*The Journal of Clinical Endocrinology & Metabolism*, 2024, **00**, 1–10
https://doi.org/10.1210/clinem/dgae124
Advance access publication 8 March 2024
**Clinical Research Article**

# Prospective Multicenter Registry–Based Study on Thyroid Storm: The Guidelines for Management From Japan Are Useful

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## Abstract

**Context:** The mortality rate in thyroid storm (TS) has been reported to be higher than 10%.

**Objective:** We aimed to evaluate the effectiveness of the 2016 guidelines for the management of TS proposed by the Japan Thyroid Association and Japan Endocrine Society.

**Methods:** In this prospective multicenter registry–based study, patients with new-onset TS were registered in the Research Electronic Data Capture (REDCap), a secure web platform. On day 30 after admission, clinical information and prognosis of each patient were added to the platform. On day 180, the prognosis was described.

**Results:** This study included 110 patients with TS. The median of Acute Physiology and Chronic Health Evaluation (APACHE) II score was 13, higher than the score (10) in the previous nationwide epidemiological study ($P = .001$). Nonetheless, the mortality rate at day 30 was 5.5%, approximately half compared with 10.7% in the previous nationwide survey. Lower body mass index, shock, and lower left ventricular ejection fraction were positively associated with poor prognosis at day 30, while the lack of fever $\geq 38$ °C was related to the outcome. The mortality rate in patients with an APACHE II score $\geq 12$ for whom the guidelines were not followed was significantly higher than the rate in patients for whom the guidelines were followed (50% vs 4.7%) ($P = .01$).

**Conclusion:** Prognosis seemed better than in the previous nationwide survey, even though disease severity was higher. The mortality rate was lower when the guidelines were followed. Thus, the guidelines are useful for managing TS.

**Key Words:** epidemiology, prospective, REDCap, thyroid crisis, Graves disease, thyrotoxicosis

**Abbreviations:** APACHE, Acute Physiology and Chronic Health Evaluation; ATD, antithyroid drug; beta-AA, beta-adrenergic receptor antagonist; BMI, body mass index; BWPS, Burch-Wartofsky Point Scale; CHF, congestive heart failure; CNS, central nervous system; CS, corticosteroid; JES, Japan Endocrine Society; JTA, Japan Thyroid Association; KI, potassium iodide; LVEF, left ventricular ejection fraction; MMI, methimazole; PTU, propylthiouracil; REDCap, Research Electronic Data Capture; SOFA, Sequential Organ Failure Assessment; TS, thyroid storm.

Thyrotoxic crisis, or thyroid storm (TS), is a life-threatening condition requiring emergency treatment (1-3). It manifests as decompensation in multiple organs, often triggered by severe stress. The mortality rate was higher than 10%. Even when patients survive, some have irreversible damages. In order to improve the prognosis of patients with TS, appropriate management as well as prompt and accurate diagnosis are needed.

**Received:** 11 January 2024. **Editorial Decision:** 29 February 2024. **Corrected and Typeset:** 21 March 2024

In 2012, the research committee on TS of the Japan Thyroid Association (JTA) undertook a nationwide epidemiological study of TS and created the diagnostic criteria (4). Based on the nationwide epidemiological study, the incidence of TS was estimated to be 0.20 per 100 000 population per year, accounting for 0.22% of all thyrotoxic patients and 5.4% of hospitalized thyrotoxic patients, and the mortality rate remained over 10% (4). The diagnostic criteria are now widely used all over the world as the JTA criteria along with the Burch-Wartofsky Point Scale (BWPS). Further, based on the evidence obtained from the nationwide epidemiological study in 2012 (4) and additional literature reviews, the research committee on TS of the JTA and Japan Endocrine Society (JES) established guidelines for the management of TS in 2016 (5).

The guidelines include 14 recommendations for the treatment of thyrotoxicosis and organ failure in the central nervous system, cardiovascular system, and hepato-gastrointestinal tract; admission criteria for the intensive care unit; and prognostic evaluation in TS (5). Characteristic features of the guidelines are described below. First, regarding antithyroid drug (ATD) choice, either methimazole (MMI) or propylthiouracil (PTU) can be the first-line option. Second, regarding the timing of iodide therapy, inorganic iodide should be administered concurrently with ATDs to patients with TS caused by thyrotoxic diseases associated with hyperthyroidism. Third, regarding the choice of beta-adrenergic receptor antagonists (beta-AAs), the nonselective beta-AA propranolol is not recommended for the treatment of severe tachycardia associated with congestive heart failure (CHF). Instead, beta-1-selective and ultrashort-acting AAs such as landiolol and esmolol are preferred. We also proposed preventive approaches for TS, roles of definitive therapy, and plans for a prospective trial about the treatment of TS. We believe that the guidelines, which contain the algorithms, are internationally applicable and useful.

However, the effectiveness of the guidelines has not been fully confirmed. In addition, many clinical questions on the management of TS remain to be answered. Although several studies on TS using a national inpatient, health insurance claim, and health or welfare database have been reported (6-8), all of the studies had been retrospective, with limitations in collecting detailed and precise clinical information. Given this context, we conducted a prospective multicenter registry–based study on TS in Japan.

