-up, pegylated interferon alpha, thyroid dysfunction

Abbreviations: CHB, chronic hepatitis B; FT3, free triiodothyronine; FT4, free thyroxine; HBV, hepatitis B virus; IFN, interferon; PegIFN-a, pegylated interferon alpha; TD, thyroid dysfunction; TSH, thyroid-stimulating hormone; TPOAb, thyroid peroxidase antibody.

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1 | INTRODUCTION

Hepatitis B virus (HBV) infection is a global public health problem. It is estimated that approximately 2 billion people worldwide have evidence of or present with HBV infection, and there are 248 million chronic carriers worldwide.[1] Treatment strategies for chronic HBV include pegylated interferon or nucleos(t)ide analogues (NA).

In randomized clinical trials, pegylated interferon achieved higher rates of HBeAg loss.[2] Long-term follow-up of patients has proven that there is a relationship between therapeutic response and higher incidence of HBsAg loss,[3] improved liver histology[4] and a reduction in cirrhosis and hepatocellular carcinoma compared to untreated controls.[5] In chronic hepatitis B (CHB) patients who achieve long-term effective virological remission through NA treatment, PegIFN-a can be used as a 'switch to' or 'add-on' strategy. Two recent studies assessed the efficacy and safety of switching to PegIFN-a for patients on long-term effective NA therapy. Following a 48-week course of PegIFN-a, 6–20% of patients cleared HBsAg.[6,7] Studies examining the relevant mechanisms reported that IFN can promote the degradation of cccDNA by hepatocytes[8] and induce multiple cellular proteins that coordinate to suppress cccDNA transcription.[9] Research increasingly affirms the importance of IFN in CHB treatment. IFN is believed to have both direct antiviral and host immunomodulation effects.[10]

Adverse events associated with IFN therapy include initial flu-like syndrome, fatigue, weight loss, hair loss, depression and induction of autoantibodies, which can result in thyroid abnormalities in up to 30% of patients, or enhancement of autoimmune diseases.[11,12] Previous studies have shown wide variation in thyroid dysfunction (TD) incidence in patients with CHB receiving IFN therapy, with rates ranging from 1.2% to 23.3% in different studies.[13,14] This may be due to several factors, including different diagnostic criteria, study populations, the dose, duration of IFN treatment and concurrent medications.

Currently, reports about the incidence, predictive factors and long-term follow-up outcomes of TD in the CHB population treated with IFN-a are limited, except for some patchy data from several large clinical trials involving IFN. The purpose of this study was to describe the incidence and long-term follow-up outcomes of TD in Chinese patients with CHB who received IFN treatment. We also aimed to identify the predictive factors of TD associated with IFN therapy in CHB patients.

2 | PATIENTS AND METHODS

2.1 | Patients

Our study group included 425 patients diagnosed with CHB. Of these, 269 patients (63.3%) were positive for hepatitis B e-antigen. All patients with normal baseline thyroid function underwent treatment with recombinant IFN-a therapy at Huashan Hospital, affiliated with Fudan University, from 2010 to 2019. All subjects provided their informed consent to participate in the study, as approved by the Ethical Committee of Huashan Hospital. Patients with the following conditions were excluded: (i) history of thyroid diseases, (ii) treatment course was less than three months, (iii) pregnancy and lactation, (iv) psychiatric history and (v) concomitant serious medical illnesses, such as malignancy, severe cardiopulmonary disease or serious infection. Among the selected patients, 344 patients (80.9%) were male and 81 patients (19.1%) were female. Their ages ranged from 31 to 40 years with a median age (±) of 34 years. The baseline characteristics, routine laboratory data, virological information and long-term follow-up outcomes of these 425 patients were collected from medical records and telephone interviews when necessary.

2.2 | IFN-a therapy regimen

Of 324 patients received PegIFN-a-2a therapy, while 92 patients received PegIFN-a-2b therapy. Additionally, 9 patients had been treated with both types of IFN. The dose of PegIFN-a-2a was 180 μg or 135 μg once a week, and that of PegIFN-a-2b was 50 μg once a week. The dose was adjusted in some patients based on the specific characteristics of each individual patient and upon a specialist's recommendation. Depending on clinical needs and patient response, the cumulative course of treatment in 129 patients (30.3%) was over 48 weeks. The duration of the follow-up period was calculated as the time from the initiation of therapy until the last time that the patient was effectively followed up. A detailed flowchart can be seen in Figure 1.

