

Relationship between TPO-Ab with aggressive behavior in major mental disorders

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KEYWORDS

thyroid, thyroid peroxidase antibody (TPO-Ab), autoantibody, suicide, aggression

ABSTRACT

Purpose: We aimed to explore the relationship between thyroid peroxidase antibody (TPO-Ab) and suicidal and aggressive behaviors in patients with major mental disorders.

Methods: We enrolled 812 inpatients with major mental disorders (schizophrenia, bipolar disorder, and major depressive disorder) in this retrospective study. Baseline interviews were conducted by two psychiatrists. The patients' suicidal and aggressive behaviors were recorded in the electronic medical record system and these patients were evaluated in terms of violence and suicide behaviors according to the risk assessment form formulated in the Work Code for the Management and Treatment of Severe Mental Illness by the Ministry of Health of China. We calculated the incidence rates of positive TPO-Ab, the suicidal and aggressive behaviors. Furthermore, we explored the relationships among risk factors for suicidal and aggressive behaviors using logistics regression analysis.

Results: Among the 812 patients, 42.6% ($n = 346$) had TPO-Abs and were defined as the positive group. Rates of suicide and aggression among the enrolled patients were 12.7% ($n = 103$) and 10.2% ($n = 83$) respectively. The percentage of patients with aggressive behaviors (13%, $n = 45$) was higher than that in the negative group (8.2%, $n = 38$). In contrast, the incidence (9.5%) of suicidal behaviors in the positive group was lower than that (15.0%) in the negative group. TPO-Ab was found to increase the risk of aggressive behavior (odd ratio (OR) = 1.64, 95%CI (1.04, 2.59), $P = 0.03$) and this effect was still evident after we adjusted for thyroid function (OR = 1.65, 95%CI (1.03, 2.64), $P = 0.04$). Furthermore, subclinical hypothyroidism (OR = 2.64, 95%CI (1.19, 5.85), $P = 0.02$) and subclinical hyperthyroidism (OR = 7.03, 95%CI (2.23, 22.20), $P = 0.001$) were found to be risk factors of aggressive behavior but not for suicide behaviors.

Conclusion: TPO-Abs can affect aggressive behavior but do not affect suicidal behaviors, in patients with major mental disorders. Thus, antibody testing is necessary for psychiatric patients with aggressive behavior. The TPO-Ab test helped the psychiatric staff to determine aggressive behavior in advance.

1 Introduction

The World Health Organization estimates that over three-quarters of a million people worldwide take their own lives yearly [1]. In the USA, suicidal and aggressive behaviors are the areas of major public health concern [2]. Between 2008 and 2018, age-adjusted suicide rates increased from 11.6 deaths per 100,000 people to 14.2 deaths per 100,000 people [3]. Individuals diagnosed with one kind of mental illness were 3–4 times more likely to have aggressive or violent behaviors than the general population [4]. Previous studies have reported that individuals with a mental illness attempt suicide at least 10 times more than the general population [5], which represents a serious clinical challenge and a social burden [6]. Identifying aggression in psychiatric wards is crucial, because aggressive behavior not only endangers the patients and medical staff, but also extends the hospitalization times [7]. Thus, it is imperative to explore the factors associated with suicide and aggressive attempts in psychiatric patients for effective prevention.

According to the current studies, aggressive behaviors is related to several factors, and the risk of aggressive behavior is increased in psychiatric disorders such as bipolar disorder, schizophrenia, and antisocial personal [8]. Other demographic risk factors associated with aggressive behavior include hospitalization times and frequency of younger age [9] and hospital admissions [10–14]. UK study showed that male patients with severe mental illness were more prone than female patients to aggressive behavior such as assault and physical aggression [15]. Although previous studies have mainly focused on the psychiatric disorders or sociocultural factors, mechanism has not been thoroughly investigated [16, 17]. Additionally, autoimmune factors have been reported to be associated with psychiatric disorders [8] as well as suicidal [19], and

aggressive behaviors [20] with the thyroid being the most commonly affected [21].