## Subjects and Methods

### Patient Recruitment

From May 2018 to April 2022, we asked the members of JTA and JES to register their patients with new-onset TS who met the JTA diagnostic criteria for TS (4) using Research Electronic Data Capture (REDCap), a secure web application for building and managing online surveys and databases designed to support data capture for clinical research (9, 10). The present study was approved by the ethics committees of Wakayama Medical University (No. 2280) and Ehime University Graduate School of Medicine (No. 1801017).

### Registry and Questionnaires

At first, each patient with new-onset TS was simply registered in REDCap, which was managed by Ehime University. The registrant set their username and password and was informed of their enrollment. At day 30 after admission, the registrant entered information on detailed clinical status (165 items; Supplementary Appendix A) (9) and prognosis (11 items; Supplementary Appendix B) (9) into REDCap. To facilitate comparisons with the previous nationwide epidemiological study (4), all the questions used in the previous nationwide epidemiological study were included, which consisted of questions about demographics, past medical history, basic thyroid disease, triggers, signs or symptoms, biomarkers, severity, treatment and management, outcomes, and follow-up. To answer further clinical questions about TS, several questions were added, which included topics such as timing of inorganic iodide therapy, ATD and beta-AA choices, corticosteroid (CS) dose, and compliance with our 2016 guidelines. Finally, the prognosis on day 180 was entered (Supplementary Appendix B) (9).

### Statistical Analysis

Patients with sequelae or who died were defined as having poor prognosis. Another outcome was death. The Student *t* test was used for continuous variables with a normal distribution, and the Wilcoxon rank-sum test was used for continuous variables with a non-normal distribution. For comparison with categorical variables, the Fisher exact test or chi-square test was used. Multivariate logistic regression analysis was performed to estimate the adjusted odds ratios (ORs) and 95% CIs of poor prognosis at day 30 and day 180. Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were available in the registry study, while we calculated APACHE II and SOFA scores using variables which were collected in this registry and were needed to calculate each score, although information on underlying diseases was not available. Calculated scores were used when entered scores were missing or when calculated scores were higher than entered scores. Entered or calculated APACHE II and SOFA scores were not available due to missing data among a certain number of patients. Body mass index (BMI), fever $\geq 38$ °C, central nervous system (CNS) symptoms, left ventricular ejection fraction (LVEF), and shock were selected as prognostic factors among the variables which were significantly associated with poor prognosis in crude analysis, taking into account clinically relevant and correlations between variables. BMI and LVEF were categorized at the nearest tertile points. Sex and age were selected as confounding factors and BMI, fever $\geq 38$ °C, CNS symptoms, LVEF, and shock were also mutually adjusted for. The trend of association was assessed according to a logistic regression model assigning consecutive integers to the level of the independent variable. Two-sided *P* values less than .05 were considered statistically significant. All statistical analyses were performed using the SAS software package, version 9.2 (SAS Institute, Inc, Cary, NC, USA).

## Results

From May 2018 to April 2022, 114 patients with TS from 52 hospitals were registered (Supplementary Fig. S1) (10). Four of them, who did not satisfy JTA diagnostic criteria, were excluded from this study. There were 93 definite cases and 17 suspected cases. Patients most commonly presented to the emergency department (33.6%), followed by general internal medicine (28.3%), endocrinology (18.6%), and cardiology (10.6%).

### Baseline Characteristics of the Patients

Baseline patient characteristics are shown in Table 1. Regarding thyroid disease, there were 103 (93.6%) patients with Graves disease and 7 (6.4%) patients with destructive thyroiditis. Approximately 30% of patients developed TS due to "irregular use or discontinuation of antithyroid medication, which was the first most common trigger of TS" (Supplementary Table S1) (11). TS triggers were present in 71.8% of patients. The second most common trigger of TS was infection, particularly upper respiratory tract infection, similar to the previous nationwide survey (Supplementary Table S1) (11). Thyroid function findings were similar to those of the nationwide survey.

Regarding clinical signs and symptoms, 41.8% of patients had fever ≥ 38 °C, lower than the percentage in the previous epidemiological study ($P = .008$). While the incidence of CNS and gastrointestinal/hepatic symptoms were similar to those found in that survey, the incidence of CHF appeared to be higher ($P = .05$). In the present registry study, the medians and interquartile ranges of the APACHE II score (12) and the SOFA score (13) were 13 [9, 16] and 4 [2, 6], respectively. These scores were higher than those in the previous nationwide epidemiological study [1, 5] (APACHE II score, 10 [6, 15], $P = .001$; SOFA score, 2 [1, 4], $P < .0001$).

The mortality rate of patients with TS at day 30 was 5.5% (6 of 109), which tended to be lower than that of the previous nationwide survey, 10.7% ($P = .13$) (Table 1). Mortality rates in definite and suspected cases were 6.5% (6 of 92) and 0% (0 of 17), respectively. Causes of death at day 30 were multiple organ failure (2 patients), arrhythmia (1 patient), respiratory failure (1 patient), and unknown (2 patients). The cause of one additional death at day 180 was multiple organ failure. Among the survivors at day 30, 14 were reported as having sequelae of some kind with disuse atrophy in 9, atrial fibrillation in 7, chronic heart failure in 6, liver failure in 3, brain damage in 2, cerebrovascular disease in 1, and chronic renal failure in 1. Similarly, among the survivors at day 180, 10 were reported as having sequelae of some kind with disuse atrophy in 6, atrial fibrillation in 5, chronic heart failure in 5, brain damage in 1, and cerebrovascular disease in 1.