2.3 | Laboratory tests and thyroid function assessments

All patients were evaluated: clinically, haematologically, biochemically and serologically at baseline. Routine biochemical and haematological tests were performed using automated techniques. Hepatitis B surface antigen, e-Antigen, and e-antibody (Abbott Laboratories) were assayed using a second-generation enzyme-linked immunosorbent assay. Thyroid function tests, including serum thyrotropin (TSH), total thyroxine (TT4) and free thyroxine (FT4), and total triiodothyronine (TT3) and free triiodothyronine (FT3), were performed by an ultrasensitive immune chemiluminescent assay (Siemens ADVIA Centaur; Roche Cobas e801).

2.4 | Statistical analysis

Statistical analysis was performed using SPSS 22.0 and GraphPad Prism 8 software. Factors included in the analysis were sex, age, body mass index, IFN type, accumulated dose, treatment course, baseline and regular follow-up clinical laboratory data of thyroid function, thyroid autoantibodies, blood routine data, liver function, antinuclear antibodies and indicators of hepatitis B virology.

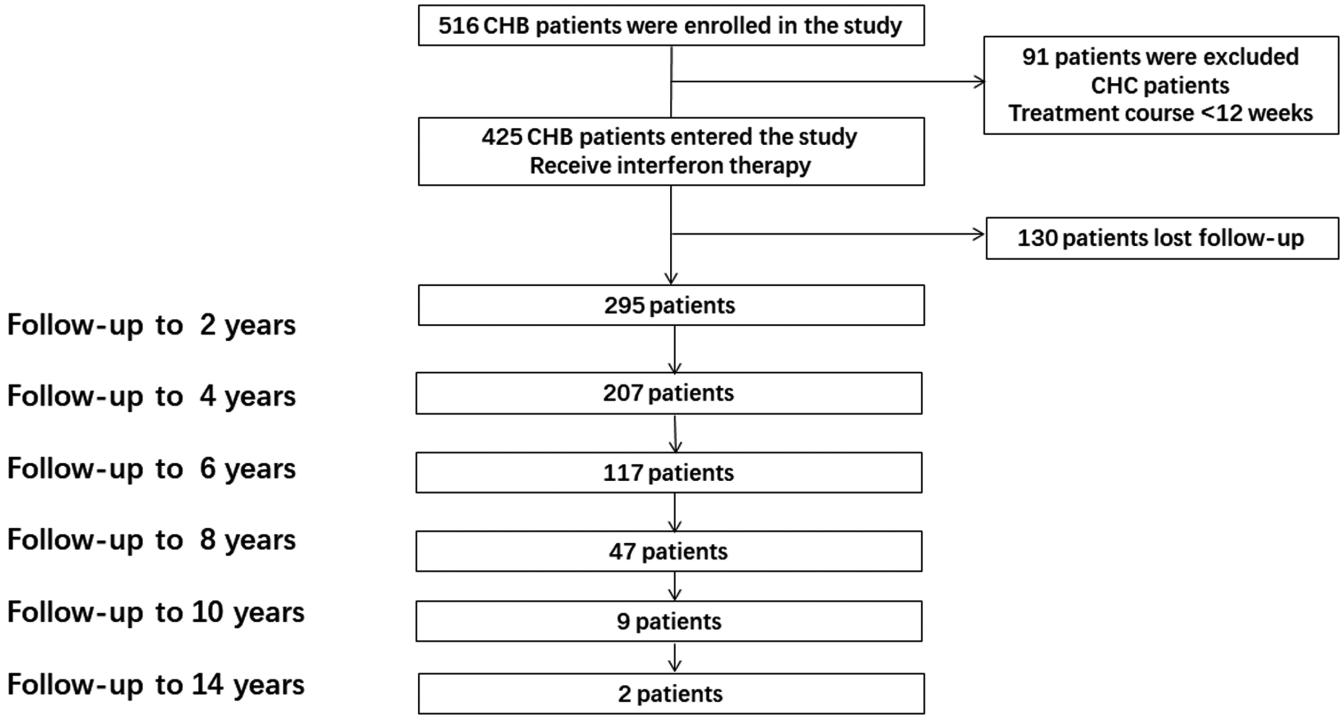

FIGURE 1 Flow diagram of patients enrolled in this study. Our study group included 425 patients diagnosed with CHB, which was proven by hepatitis B virus serological markers and hepatitis B surface antigen remaining positive for more than six months. Among the selected patients, 269 patients (63.3%) were positive for hepatitis B e-antigen. 344 patients (80.9%) were male and 81 patients (19.1%) were female. Their ages ranged from 31 to 40 years with a median age (±) of 34 years. All patients with normal baseline thyroid function underwent treatment with recombinant IFN-a therapy at Huashan Hospital, affiliated to Fudan University, from 2010 to 2019

TABLE 1 Baseline characteristics of chronic hepatitis B patients

	HBeAg positive $n = 269$	HBeAg negative $n = 156$	p value
Male, n%	208 (77%)	136 (87%)	.013
Age, years	33 (30–38)	38 (33–45)	.000
BMI, kg/m²	22.04 (20.35–23.73)	22.86 (20.81–24.71)	.002
Treatment >48weeks	80 (29%)	49 (31%)	.718
Follow-up, months	40 (24–62)	52 (30–71)	.085
Leukocyte, 10^9/L	5.28 (4.36–6.02)	5.27 (4.26–6.27)	.588
ALT, U/L	134 (59–291)	35 (21–86)	.000
HBV DNA, log10	6.81 (2.94–7.48)	2.69 (2.69–3.97)	.000
HBsAg, log10	3.88 (3.27–4.42)	2.82 (1.96–3.30)	.000
TSH, mU/L	1.60 (1.06–2.15)	1.46 (1.09–2.02)	.464
FT3, pmol/L	4.86 (4.52–5.24)	5.01 (4.60–5.28)	.051
FT4, pmol/L	14.82 (13.63–16.19)	14.69 (13.48–16.02)	.775