TPO-Ab is a type of immune antibody that has been linked to affective disorders [22–26], poor results in various domains, such as somatization, obsessive–compulsive symptoms, and depression even in the absence of thyroid dysfunction [27] and adverse outcomes [28]. TPO-Ab has also been associated with psychiatric diseases such as bipolar depression or schizophrenia [29], although there is limited neuropathological data or clinical information [26]. function being considered a factor is because hypothyroidism and hyperthyroidism often affect psychiatric and cognitive functioning. For example, patients with schizophrenia have been found to have low concentrations of thyroid-stimulating hormone (TSH) and increased levels of TPO-Ab [30].

However, there are increasing reports of patients with autoimmune thyroid disease, neurological or psychiatric symptoms occurring regardless of the thyroid hormone status [31]. Therefore, encephalopathy has been considered a possible mechanism of autoimmune thyroiditis [32, 33]. In addition to autoimmune etiology, vasculitis, and autoimmunity directed against common brain-thyroid antigens represent the most likely aetiologic mechanisms. Several other mechanisms have been proposed, including cerebral vasculitis, global cerebral hypoperfusion, cerebral tissue-specific autoimmunity, and neuronal deficit related to thyrotropin-releasing hormone [34].

Presently, few studies have noticed the role of TPO-Ab in suicidal or aggressive behaviors of individuals with psychosis [35, 36]. Thus, the relationship between TPO-Ab and suicidal and aggressive behavior remains uncertain. In this study, we aim to identify whether TPO-Ab increases the risk of suicidal or aggressive behaviors irrespective of thyroid function, using

data from retrospective studies representative of individuals with psychotic.

2 Methods

2.1 Studied population

We selected a sample of 2015 inpatients from Shenzhen Kangning hospital between 2018 and 2019. The inclusion criteria were as follows: (1) the adult patients must be above 18 years old; (2) the patients must have a definite diagnosis of a major mental illness (depression, bipolar disorder, or schizophrenia); (3) the patients must have a clear consciousness and the ability to cooperate with the questionnaire survey. Patients were excluded if they had no record of impulsive or suicidal behaviors; or had not completed thyroid function tests; had a previous diagnosis of thyroid disease or were on medications regulating thyroid function. The diagnosis of diseases was based on the International Classification of Diseases, Tenth Revision (ICD-10). Psychiatric consultation of the patients was completed by two psychiatrists with the title of attending or above. A total of 812 patients were enrolled and every patient provided the signed informed consent. The Institutional Review Boards of Shenzhen Kangning Hospital approved the study.

2.2 Main outcomes

The main outcome of our interest was suicidal and aggressive behaviors. Suicidal behavior was defined as a potentially self-injurious act committed with at least some wish to die. Aggression was defined as physical violence toward people or objects or verbal threats and intimidation. To assess the risk level of the patients' behaviors, we used the risk assessment form formulated in the Work Code for the Management and Treatment of Severe Mental

Illness by the Ministry of Health of China.

The screening questionnaire to access suicidal behavior in each patient the following six questions: (1) "do you think it's better to die now or to die last month?" with a response of "yes" scored as 1 point; (2) "did you want to hurt yourself last month?" with a response of "yes" scored as 2 points; (3) "did you think about suicide last month?" with a response of "yes" scored as 6 points; (4) "was there a suicide plan last month?" with a response of "yes" scored as 10 points; (5). "did you attempt suicide last month?" with a response of "yes" scored as 10 points; (6) "have you ever attempted suicide in your whole life?" with a response of "yes" scored as 4 points. Subsequently, the total score of these six questions was calculated. Patients who scored above 10 were considered a high risk for suicidal behavior and were classified as the suicide group, while patients who scored below 10 were classified as the no-suicide group.