The relationship between BWPS scores and diagnosis based on the JTA diagnostic criteria is shown in Supplementary Table S2 (14). BWPS scores were ≥ 25 in 95% (100 of 105) of patients. BWPS scores were ≥ 45 in 86% (76 of 88) of definite cases but only 47% (8 of 17) of suspected cases.

### Comparisons of Demographic and Clinical Characteristics of Patients in the Good vs Poor Prognosis Groups

On day 30, nonsurvivors were likely to be older, to have lower BMI, body temperature, and LVEF, and to have higher incidence of shock than survivors (Table 2). They had higher APACHE II scores, strongly suggesting that their condition was more severe. On day 180, similar differences were observed between nonsurvivors and survivors. Those in the good and poor prognosis groups were basically similar to those at day 30 (Table 3).

### Logistic Regression Analysis of Prognostic Factors

Because the number of nonsurvivors was small, multivariate analysis was performed for only the good and poor prognosis outcome. After mutual adjustment for age, sex, BMI, fever, CNS symptoms, LVEF, and shock, lower BMI and shock were independently positively associated with poor prognosis at day 30, while the lack of fever ≥ 38 °C was independently related to poor prognosis at day 30 (Table 4). Only lower LVEF was independently associated with poor prognosis at day 180.

### Relationships Between Prognosis and Therapeutic Modalities

ATD was administered to 105 (96.3%) patients, of whom 101 (96.2%) received only MMI, 3 (2.9%) received only PTU, and 1 (1.0%) received both (Table 5). Forty-seven (43.1%) patients received intravenous MMI. Since none who received PTU died, it was not possible to obtain any statistically significant results.

Potassium iodide (KI) or inorganic iodide was administered to 108 (99.1%) patients (Table 5), of whom 74 (68.5%) received it before ATD administration or simultaneously, and 8 (7.4%) received it within 1 hour after ATD administration. Of the remaining 21 (19.4%) patients who received it more than 1 hour after ATD administration, 3 (14.3%) died. The fatality rate at day 30 tended to be lower in the early KI administration group (3 of 82, 3.7%) ($P = .10$).

CS were administered to 99 (90.8%) patients (Table 5), of whom 21 (21.2%) were given less than 200 mg of hydrocortisone or an equivalent dose of another CS, which was considered to be an insufficient dose (4, 15). The fatality rate among patients with an insufficient dose and those with a sufficient dose were 14.3% and 3.9%, respectively. (Table 5). Among patients with an APACHE II score of ≥ 12 (44 patients), this difference was statistically significant at day 30 (3 of 8 [37.5%] vs 2 of 36 [5.6%] ($P = .03$) (Table 6).

Beta-AAs were administered to 102 (93.6%) patients. Intravenous beta-AAs and beta-1-selective-AAs were given to 55 (53.9%) and 91 (89.2%) patients, respectively (Table 5). Among 46 patients with an APACHE II score of ≥ 12, 42 (91.3%) received a beta-1-selective-AA (Table 6).

The JTA and JES guidelines were followed for 86 (78.9%) patients. Adherence to the guidelines was measured based on registrant responses to the question at day 30 (item #165 in Supplementary Appendix A) (9). The fatality rate among patients for whom guidelines were not followed and those for whom the guidelines were followed was 13.0% and 3.5% at day 30, respectively, and 13.0% and 4.8% at day 180, respectively (Table 5). In patients with an APACHE II score of ≥ 12, following the guidelines was significantly inversely related to death at day 30 and 180 and poor prognosis at day 180 (50.0% vs 4.7%; $P = .01$ for death at day 30, 50% vs 7.1%, $P = .02$ for death at day 180, and 66.7% vs 21.4%; $P = .04$ for poor prognosis at day 180) (Table 6).

## Discussion

In a previous nationwide epidemiological study conducted in Japan, the incidence of TS, including both definite and suspected cases, was estimated to be 1283 ± 105 (95% CI, 1077-1489) per 5 years (4). Since 110 cases were registered over 4 years, approximately 10.7% of all cases were estimated to be registered in the present study. This participation rate was much lower than the response rates in the previous nationwide survey, 52.5% in SURVEY-1 and 80.8% in SURVEY-2 (4). We asked only the members of JTA and JES