Note: Values are expressed as median (range) or number of patients (%).

Quantitative variables were expressed as medians and ranges. The Kaplan–Meier method was used to evaluate the incidence rates from the first diagnosis of hepatitis B infection to the occurrence of TD. Quantitative variables were compared using a Student's *t*-test. Unpaired data were compared using the Mann–Whitney test, and frequencies among different groups were compared using a chi-squared test. Univariate logistic regression analysis and multivariate logistic regression analysis were used to explore the independent effects of the baseline factors on TD incidence, and the difference between groups was reported using 95% confidence intervals (CIs). A two-sided *p*-value less than .05 was considered to be significant. Propensity score matching (PSM) was also applied in the study to reduce the influences of confounders, utilizing the R plug-in of SPSS to achieve matching.

3 | RESULTS

3.1 | Incidence and long-term follow-up outcomes of TD

The characteristics of all patients with CHB are shown in Table 1. At the end of IFN-a therapy, 67 patients (15.8%) developed TD, including 31 patients (46.3%) with hyperthyroidism, 28 patients (41.8%) with hypothyroidism and 8 patients (11.9%) with biphasic thyroiditis. A total of 49 men and 18 women were affected. As can be seen in Figure 2, TD onset most often occurred within 24 weeks of the first treatment with IFN. The cumulative incidences at 3, 6, and 9 months after initiation of IFN therapy were 18.7%, 22.0%, and 22.4%. By the end of follow-up, the cumulative incidence was 24.2%. Patients rarely showed overt TD symptoms throughout the study, but a subclinical TD was more commonly seen. Subclinical TD can be divided into subclinical hyperthyroidism and subclinical hypothyroidism, which are characterized by abnormal TSH but normal FT3 and FT4. Transient and subclinical TD accounted for 56.7% of all TD observed, and only 10 patients (14.7%) presented with overt TD. Among the 31 patients with hyperthyroidism, 19 patients presented with subclinical hyperthyroidism, while only 12 patients presented with overt hyperthyroidism. A total of 28 patients with hypothyroidism and 9 hypothyroid subjects (32.1%) experienced overt hypothyroidism. Such patients are often difficult to diagnose until they are identified through a routine health examination or regular outpatient follow-up. The distribution of TD during IFN treatment can be seen in Figure 3.