The patient's aggressive behavior was also accessed using a questionnaire to determine whether uncontrollable aggressive behavior with certain social risks had occurred in the past week. The assessment form ranked violent behavior from minor to major on 6-point scale. Level 0: no behavior matching levels 1–5; Level 1: verbal threats or shouting, but no battering behaviors; Level 2: battering behaviors confined to home or directed toward properties only and could be persuaded to stop; Level 3: obvious battering behaviors directed toward properties only but regardless of place, and could not be persuaded to stop; Level 4: persistent battering behaviors directed toward properties or people and could not be persuaded to stop, regardless of the occasions; Level 5: any violence against a person using a controlled and dangerous weapon, arson, explosion, or other means, whether at home or in a public place. Patients placed at Level 3 and

above were considered to have a high risk of aggressive behaviors and were defined as the aggression group, while those at level 3 or below were defined as the nonaggression group.

Patients with a high risk for suicidal and aggressive behaviors were defined as the suicide and aggression groups, whereas those with a low risk were defined as the no-suicide and no-aggression groups. If answers were uncertain or the patients could not cooperate with the mental examination due to their current mental symptoms, their family members, relatives or friends were interviewed to draw a conclusion as the supplementary information. Records of suicidal and aggressive behaviors can be obtained from the electronic case system of Shenzhen Kangning Hospital.

2.3 Classification of TPO-Ab

TPO-Ab was measured using an electrochemiluminescence immunoassay. Although most automated assays for TPO-Ab are standardized to the same international reference material, inconsistencies remain among different manufacturers' assays [30]. Moreover, the cutoff for positive TPO-Ab continues to be debated [37, 38]. It is often impractical for clinical laboratories to establish local reference intervals for all tests they perform. Consequently, clinical laboratories use reference intervals reported in the literature or provided by the assay manufacturer, which may only be appropriate for the local patient population [39].

The manufacture-defined cutoff for TPO-Ab was 28 IU/mL. All thyroid function and antibody tests were performed at the Nuclear Medicine Laboratory of Shenzhen Kangning Hospital. Patients whose TPO-Ab was above 28 IU/mL were defined as the positive group while those with a TPO-Ab level below 28 IU/mL were defined as the negative group.

2.4 Assessment of covariates

Thyroid functions were assessed using various assays. These assays' reference ranges were listed as follows: The reference ranges for these assays defined by manufacturer and listed as follows: FT4 = 11.5–22.7 pmol/L, TSH = 0.55–4.78 μ U/mL [40]. Participants were classified into five groups based on their thyroid function tests:

(1) Hyperthyroidism was defined as a TSH concentration < 0.1 mU/L with an elevated FT4 level.

(2) Subclinical hyperthyroidism was defined as a TSH concentration < 0.55 mU/L with a normal FT4 level.

(3) Euthyroidism was defined as a normal TSH concentration (0.55–4.78 mU/L).

(4) Subclinical hypothyroidism was defined as a $4.78 < \text{TSH} < 20$ mU/L with a normal FT4 concentration.

(5) Overt hypothyroidism was defined as a TSH concentration > 4.78 mU/L with an FT4 level below the normal level [41].

History of psychiatry (PH), length of hospitalization, and expenses during hospitalization were recorded in the clear electronic and paper medical system. Regarding disease categories, we selected the three most common mental illnesses: depression, bipolar disorder, and schizophrenia.

2.5 Statistical analysis

Descriptive characteristics for categorical variables were summarized as frequencies, and significant differences were evaluated using the χ^2 -test. Continuous variables were summarized as mean $\pm$ standard deviation (SD), using a *t*-test.

The Hosmer–Lemeshow (HL) test showed that the regression equation had a good fitting degree, and the binary logistic regression model can effectively reflected the relationship between variables. The Box–Tidwell test indicated a linear

relationship between the stratification variables and log-transformed outcomes. The tolerance and VIF values were all less than 10, and the tolerance values were above 0.1, suggesting no multicollinearity existed among the variables. Subsequently, logistic regression analysis was used to detect the relationship between TPO-Ab and aggressive/suicidal behavior. All the calculated *P* values were two-tailed, and $P < 0.05$ was considered significantly different. All analyses were performed using SPSS, version 26.