**Table 1. Characteristics of patients with thyroid storm in the present registry study and the previous nationwide epidemiological study in 2012**

| | | The present registry study | | | Nationwide epidemiological study in 2012 | | | $P^a$ |
|---|---|---|---|---|---|---|---|---|
| | | **Total** | **TS1 (definite)** | **TS2 (suspected)** | **Total** | **TS1 (definite)** | **TS2 (suspected)** | |
| Number | | 110 | 93 | 17 | 356 | 282 | 74 | .27[b] |
| Age, years | | 45.4 ± 16.4 (16-92) | 45.8 ± 16.8 (16-92) | 43.1 ± 13.9 (16-75) | 45.2 ± 16.7 (7-88) | 45.2 ± 17.3 (7-88) | 44.2 ± 14.6 (21-81) | .91 |
| Sex, female (%) | | 72 (66.1%) | 61 (65.6%) | 12 (70.6%) | 263 (73.9%) | 204 (72.3%) | 59 (79.7%) | .14 |
| BMI | | 21.3 ± 5.1 (n = 108) | 20.9 ± 4.9 (n = 90) | 23.2 ± 5.9 | 20.7 ± 3.9 (n = 275) | 20.7 ± 4.0 (n = 218) | 20.6 ± 3.7 (n = 57) | .17 |
| Basic thyroid diseases | Graves disease<br>Others | 103 (93.6%)<br>7 (6.4%) | 86 (92.5%)<br>7 (7.5%) | 17 (100.0%)<br>0 (0.0%) | 346 (98.9%)<br>4 (1.1%) | 275 (98.9%)<br>3 (1.1%) | 71 (98.6%)<br>1 (1.4%) | **.005** |
| Precipitating factors | | 79 (71.8%) | 67 (72.0%) | 12 (70.6%) | 248 (71.2%) | 201 (71.8%) | 47 (69.1%) | 1.0 |
| Free T4 (ng/dL) | ≥ 5 | 81/109 (74.3%) | 71/92 (77.2%) | 10/17 (58.8%) | 250/353 (70.8%) | 195/279 (69.9%) | 55/74 (74.3%) | .48 |
| | < 5 | 28/109 (25.7%) | 21/92 (22.8%) | 7/17 (41.2%) | 103/353 (29.2%) | 84/279 (30.1%) | 19/74 (25.7%) | |
| Free T3 (pg/mL) | ≥ 20 | 55/104 (52.9%) | 48/88 (54.6%) | 7/16 (43.8%) | 152/337 (45.1%) | 122/267 (45.7%) | 30/70 (42.9%) | .31 |
| | 15 to < 20 | 13/104 (12.5%) | 10/88 (11.4%) | 3/16 (18.8%) | 58/337 (17.2%) | 46/267 (17.2%) | 12/70 (17.1%) | |
| | < 15 | 36/104 (34.6%) | 30/87 (34.1%) | 6/16 (37.5%) | 127/337 (37.7%) | 99/267 (37.1%) | 28/16 (40.0%) | |
| Free T3/free T4 | ≥ 4 | 58/104 (55.8%) | 51/88 (58.0%) | 7/16 (43.8%) | 162/335 (48.4%) | 131/265 (49.4%) | 31/70 (44.3%) | .15 |
| | 2 to < 4 | 32/104 (30.8%) | 26/88 (30.0%) | 6/16 (37.5%) | 138/335 (41.2%) | 105/265 (39.6%) | 33/70 (47.1%) | |
| | < 2 | 14/104 (13.5%) | 11/88 (12.5%) | 3/16 (18.8%) | 35/335 (10.4%) | 29/265 (10.9%) | 6/70 (8.6%) | |
| Fever ≥38 °C | | 46 (41.8%) | 40 (43.0%) | 6 (35.3%) | 195 (56.9%) | 155 (57.0%) | 40 (56.3%) | **.008** |
| Pulse rate ≥ 130/min | | 83 (75.5%) | 71 (76.3%) | 12 (70.6%) | 260 (74.9%) | 215 (77.9%) | 45 (63.4%) | 1.0 |
| CNS symptoms[c] | | 78 (70.9%) | 78 (83.9%) | 0 (0.0%) | 240 (67.4%) | 238 (84.4%) | 2 (2.7%) | .56 |
| GI/hepatic symptoms[d] | | 84 (76.4%) | 72 (77.4%) | 12 (70.6%) | 243 (68.3%) | 196 (69.5%) | 47 (63.5%) | .12 |
| CHF[e] | | 55 (50.0%) | 52 (55.9%) | 3 (17.7%) | 139 (39%) | 111 (39.4%) | 28 (37.8%) | .05 |
| | NYHA classification IV | 47 (42.7%) | 44 (47.3%) | 3 (17.7%) | 75 (21.1%) | 68 (24.1%) | 7 (9.5%) | **< .0001** |
| | Killip classification ≥ III | 31 (28.2%) | 29 (31.2%) | 2 (11.8%) | 77 (21.6%) | 64 (22.7%) | 13 (17.6%) | .16 |
| APACHE II score | | 13 [9, 16] (n = 85) | 13 [9, 16] (n = 75) | 11 [8, 13] (n = 10) | 10 [6, 15] (n = 356) | 10 [6.75, 16] (n = 282) | 7.5 [4.75, 10] (n = 74) | **.001** |
| SOFA score | | 4 [2, 6] (n = 86) | 4 [2, 6] (n = 77) | 4 [2, 6] (n = 9) | 2 [1, 4] (n = 356) | 1 [0, 2] (n = 282) | 2 [1, 5] (n = 74) | **< .0001** |
| Mortality rate | at day 30 | 6/109 (5.5%) | 6/92 (6.5%) | 0/17 (.0%) | 38/356 (10.7%) | 31/282 (11%) | 7/74 (9.5%) | .13 |
| | at day 180 | 7/106 (6.6%) | 7/90 (7.8%) | 0/16 (0.0%) | | | | .26 |