In long-term follow-up, considering that 130 patients were lost to follow-up, as shown in Figure 4, most patients who developed TD were able to recover in six months without extra treatment. Of these, all 6 patients with biphasic thyroiditis who underwent follow-up regained normal thyroid function without any intervention. However, 8 patients (39.1%) with hyperthyroidism remained abnormal during follow-up, and 5 of them (55.6%) required endocrine medication due to obvious clinical symptoms. In contrast, in the hypothyroidism group, 4 patients (19.0%) remained abnormal and none required endocrine medication. Additionally, 242 patients with normal thyroid function were effectively followed up after IFN therapy. Of these, 4 patients developed asymptomatic subclinical thyroid abnormalities during our follow-up, and 3 patients developed subclinical hypothyroidism, including 2 patients in the second year and 1 patient in the eighth. Another patient developed subclinical hyperthyroidism in the sixth year. Because the early follow-up may yield inaccurate thyroid antibody results, we may not have enough thyroid antibody follow-up data. As far as the data we obtained, 44 euthyroid patients with positive thyroid antibody results during therapy retained their thyroid functionality in the follow-up.

3.2 | Risk factors for thyroid dysfunction

An unadjusted analysis was performed to examine the relationships between variables and TD. Haemoglobin, erythrocyte, FT4, TSH, TPOAb and TgAb were considered correlated after univariate logistic regression analysis. Subsequent multivariate logistic regression analyses showed that FT4, TSH and TPOAb were related. Furthermore, we analysed the two main phenotypes of thyroid dysfunction, including hyperthyroidism and hypothyroidism. Since biphasic thyroiditis is much rarer than the other two types of TD, we were unable to analyse this particular type of TD. More details can be seen in supplementary materials (Table S1).

The preliminary results of univariate and multivariate analysis are summarized in supplementary materials (Tables S2 and S3). According to the results, the related factors associated with a high risk for the development of hyperthyroidism were FT4, TSH, and TPOAb. Among these factors, high levels of FT4 (odds ratio: 0.464; 95%CI: 0.248–0.868) and TSH (odds ratio: 0.195; 95%CI: 0.040–0.946) were

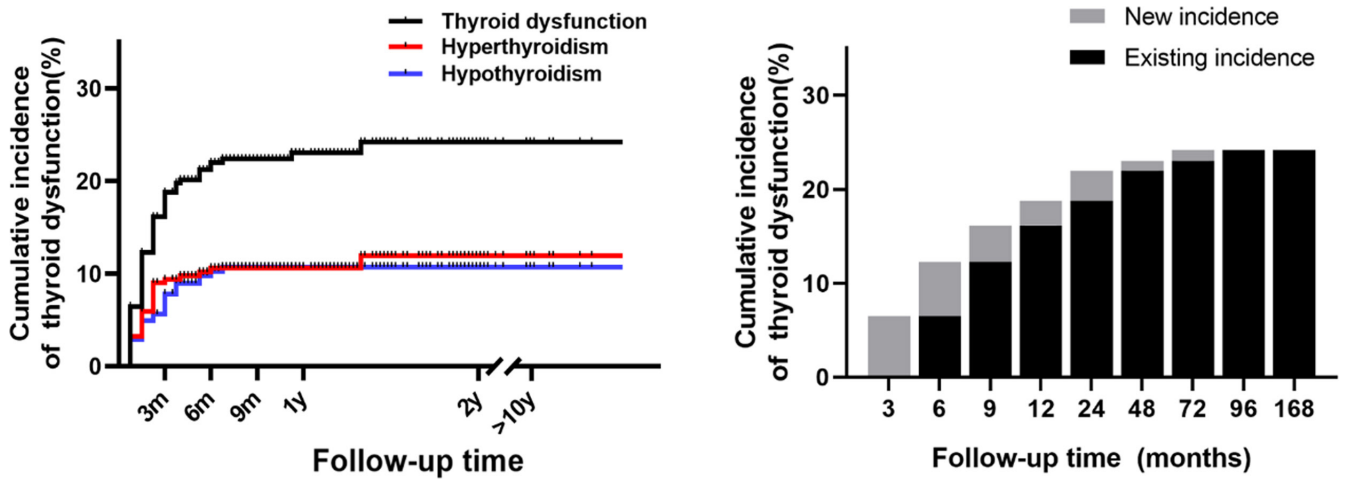

FIGURE 2 Cumulative incidence of thyroid dysfunction including hyperthyroidism and hypothyroidism. TD onset most often occurred within 24 weeks of the first treatment with IFN. The cumulative incidences at 3, 6 and 9 months after initiation of IFN therapy were 18.7%, 22.0% and 22.4%. By the end of follow-up, the cumulative incidence was 24.2%