3 Results

As shown in Fig. 1, we selected 812 patients with a definite diagnosis of a major mental disorder (depression, bipolar disorder, or schizophrenia). Subsequently, we calculated the incidence of positive and negative TPO-Ab among the patients, which were 42.6% ($n = 346$) and 57.4% ($n = 466$) respectively. Furthermore, the incidence rates of suicidal and aggressive behaviors were 12.7% ($n = 103$) and 10.2% ($n = 83$), respectively.

3.1 General information and diagnosis of the positive and TPO-Ab group

Patients in the positive group were older (40.11 ± 0.76) than those in the negative group (37.84 ± 0.69 , $P = 0.03$). There was no significant difference

in the incidence of men and women in both groups ($P = 0.10$). The positive group had more patients ($n = 206$, 59.5%) with PH than the negative group ($n = 233$, 50%; $P = 0.01$). The length of hospitalization was greater in the positive TPO-Ab group (66.48 ± 5.59) than in the negative group (38.81 ± 2.98 ; $P = 0.02$). Hospitalization times were longer in the positive group ($35,213 \pm 2,273$) than the negative ($25,163 \pm 1,134$) group, which was statistically significant (Table 1).

Regarding the disease categories, the incidence of schizophrenia was higher in the positive group (61.6%; $n = 213$) than in the negative TPO-Ab group (44.4%; $n = 207$), and it was statistically significant, achieving statistical significance ($P < 0.001$). Bipolar disorder also had a higher incidence rate in the positive group (28.0%) than in the negative group (24.9%). In contrast, the incidence rate of depression was lower in the positive group (10.4%) than in the negative group (30.7%). Subclinical hyperthyroidism (2.1%) and euthyroidism (88.0%) were higher in negative TPO-Ab group than in the positive TPO-Ab group. However, the incidence rates of thyroid dysfunction (hyperthyroidism, subclinical hypothyroidism and hypothyroidism) were 7.5%, 6.6%, and 2.3% in the positive group, respectively, all higher than those (3.9%, 2.1%, and 3.9%) in the negative TPO-Ab group.

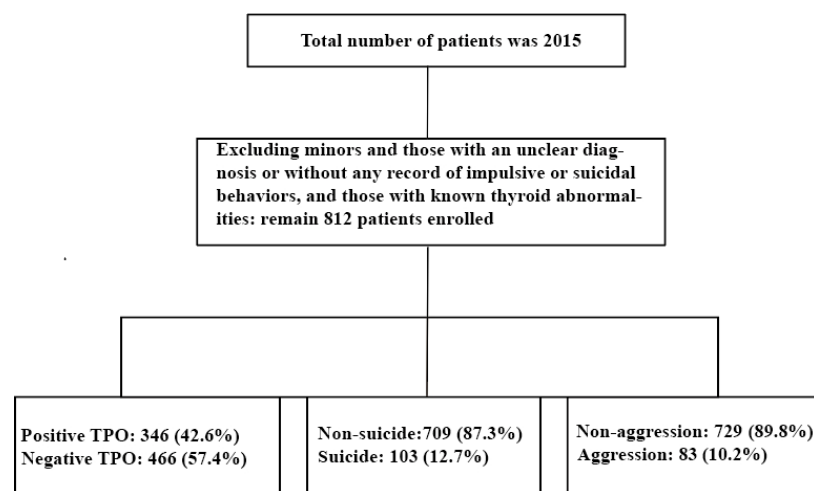


Figure 1 Flowchart for selecting patients for this study.