Systeme International (SI) units for free T4, picomoles per liter (conversion factor, 12.87); for free T3 to picomoles per liter (0.0154).
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CHF, congestive heart failure; CNS, central nervous system; GI, gastrointestinal; NYHA, New York Heart Association; SOFA, Sequential Organ Failure Assessment; TS, thyroid storm; TS1, definite TS; TS2, suspected TS.
[a]Total of Registry study vs Total of Nationwide survey. Bold letters indicate the *P* value is < .05, which is considered statistically significant.
[b]The ratio of TS1 vs TS2
[c]CNS symptoms consisted of agitation, restlessness, delirium, mental aberration or psychosis, somnolence or lethargy, convulsion, and coma.
[d]GI/hepatic symptoms consisted of abdominal pain, diarrhea, nausea or vomiting, and jaundice with liver dysfunction.
[e]CHF consisted of pedal edema, bibasilar rales, and pulmonary edema.

**Table 2. Demographic and clinical characteristics according to prognosis at day 30**

| Variables | | All patients | Survival on day 30 | Death on day 30 | *P* | Good prognosis[a] on day 30 | Poor prognosis[a] on day 30 | *P* |
|---|---|---|---|---|---|---|---|---|
| Number | | 109 | 103 | 6 | | 89 | 20 | |
| TS1:TS2 | | 92:17 | 86:17 | 6:0 | .59 | 72:17 | 20:0 | **.04** |
| Age, years | | 45.5 ± 16.4 (16-92) | 44.5 ± 15.9 | 61.7 ± 18.5 | **.01** | 43.6 ± 15.5 | 53.8 ± 18.3 | **.01** |
| Sex, female (%) | | 72 (66.1%) | 67 (65.1%) | 5 (83.3%) | .66 | 59 (66.3%) | 13 (65.0%) | .91 |
| BMI | | 21.3 ± 5.1 | 21.5 ± 5.0 (n = 101) | 17.5 ± 4.4 | .06 | 21.7 ± 5.3 (n = 87) | 19.4 ± 3.3 | **.02** |
| Basic thyroid diseases | Graves disease<br>Others | 102 (93.6%)<br>7 (6.4%) | 97 (94.2%)<br>6 (5.8%) | 5 (83.3%)<br>1 (16.7%) | .34 | 84 (94.4%)<br>5 (5.6%) | 18 (90.0%)<br>2 (10.0%) | .61 |
| Precipitating factors | | 68 (62.4%) | 65 (63.1%) | 3 (50.0%) | .67 | 56 (62.9%) | 12 (60.0%) | .81 |
| Free T4 (ng/dL) | ≥ 5 | 81/108 (75.0%) | 76/102 (74.5%) | 5 (83.3%) | 1.00 | 65/88 (73.9%) | 16 (80.0%) | .57 |
| | < 5 | 27/108 (25.0%) | 26/102 (25.5%) | 1 (16.7%) | | 23/88 (26.1%) | 4 (20.0%) | |
| Free T3 (pg/mL) | ≥ 20 | 55/103 (53.4%) | 52/97 (53.6%) | 3 (50.0%) | 1.00 | 48/85 (56.5%) | 7/18 (38.9%) | .40 |
| | 15 to < 20 | 16/103 (12.6%) | 12/97 (12.4%) | 1 (16.7%) | | 10/85 (11.8%) | 3/8 (16.7%) | |
| | < 15 | 35/103 (34.0%) | 33/97 (34.0%) | 2 (33.3%) | | 27/85 (31.8%) | 8/18 (44.4%) | |
| Free T3/Free T4 | ≥ 4 | 58/103 (56.3%) | 55/97 (56.7%) | 0 (0.0%) | .49 | 50/85 (58.8%) | 8/18 (44.4%) | .11 |
| | 2 to < 4 | 31/103 (30.1%) | 28/97 (28.9%) | 3 (50.0%) | | 22/85 (25.9%) | 9/18 (50.0%) | |
| | < 2 | 14/103 (13.6%) | 14/97 (14.4%) | 3 (50.0%) | | 13/85 (15.3%) | 1/18 (5.6%) | |
| Fever ≥ 38 °C | | 45 (41.3%) | 45 (43.7%) | 0 (0.0%) | **.04** | 42 (47.2%) | 3 (15.0%) | **.008** |
| Pulse rate ≥ 130/min | | 82 (75.3%) | 76 (73.8%) | 6 (100.0%) | .33 | 64 (71.9%) | 18 (90.0%) | .15 |
| CNS symptoms | | 77 (70.6%) | 71 (68.9%) | 6 (100.0%) | .18 | 58 (65.2%) | 19 (95.0%) | **.008** |
| GI/hepatic symptoms | | 83 (76.2%) | 80 (77.7%) | 3 (50.0%) | .15 | 71 (79.8%) | 12 (60.0%) | .08 |
| CHF | | 55 (50.5%) | 51 (49.5%) | 4 (66.7%) | .68 | 40 (44.9%) | 15 (75.0%) | **.02** |
| | NYHA classification IV | 47 (43.1%) | 43 (41.8%) | 4 (66.7%) | .40 | 34 (38.2%) | 13 (65.0%) | **.03** |
| | Killip classification ≥ III | 31 (28.4%) | 29 (28.2%) | 2 (33.3%) | 1.00 | 21 (23.6%) | 10 (50.0%) | **.02** |
| LVEF (%) | | 54.9 [39.0, 61.2] (n = 90) | 55.5 [40.6, 62.0] (n = 86) | 17.0 [11.0, 33.5] (n = 4) | **.005** | 58.2 [46.0, 62.3] (n = 73) | 29.0 [22.0, 45.0] (n = 17) | **< .0001** |
| MOF | | 19/108 (17.6%) | 18/102 (17.7%) | 1 (16.7%) | 1.00 | 11/88 (12.5%) | 8 (40.0%) | **.007** |
| DIC | | 12/108 (11.1%) | 11/102 (10.8%) | 1 (16.7%) | .52 | 7/88 (8.0%) | 5 (25.0%) | **.04** |
| Shock | | 27/107 (25.2%) | 23/101 (22.8%) | 4 (66.7%) | **.03** | 15/88 (17.1%) | 12/19 (63.2%) | **.0001** |
| APACHE II score | | 13 [8.5, 16] (n = 84) | 12 [8, 16] (n = 79) | 18 [16, 23] (n = 5) | **.01** | 12 [8, 16] (n = 67) | 16 [13, 21] (n = 17) | **.01** |
| SOFA score | | 4 [2, 6] (n = 85) | 4 [2, 6] (n = 80) | 6 [2, 6] (n = 5) | .50 | 3 [2, 5.5] (n-68) | 6 [4, 10] (n = 17) | **.005** |