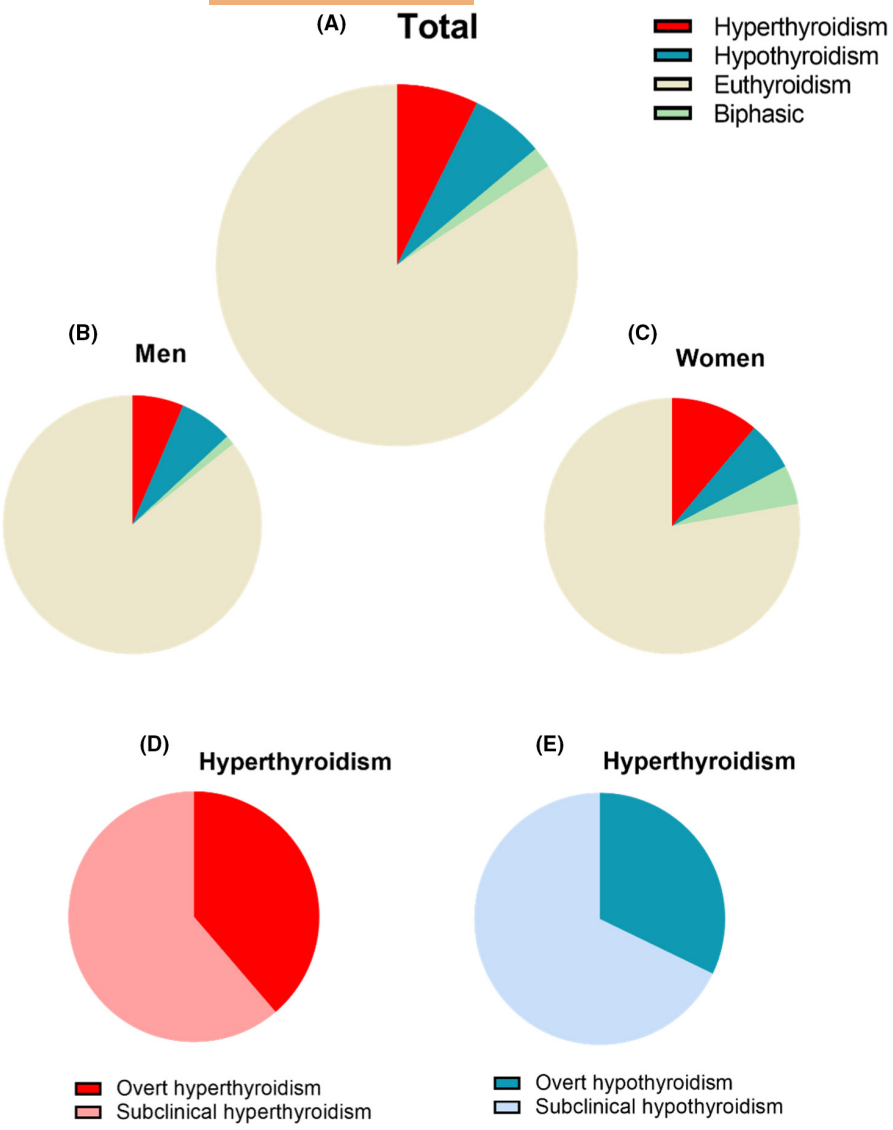

FIGURE 3 Distribution of thyroid dysfunction during the IFN treatment. Of 67 patients (15.8%) developed TD, including 31 patients (46.3%) with hyperthyroidism, 28 patients (41.8%) with hypothyroidism and 8 patients (11.9%) with biphasic thyroiditis. Transient and subclinical TD accounted for 56.7% of all TD observed, and only 10 patients (14.7%) presented with overt TD. Among the 31 patients with hyperthyroidism, 19 patients presented with subclinical hyperthyroidism, while only 12 patients presented with overt hyperthyroidism. A total of 28 patients with hypothyroidism and 9 hypothyroid subjects (32.1%) experienced overt hypothyroidism