Table 1 Characteristics of patients with and without TPO-Ab

Variable	Patients (<i>n</i> = 812)		<i>P</i>
	positive TPO-Ab group (<i>n</i> = 346, 42.6%)	negative TPO-Ab group (<i>n</i> = 466, 57.4%)	
Age, mean ± SD	40.11 ± 0.76	37.84 ± 0.69	0.03
Sex, <i>n</i> (%)			0.10
Male	180 (52.0)	215 (46.1)	
Female	166 (48.0)	251 (53.9)	
PH, <i>n</i> (%)			0.01
Yes	206 (59.5)	233 (50.0)	
No	140 (40.5)	233 (50.0)	
Length of Hospitalization	66.48 ± 5.59	38.81 ± 2.98	0.02
Hospitalization number	4.91 ± 0.4	3.67 ± 0.29	0.01
Hospitalization expenses	35,213 ± 2273	25,163 ± 1134	< 0.001
Thyroid function, <i>n</i> (%)			0.04
Hyperthyroidism	26 (7.5)	18 (3.9)	
Subclinical hyperthyroidism	4 (1.2)	10 (2.1)	
Euthyroidism	285 (82.4)	410 (88.0)	
Subclinical hypothyroidism	23 (6.6)	18 (3.9)	
Overt hypothyroidism	8 (2.3)	10 (2.1)	
Diagnosis, <i>n</i> (%)			< 0.001
Schizophrenia	213 (61.6)	207 (44.4)	
Bipolar	97 (28.0)	116 (24.9)	
Depression	36 (10.4)	143 (30.7)	
Suicide, <i>n</i> (%)			0.02
Yes	33 (9.5)	70 (15.0)	
No	313 (90.5)	396 (85.0)	
Aggression, <i>n</i> (%)			0.02
No	301 (87.0)	428 (91.8)	
Yes	45 (13.0)	38 (8.2)	

3.2 Suicide and aggression in the positive and negative TPO-Ab groups

There were significant differences between suicidal and aggressive behaviors in the positive and negative TPO-Ab groups. The incidence of aggressive behavior was higher in the positive TPO-Ab group (13.0%; *n* = 45), much higher than in the negative group (8.2%; *n* = 38) (*P* = 0.02). Nevertheless, the incidence of suicide was lower in the positive group, less (9.5%; *n* = 33) than in the negative group (15.0%, *n* = 70, *P* = 0.02) (Table 1).

3.3 Clinical characteristics of patients in the suicide and no-suicide groups

Ages were statistically different between the suicide and no-suicide groups (*P* < 0.001). The incidence of females was higher in the suicide group (74.8%) than in the no-suicide group (48.0%). However, hospitalization length, times, and expenses were lower in the suicide group than in the no-suicide patients (*P* < 0.05).

Unexpectedly, the no-suicide group had a greater incidence (44.1%) of TPO-Ab than the suicide group. In the suicide group, only the

incidence rate of depression (63.1%) was higher than that (16.1%) in the no-suicide group ($P < 0.001$). There were no differences in the incidence of thyroid function between the suicide and no-suicide groups ($P = 0.13$) (Table 2).

3.4 Clinical characteristics of patients with aggression or not

There was no significant sex difference between the aggression and no-aggression groups. Hospitalization length, times, and expenses did not reach a statistical difference.

The incidences of TPO-Ab and thyroid function were significantly different between the both groups. Incidences of schizophrenia and bipolar disorder were 63.9% ($n = 53$) and 36.1% ($n = 30$) in the aggression group, and 50.3% ($n = 367$) and 25.1% ($n = 183$) in the no-aggressive group, respectively ($P < 0.001$). There were no depressed patients in the aggression group but there were 24.6% ($n = 179$) of patients with depression in the no-aggressive group. Except for euthyroidism and hypothyroidism, subclinical hypothyroidism (10.8%), subclinical hyperthyroidism (6.0%), and

Table 2 Characteristics of patients with suicidal and aggressive behaviors or not