Bold letters show $P < .05$, which was considered statistically significant.
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CHF, congestive heart failure; CNS, central nervous system; GI, gastrointestinal; LVEF, left ventricle ejection fraction; MOF, multiple organ failure DIC, disseminated intravascular coagulation; NYHA, New York Heart Association; SOFA, Sequential Organ Failure Assessment; TS, thyroid storm; TS1, definite TS; TS2, suspected TS.
[a]Patients who survived without any sequelae were defined as having good prognosis. Patients with sequelae or who died were defined as having poor prognosis.

**Table 3. Demographic and clinical characteristics according to prognosis at day 180**

| Variables | | All patients | Survival on day 180 | Death on day 180 | *P* | Good prognosis[a] on day 180 | Poor prognosis[a] on day 180 | *P* |
|---|---|---|---|---|---|---|---|---|
| Number | | 106 | 99 | 7 | | 89 | 17 | |
| TS1:TS2 | | 90:16 | 83:16 | 7:0 | .59 | 73:16 | 17:0 | .07 |
| Age, years | | 45.3 ± 16.5 | 44.3 ± 16.0 | 59.4 ± 17.9 | **.02** | 43.3 ± 15.6 | 55.7 ± 17.6 | **.004** |
| Sex, female | | 71 (67.0%) | 65 (65.7%) | 6 (85.7%) | .42 | 59 (66.3%) | 12 (70.6%) | .73 |
| BMI | | 21.3 ± 5.1 (n = 104) | 21.5 ± 5.1 | 18.3 ± 4.5 | .10 | 21.7 ± 5.3 (n = 87) | 19.3 ± 3.6 | .08 |
| Basic thyroid diseases | Graves disease<br>Others | 99 (93.4%)<br>7 (6.6%) | 93 (93.9%)<br>6 (6.1%) | 6 (85.7%)<br>1 (14.3%) | .39 | 84 (94.4%)<br>5 (5.6%) | 15 (88.2%)<br>2 (11.8%) | .31 |
| Precipitating factors | | 65 (61.3%) | 61 (61.6%) | 4 (57.1%) | 1.00 | 55 (61.8%) | 10 (58.8%) | .82 |
| Free T4 (ng/dL) | ≥ 5 | 79/105 (75.2%) | 74/98 (75.5%) | 2 (28.6%) | 1.00 | 67/88 (76.1%) | 12 (70.6%) | .76 |
| | < 5 | 26/105 (24.8%) | 24/98 (24.5%) | 5 (71.4%) | | 21/88 (23.9%) | 67 (76.1%) | |
| Free T3 (pg/mL) | ≥ 20 | 53/100 (53.0%) | 50/93 (53.8%) | 3 (42.9%) | .40 | 48/85 (56.5%) | 5/15 (33.3%) | .13 |
| | 15 to < 20 | 13/100 (13.0%) | 11/93 (11.8%) | 2 (28.6%) | | 9/85 (10.6%) | 4/15 (26.7%) | |
| | < 15 | 34/100 (34.0%) | 32/93 (43.4%) | 2 (28.6%) | | 28/85 (32.9%) | 6/15 (40.0%) | |
| Free T3/Free T4 | ≥ 4 | 56/100 (56.0%) | 53/93 (56.0%) | 3 (42.9%) | .27 | 50/85 (58.8%) | 6/15 (40.0%) | .12 |