protective factors, and TPOAb positivity (odds ratio: 19.178; 95%CI: 1.993–184.543) was a risk factor. Correspondingly, a high level of TSH (odds ratio: 9.866; 95%CI: 3.245–29.998) indicated a higher risk of hypothyroidism.

Some characteristics of the enrolled population may cause statistical bias, such as a high proportion of men in our study. For further analysis, propensity score matching methods were used to balance the bias between the groups. After 1:4 propensity score matching, there was better comparability between groups of data. Another logistic regression analysis was performed to show that high levels of TSH (odds ratio: 0.110; 95%CI: 0.016–0.740) and FT4 (odds ratio: 0.489; 95%CI: 0.280–0.853) were still protective factors for hyperthyroidism. Using the same method, it was found that a high level of TSH (odds ratio: 6.986; 95%CI: 2.480–19.684) remained a risk factor for hypothyroidism. These consequences in Table 2 were consistent with the results before matching. Details can be seen in the supplementary materials.

Moreover, we calculated TSH levels before treatment in patients with different thyroid dysfunctions. Median TSH levels were 1.50 mU/L among euthyroidism, 1.25 mU/L in those developing hyperthyroidism and 2.88 mU/L in those developing hypothyroidism, which also suggested that high TSH often led to hypothyroidism while low TSH led to hyperthyroidism. This trend can be seen more intuitively in supplementary materials (Figure S1).

4 | DISCUSSION

The occurrence of TD associated with IFN therapy is widely reported. However, existing literature examining IFN also includes chronic hepatitis C, malignant melanoma, multiple sclerosis and others, and no previous studies have focused specifically on IFN therapy for CHB. Furthermore, most previous studies have solely examined incidence and risk factors, lacking data about the long-term course of these complications. Additionally, the clinical observation time in these studies is often limited to 6–12 months after therapy or ended when patients completed the treatment. Until the present, there have been no specific studies of CHB patients assessing the relationship between TD and PegIFN-2a therapy in patients.

Our study is the first that has aimed to evaluate the natural history of IFN-related thyroid dysfunction in CHB patients during an average follow-up of 4.1 years after patients received IFN therapy. Such a long-term follow-up retrospective analysis is critical for the observation of different courses of IFN-related TD, as well as for the identification of predictive markers for this disease.

Previous studies have shown that the incidence of TD related to IFN in CHB patients differs greatly from study to study, with the lowest incidence of 1.2% described in America[13] and the highest incidence of 23.3% found in China.[14] The outcomes of patients with TD in previous studies and data are controversial. The diverse genetic predisposition of the subjects may be one of the dominant factors attributed to the variability of TD occurrence. Research has shown that Asian ethnicity is an independent risk factor for the development of TD, with a higher incidence than other ethnicities receiving IFN therapy.[11] The incidence of TD during IFN treatment across all patients included in our study is 15.8%, which is consistent with reports from existing literature. Because different patients had different treatment courses and follow-up procedures, a Kaplan–Meier curve could be used to calculate the cumulative incidence. Ultimately, we found a cumulative incidence of 24.2%, and most TD patients had hyperthyroidism. This is different from the typical results in chronic hepatitis C patients with TD, who primarily developed hypothyroidism according to previous literature. We further classified the patients with TD. Ignoring bipolar thyroiditis, we found that 64.4% of patients presented with subclinical TD. Considering the impact of the high prevalence of TD in the Chinese population, we searched the epidemiological literature for thyroid disease in China. According to the results of an epidemiological survey in 2011, the incidences of subclinical and overt hyperthyroidism are 0.7% and 0.9%, respectively. The incidence of overt hypothyroidism is 1.1%. Compared to the incidence we obtained in our study, these original morbidity rates are within the acceptable range and have limited impact. It is interesting to note that the incidence of subclinical hypothyroidism in the Chinese population was 16.7%. This suggests that the Chinese people themselves have a high incidence of subclinical hypothyroidism. Some experts believe that the long-term mandatory universal salt iodization in China may affect their thyroid function, especially in the coastal areas of China. In general, high iodine intake is associated with hypothyroidism, whereas low iodine intake is related to hyperthyroidism.[12] In our study, 19 patients (28.3%) developed subclinical hypothyroidism, and most of these patients lived in coastal areas. We have reason to believe that this figure is slightly higher than the actual incidence by background morbidity. This may require more detailed epidemiological data and appropriate statistical methods to balance the gap. In addition, most patients developed TD before the first 24 weeks, which is why close monitoring in the early stages of IFN therapy is quite necessary.