Variable	Suicide ($n = 103$)	No-suicide ($n = 709$)	P	Aggression ($n = 83$)	No-aggression ($n = 729$)	P
Age, mean $\pm$ SD	33.78 $\pm$ 15.49	39.54 $\pm$ 14.37	< 0.001	37.30 $\pm$ 12.89	38.98 $\pm$ 14.82	0.27
Sex, n (%)						0.05
Male	26 (25.2)	396 (52.0)		49 (59.0)	346 (47.5)	
Female	77 (74.8)	340 (48.0)	< 0.001	34 (41.0)	383 (52.5)	
History, n (%)			0.002			0.15
Yes	41 (39.8)	398 (56.1)		51 (61.4)	388 (53.2)	
No	62 (60.2)	311 (43.9)		32 (38.6)	341 (46.8)	
TPO-Ab, n (%)			0.02			0.02
Yes	33 (32.0)	313 (44.1)		45 (54.2)	301 (41.3)	
No	70 (68.0)	396 (55.9)		38 (45.8)	428 (58.7)	
Length of hospitalization	28.06 $\pm$ 36.66	53.87 $\pm$ 88.98	< 0.001	51.07 $\pm$ 83.09	50.55 $\pm$ 84.81	0.96
Hospitalization number	2.03 $\pm$ 2.40	4.52 $\pm$ 7.26	< 0.001	3.93 $\pm$ 5.81	4.23 $\pm$ 7.00	0.66
Hospitalization expenses	21866 $\pm$ 16130	30547 $\pm$ 35314	< 0.001	29295 $\pm$ 33797	29463 $\pm$ 33615	0.97
Diagnosis, n (%)						< 0.001
Schizophrenia	12 (11.7)	408 (57.5)		53 (63.9)	367 (50.3)	
Bipolar	26 (25.2)	187 (26.4)		30 (36.1)	183 (25.1)	
Depression	65 (63.1)	114 (16.1)		0 (0.0)	179 (24.6)	
Thyroid function			0.13			0.002
Hyperthyroidism	2 (1.9%)	42 (5.9%)		5 (6.0%)	39 (5.3%)	
Subclinical hyperthyroidism	1 (1.0%)	13 (1.8%)		5 (6.0%)	9 (1.2%)	
Euthyroidism	94 (91.3%)	601 (84.8%)		63 (75.9%)	632 (86.7%)	
Subclinical hypothyroidism	2 (1.9%)	39 (5.5%)		9 (10.8%)	32 (4.4%)	
Hypothyroidism	4 (3.9%)	14 (2.0%)		1 (1.2%)	17 (2.3%)	

hyperthyroidism (6.0%) were more common in the aggression group than the no-aggression group ($P = 0.002$) (Table 2).

3.5 Suicide

From the logistic regression analysis (Table 3), TPO-Ab tended to be a protective factor (odd ratio (OR) = 0.63, 95%CI (0.40, 0.98), $P = 0.04$) for suicide after adjusting for sex and the disease categories in Model 1. However, this effect was nonexistent after sequential adjustment for thyroid function status in Model 2. Being female

was a risk factor for suicide behavior in Model 1 and Model 2, but thyroid function status did not affect suicidal behaviors.

3.6 Aggression

The effects of TPO-Ab on aggressive behavior differed from those on suicidal behavior. TPO-Ab significantly increased the risk of aggressive behavior (OR = 1.64, 95%CI (1.04, 2.59), $P = 0.03$) in the Model 1. This effect still existed after further adjustment for thyroid function status (OR = 1.65, 95%CI (1.03, 2.64), $P = 0.04$) in Model 2.

Table 3 Risks for suicide or aggression

	Suicide	R2	HL-test	P	Aggression	R2	HL-test	P
		0.073	0.94			0.023	0.89	
TPO-positive								
No	Ref				Ref			
Yes	0.63 (0.40, 0.98)			0.04	1.64 (1.04, 2.59)			0.03
Sex								
Male	Ref				Ref			
Female	3.11 (1.95, 4.98)			<0.001	0.65 (0.41, 1.04)			0.65
Diagnosis								
Schizophrenia	Ref				Ref			
Bipolar disorder	1.15 (0.71, 1.87)			0.57	0.89 (0.50, 1.57)			0.68
Depression	0.85 (0.48, 1.49)			0.57	1.07 (0.61, 1.88)			0.82
Model2	0	0.092	0.99			0.046	0.86	
TPO-Ab								
No	Ref				Ref			
Yes	0.66 (0.42, 1.04)			0.07	1.65 (1.03, 2.64)			0.04
Sex								
Male	Ref				Ref			
Female	3.18 (1.99, 5.12)			< 0.001	0.63 (0.39, 1.01)			0.05
Diagnosis								
Schizophrenia	Ref				Ref			
Bipolar disorder	1.16 (0.71, 1.89)			0.55	0.87 (0.49, 1.55)			0.63
Depression	0.81 (0.46, 1.44)			0.48	1.16 (0.65, 2.07)			0.61
Thyroid functions								
Euthyroidism	Ref				Ref			
Sub-hypothyroidism	0.35 (0.08, 1.49)			0.16	2.64 (1.19, 5.85)			0.02
hypothyroidism	1.89 (0.58, 6.10)			0.29	0.59 (0.08, 4.58)			0.62
Sub-hyperthyroidism	0.39 (0.05, 3.05)			0.37	7.03 (2.23, 22.20)			0.001
Hyperthyroidism	0.29 (0.07, 1.24)			0.10	1.25 (0.47, 3.34)			0.65