| | 2 to < 4 | 30/100 (30.0%) | 26/93 (28.0%) | 4 (57.1%) | | 22/85 (25.9%) | 8/15 (53.3%) | |
| | < 2 | 14/100 (14.0%) | 14/93 (15.1%) | 0 (0.0%) | | 13/85 (15.3%) | 1/15 (6.7%) | |
| Fever ≥ 38 °C | | 43 (40.6%) | 43 (43.4%) | 0 (0.0%) | **.04** | 41 (46.1%) | 2 (11.8%) | **.008** |
| Pulse rate ≥ 130/min | | 80 (75.5%) | 73 (73.7%) | 7 (100.0%) | .19 | 65 (73.0%) | 15 (88.2%) | .23 |
| CNS symptoms | | 75 (70.8%) | 68 (68.7%) | 100% (7/7) | .10 | 60 (67.4%) | 15 (88.2%) | .14 |
| GI/hepatic symptoms | | 82 (77.4%) | 78 (78.8%) | 4 (57.1%) | .19 | 72 (80.9%) | 10 (58.8%) | .06 |
| CHF | | 53 (50.0%) | 48 (48.5%) | 5 (71.4%) | .44 | 40 (44.9%) | 13 (76.5%) | **.02** |
| NYHA classification IV | | 46 (43.4%) | 41 (41.4%) | 5 (71.4%) | .24 | 34 (38.2%) | 12 (70.6%) | .01 |
| Killip classification ≥ III | | 30 (28.3%) | 27 (27.3%) | 3 (42.9%) | .40 | 21 (23.6%) | 9 (52.9%) | .02 |
| LVEF (%) | | 55.0 [39.5, 61.6] (n = 88) | 57.3 [41.0, 62.0[(n = 83) | 22.0 [12.0, 35.0] (n = 5) | **.003** | 58.4 [43.7, 62.3] (n = 74) | 28.5 [20.0, 45.0] (n = 14) | **< .0001** |
| MOF | | 18/105 (17.1%) | 16/98 (16.3%) | 2 (28.6%) | .34 | 12/88 (13.6%) | 6 (35.3%) | .07 |
| DIC | | 11/105 (10.5%) | 9/98 (9.2%) | 2 (28.6%) | .16 | 7/88 (8.0%) | 4 (23.5%) | .08 |
| Shock | | 23/104 (24.0%) | 20/97 (20.6%) | 5 (71.4%) | **.008** | 16/87 (18.7%) | 9 (52.9%) | **.005** |
| APACHE II score | | 13 [8, 16] (n = 82) | 12 [8, 16] (n = 76) | 17 [16, 23] (n = 6) | **.01** | 12 [8, 16] (n = 67) | 16 [13, 21] (n = 15) | **.02** |
| SOFA score | | 4 [2, 6] (n = 83) | 3 [2, 6] (n = 77) | 6 [2, 14] (n = 6) | .18 | 3 [2, 5.5] (n = 68) | 6 [4, 10] (n = 15) | **.008** |

Bold letters show $P < .05$, which was considered statistically significant.
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CHF, congestive heart failure; CNS, central nervous system; GI, gastrointestinal; LVEF, left ventricle ejection fraction; MOF, multiple organ failure DIC, disseminated intravascular coagulation; NYHA, New York Heart Association; SOFA, Sequential Organ Failure Assessment; TS, thyroid storm; TS1, definite TS; TS2, suspected TS.
[a]Patients who survived without any sequelae were defined as having good prognosis. Patients with sequelae or who died were defined as having poor prognosis.