Few existing studies have performed long-term follow-up evaluation of thyroid function changes in CHB patients who received IFN therapy. Our study reveals the outcomes of these patients, including

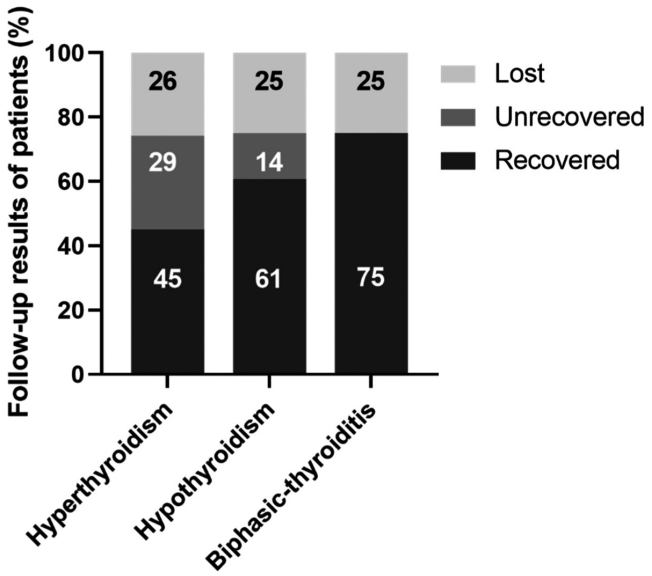

FIGURE 4 Follow-up results of patients with Thyroid dysfunction. Most patients who developed TD were able to recover in six months without extra treatment. Of these, all 6 patients with biphasic thyroiditis who underwent follow-up regained normal thyroid function without any intervention. However, 8 patients (39.1%) with hyperthyroidism remained abnormal during follow-up, and 5 of them (55.6%) required endocrine medication due to obvious clinical symptoms. In contrast, in the hypothyroidism group, 4 patients (19.0%) remained abnormal and none required endocrine medication

TABLE 2 Risk factors associated with thyroid dysfunction including hypothyroidism and hyperthyroidism by multivariate logistic regression analyses after propensity score matching

Hyperthyroidism			Hypothyroidism		
Variables	*p* value	Odd ratio 95% Confidence interval	Variables	*p** value	Odd ratio 95% Confidence interval
FT4	**.012**	**0.489 (0.280~0.853)**	**TSH**	**.000**	**6.986 (2.480~19.684)**
TSH	**.023**	**0.110 (0.016~0.740)**	HBsAg	.095	
FT3	.057	6.028 (0.947~38.376)	FT4	.139	
TT4	.335		HBeAg	.279	

Note: p value was given for the comparison between patients with hyperthyroidism and patients without hyperthyroidism.
*p** value was given for the comparison between patients with hypothyroidism and patients without hypothyroidism.
Variables in bold indicate statistically significant differences.

those with and without TD. The causes of the different outcomes in various studies are still unknown. It seems that hypothyroidism is more likely to self-limit recovery than hyperthyroidism. We speculate that this may be related to the possible mechanism of TD induced by IFN. Some scholars think that interferon may have a direct toxic effect on thyroid tissues[13] to cause hyperthyroidism, which means it is difficult for patients to recover from the resulting tissue damage. The occurrence of hypothyroidism may be more related to the autoimmune regulation effect of IFN,[15] such that thyroid function can be quickly returned to normal after IFN withdrawal. Follow-up of patients with normal thyroid function during IFN therapy showed that only 4 patients presented with, TD and all had subclinical TD. Furthermore, 3 of them had subclinical hypothyroidism. The follow-up time points at which TD was discovered began at least two years after treatment. As previously mentioned, we cannot ignore the inherent incidence of thyroid disease in the Chinese population. Whether these 4 patients' TD can be considered IFN-independent remains questionable. The long-term safety of IFN in the treatment of CHB is still worth affirming. However, we should note that the number of patients enrolled in a study is crucial for investigating significant correlations. The more patients that are included, the more reliable the conclusion.