However, sex showed no significant difference between aggressive and no-aggressive groups. hypothyroidism (OR = 2.64, 95%CI (1.19, 5.85), $P = 0.02$) and subclinical hyperthyroidism (OR = 7.03, 95%CI (2.23, 22.20), $P = 0.001$) significantly increased the risk for aggressive behavior (Table 3).

4 Discussion

This population-based retrospective study reported the relationship between TPO-Ab and aggressive behavior among patients with major mental disorders.

4.1 Incidence of positive TPO-Ab

The first population-based study on the positive thyroid antibody conducted in Northern England found high antibody titers in 4.6% of women and 1.6% of men between 1962 and 1963 [42]. The incidence of Hashimoto's thyroiditis (characterized by elevated antibodies) has rapidly increased in recent decades [43] and has become the most common cause of thyroid diseases. Presently, its incidence is 0.3–1.5 cases per 1,000 people [44]. The incidence of thyroid antibodies was 18.9% for general population [45]. Among 249 nonselected, hospitalized, chronic geriatric patients, the incidence of positive TPO-Ab was 15.3% [46]. In one study, the incidence of TPO-Ab among patients with schizophrenia was 20%, higher than that among the general population [47]. Antibody titer in patients with other psychiatric illnesses (depression, anergia, affective symptoms, and post-partum depression) [48, 49] was also higher than that in the general population [50, 51]. In a retrospective study, the average incidence of TPO-Ab was 42.6%, much higher than that in the people without thyroid disorder and lower than that in the people with thyroid dysfunction [52]. The incidence of positive TPO-Ab was 32.0% in the suicide group, lower than the average

incidence of TPO-Ab (42.6%).

Differences in these incidence rates may be due to the clinical definition of thyroid disease and the selection of different disease populations from various areas. Genetic and environmental factors may also contribute to these variations. As with the age, sex, or disease composition of the samples, studies differ concerning assay methods, distribution area, and choices of cut-off points for titers considered positive.

4.2 Incidence of suicide and aggression

The incidence of aggressive behavior was 13.0% in the positive TPO-Ab group and 8.2% in the negative TPO-Ab group. However, the incidence of suicidal behavior was 9.5% in the positive TPO-Ab group, lower than that in the negative group (15.0%).

One study indicated a range percent from 76 per 100,000 admissions in Germany [53] to 116/167 (women/men) per 100,000 admissions from a study in Japan [54] and 368 per 100,000 admissions in Australia [55]. Individuals with severe depressive symptoms are usually admitted to an inpatient service and their suicide rates (21%) are double those of outpatients [56]. Most suicides occur in individuals with mental illness [57], and all mental disorders could increase suicide-associated mortality [58].

4.3 Relationship between TPO-Ab, thyroid function status and aggression behaviors

Our results suggested that TPO-Ab increased the risk of aggressive behavior, consistent with an epidemiology study [59]. Neuroendocrine mechanisms were considered central to aggressive behavior [60], along with the pathological inflammation mechanism, which was confirmed by higher white blood cell counts [61]. Cerebral dysfunction, vasculitis process [62], and lymphocytic infiltration around small arterioles or venules are other possible mechanisms [63].