To date, only a few studies have evaluated the incidence of TD in CHB patients treated with different IFN therapy regimens. We compared the incidences of TD between PegIFN-2a and PegIFN-2b treatments and found no significant difference. The combined nucleotide analogues need to be further collected and studied.

To explore the factors associated with TD, we analysed the baseline characteristics using univariate and multivariate logistic regression and found that TSH, TPOAb and FT4 were relevant factors. Concretely, a high level of TSH predicts an increased incidence of hypothyroidism. On the contrary, a low level of TSH indicates the possibility of hyperthyroidism. This is consistent with previous research on chronic hepatitis C. TPOAb has also been shown to be a risk factor for hyperthyroidism in our study. Because our early thyroid antibody data are partially missing, antibody analysis of hypothyroidism is of little reference value. What is noteworthy is that logistic regression analysis showed that a high level of FT4 was a protective factor for hyperthyroidism. This conclusion is still dependable after the propensity score matching, which has never been reported before in the literature. The underlying mechanism of this observation remains to be explored.

In the previous studies, gender is an independent factor in predicting the occurrence of IFN-associated TD. Usually, females have an increased risk for the development of TD during IFN therapy. Several studies have reached similar conclusions. However, in our analysis, gender was not a relevant factor. This might have occurred because, as is known, CHB patients are more often men than women. The population we studied has a specific sex ratio, in which 80.9% of the patients were males, which may prevent us from reaching meaningful and credible conclusions about gender. Similarly, significant differences in haemoglobin and erythrocytes in baseline data can also be explained with the large sex ratio difference. Subsequent multivariate logistic regression analyses and propensity score matching can balance out these biases.

In our study, CHB patients who received PegIFN-2a therapy were likely to have hyperthyroidism, which is often hard to recover from without medication compared to hypothyroidism. Pretreatment TSH, FT4 and TPOAb were the related factors for TD. Notably, lower and higher pretreatment TSH predicts the possibility of hyperthyroidism and hypothyroidism. We can assess the risk that CHB patients will develop TD before IFN therapy. In clinical practice, screening for thyroid function is recommended at baseline and every three months during treatment with IFN. In this way, most TD can be detected in time. For patients who have already developed TD, their thyroid function returned to normal quickly after stopping IFN therapy. The NA plus PegIFN-a therapeutic regimen is the current research hotspot in the field of CHB. Its efficacy has been recognized in numerous papers and in several clinical practice guidelines. Subsequent studies require more comprehensive clinical data on the side effects of PegIFN-a to ensure patient safety.

Relatively complete thyroid antibody and thyroid ultrasound results are still necessary to assess thyroid health status, which was missing in our study. Our findings still require further investigation using detailed multidimensional data from a much larger, multicentre, long-term follow-up prospective study. The specific pathogenesis also requires more basic research to develop a full understanding.

In conclusion, TD is a common but acceptable side effect of IFN therapy for CHB. Most thyroid dysfunctions are controllable and reversible. This retrospective study can help us better understand long-term changes in the thyroid function of CHB patients who receive PegIFN-2a therapy and may provide medication guidance.

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AUTHOR CONTRIBUTIONS

Jiming Zhang, Richeng Mao, Yanli Qin and Zhenxuan Ma involved in study conception and design. Zhenxuan Ma, Yidi Jia, Yiran Xie, Yifei Guo, jingjing He, Yongmei Zhang, Fahong Li, Jie Yu, Haoxiang Zhu, Feifei Yang, and Yu Zhang involved in acquisition of data. Zhenxuan Ma, Richeng Mao and Xun Qi analysed the data and drafted the manuscript. Guarantor of the article is Zhenxuan Ma. The corresponding author attests that all listed authors fulfil authorship criteria.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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