Mussig et al. showed a relationship between anti-TPO levels and symptomatic distress [27]. A test showing that mice with a genetic background of TPO-Cre displayed aggressive behavior supported the hypothesis that an altered thyroid signal is related to aggressive behavior. Data from a 10-year observation of TPO-Ab variations in a population-based prospective study in Iran showed an increasing trend in TPO-Ab levels over time, accompanied by an increase in hypothyroidism incidence [64–66]. Similarly, certain thyroid status (subclinical hyperthyroidism and subclinical hypothyroidism) increased the risk for aggressive behavior in our study. Thus, Thyroid function and psychiatric disorders, especially mood disorders, are proven to be correlated [67].

The effects of antibodies and dysthyroidism on mental illness are not inconsistent. Findings by Fountoulakis et al. [68] and Kupka et al. [69] summarized that depression might be characterized by the activation of autoimmune processes but not the thyroid dysfunction. However, Williams et al. [70] reported no relationship between low thyroid function and the risk of developing depression over the lifespan, based on the findings from the Caerphilly Prospective Study, which included over 2,200 middle-aged men, and a meta-analysis of five studies. Thus, this may be an exciting area of research requiring further study.

4.4 Relationship between TPO-Ab, thyroid function, and suicide

Our study showed that TPO-Ab was a protective factor for the suicidal behavior, but thyroid function status had no relationship with suicidal behavior. This phenomenon may indicate that immunity, not thyroid function, plays an important role in suicidal behavior. Some researchers have attached great importance to thyroid autoimmunity regarding suicide [24, 71], while others suggested

that TPO-Ab was an independent risk factor for suicide attempts [36]. Lang et al. [35] found that subclinical hypothyroidism was related to attempted suicide in depressed patients. A previous study showed significantly lower free FT3 levels in psychiatric patients who had attempted suicide than in those who had not [72]. Some studies examined the association between thyroid function and suicidal behaviors in major depression disorder [73]. The inconsistent results need more evidence and further research.

4.5 Relationship between sex and suicidal and aggressive behaviors

In our study, there was no sex difference in aggressive behaviors, consistent with another study on psychiatric inpatients [74]. Our data showed no difference in suicidal and aggressive behaviors among individuals diagnosed with depression, bipolar disorder, and schizophrenia, although this finding was inconsistent with other studies [75]. One study stated that women are more prone to suicide [75], which was contrary to our findings. These differences may be due to the choice of different groups of people. However, further study is required.

4.6 Clinical implications

Aggression, suicidal behavior, and changes in thyroid function are common in people with mental disorders. Our data support that positive thyroid antibodies lead to increased hospitalization rates and expenses. TPO-Ab is a risk factor for aggressive behavior but not suicide. Thus, psychiatric individuals may benefit from treatment to prevent aggressive behaviors if TPO-Ab is detected in advance. Thyroid antibody screening in patients with mental illness is recommended, especially for those with aggressive behavior.

4.7 Strengths and weaknesses

A major strength of our study is the use of a

population-based retrospective study of psychiatric patients designed to examine the role of TPO-Ab in suicide and aggression. We performed analyses using multiple models: including stratification by inpatients status, the incidence of TPO-Ab and suicide, and aggressive behaviors. Our findings showed an independent effect of TPO-Ab on aggressive behaviors. This positive TPO-Ab finding can help us detect the aggression risk factor in the remainder of our analyses. However, our study had several limitations. First, we did not assess all of the clinical factors that may increase the suicide risk, such as life adversity. While our assessment of suicidal behavior used a standard rating scale, we neither systematically collected data about the timing of suicide attempts or aggression, nor studied individuals who had attempted suicide. Second, we did not include other blood-based immune markers linked with suicidal behaviors or aggression such as inflammatory cytokines. Furthermore, we cannot eliminate the possibility of medications being a confounding factor.

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Author contributions

All authors were involved in drafting of the article or revising it critically for intellectual content. They have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: all authors.

Declaration of conflicting interests

All authors declare no conflicts of interest

regarding this article.

Ethical approval

Clinical data and the use of data are approved by the ethical committee of Shenzhen Kangning Hospital.

Consent to participate

Data were obtained from medical charts: every patient signed our institutional consent for the management of personal data.

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