**Table 4. Relationship between selected prognostic factors and poor prognosis on day 30 and day 180**

| Variables | | Poor prognosis at day 30 | | | | | | | Poor prognosis at day 180 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N = 86 (poor/good = 16/70) | | | | | | | N = 84 (poor/good = 14/70) | | | | | | |
| | | Age and sex adjusted | | | | Multivariate analysis[a] | | | Age and sex adjusted | | | | Multivariate analysis[a] | | |
| | | Risk (%) | OR | 95% CI | *P* | OR | 95% CI | *P* | Risk (%) | OR | 95% CI | *P* | OR | 95% CI | *P* |
| BMI | T1 (< 19) | 7/28 (25.0) | 2.25 | 0.51-11.94 | .29 | 9.89 | 1.10-133.62 | **.04** | 6/27 (22.2) | 1.79 | 0.38-9.79 | .47 | 4.43 | 0.61-38.10 | .14 |
| | T2 (19 to < 22.6) | 6/30 (20.0) | 1.73 | 0.89-9.22 | .47 | 4.28 | 0.52-47.52 | .18 | 5/29 (17.2) | 1.39 | 0.29-7.64 | .68 | 2.30 | 0.34-18.32 | .39 |
| | T3 (22.6+) | 3/28 (10.7) | 1.00 | | | 1.00 | | | 3/28 (10.7) | 1.00 | | | 1.00 | | |
| | *P* for trend | | 0.30 | | | 0.04 | | | | 0.47 | | | 0.14 | | |
| Fever ≥ 38 °C | | 3/35 (8.6) | 0.28 | 0.06-1.01 | .052 | 0.13 | 0.01-0.75 | **.02** | 2/33 (6.1) | 0.23 | 0.03-0.95 | **.04** | 0.20 | 0.02-1.13 | .07 |
| CNS symptoms | | 15/60 (25.0) | 7.86 | 1.42-147.60 | **.0004** | 5.19 | 0.61-121.48 | .14 | 12/58 (20.7) | 2.92 | 0.69-20.17 | .16 | 1.25 | 0.21-10.22 | .82 |
| LVEF (%) | T1 (< 44) | 12/28 (42.9) | 30.93 | 4.58-640.44 | **< .0001** | 44.42 | 3.98-> 999.99 | **.001** | 10/27 (37.0) | 29.07 | 4.06-622.06 | **.0003** | 30.53 | 3.23-779.03 | **.002** |
| | T2 (44 to < 60) | 3/25 (12.0) | 4.53 | 0.52-97.08 | .18 | 3.90 | 0.33-103.79 | .29 | 3/24 (12.5) | 4.94 | 0.55-107.41 | .16 | 4.40 | 0.42-105.14 | .22 |
| | T3 (60+) | 1/33 (3.0) | 1.00 | | | 1.00 | | | 1/33 (3.0) | 1.00 | | | 1.00 | | |
| | *P* for trend | | < 0.0001 | | | 0.0004 | | | | 0.0002 | | | 0.001 | | |
| Shock | | 10/24 (41.7) | 8.72 | 2.53-35.21 | **.0005** | 6.72 | 1.42-41.18 | **.02** | 7/22 (31.8) | 5.06 | 1.38-20.35 | **.01** | 2.55 | 0.55-12.32 | .23 |

Bold letters show $P < .05$, which was considered statistically significant.
Abbreviations: BMI, body mass index; CNS, central nervous system; LVEF, left ventricular ejection fraction; OR, odds ratio.
[a]The model adjusted for age, sex, BMI, fever, CNS symptoms, LVEF, and shock

**Table 5. Relationships between therapeutic modalities and prognosis in all subjects**

| | | Death at day 30 | *P* | Poor prognosis[a] at day 30 | *P* | Death at day 180 | *P* | Poor prognosis[a] at day 180 | *P* |
|---|---|---|---|---|---|---|---|---|---|
| ATD | Without | 0/4 (0.0) | 1.00 | 0/4 (0.0) | 1.00 | 0/3 (0.0) | 1.00 | 0/3 (0.0) | 1.00 |
| | With | 6/105 (5.7) | | 20/105 (19.1) | | 7/103 (6.8) | | 17/103 (16.5) | |
| | PTU only | 0/3 (0.0) | 1.00 | 0/3 (0.0) | 1.00 | 0/3 (0.0) | 1.00 | 0/3 (0.0) | 1.00 |
| | MMI only | 6/101 (5.9) | | 20/101 (19.8) | | 7/92 (7.1) | | 17/99 (17.2) | |
| KI | Without | 0/1 (0.0) | 1.00 | 0/1 (0.0) | 1.00 | 0/1 (0.0) | 1.00 | 0/1 (0.0) | 1.00 |
| | With | 6/108 (5.6) | | 20/108 (18.5) | | 7/105 (6.7) | | 17/105 (16.2) | |
| | Timing related to ATD administration | | .10 | | .55 | | .16 | | .34 |
| | After 1 hour | 3/21 (14.3) | | 5/21 (23.8) | | 3/21 (14.3) | | 5/21 (23.8) | |
| | Pre, simultaneous or within 1hr | 3/82 (3.7) | | 15/82 (18.3) | | 4/80 (5.0) | | 12/80 (15.0) | |
| CS | Without | 0/10 (0.0) | 1.00 | 1/10 (10.0) | .69 | 0/10 (0.0) | 1.00 | 1/10 (10.0) | 1.00 |
| | With | 6/99 (6.1) | | 19/99 (19.2) | | 7/96 (7.3) | | 16/96 (16.7) | |
| | Insufficient dosage | 3/21 (14.3) | .11 | 1/21 (19.1) | 1.00 | 3/21 (14.3) | .17 | 5/21 (23.8) | .15 |
| | Sufficient | 3/78 (3.9) | | 15/78 (19.2) | | 4/75 (5.3) | | 11/75 (14.7) | |
| Beta-AA | Without | 1/7 (14.3) | .34 | 3/7 (42.9) | .11 | 1/6 (16.7) | .34 | 2/6 (33.3) | .25 |
| | With | 5/102 (4.9) | | 17/102 (16.7) | | 6/100 (3.0) | | 15/100 (15.0) | |
| | Oral or patch | 3/47 (6.4) | .29 | 6/47 (12.8) | .33 | 3/47 (6.4) | .32 | 4/47 (8.5) | .10 |
| | Intravenous | 2/55 (3.6) | | 11/55 (20.0) | | 3/53 (5.7) | | 11/53 (20.9) | |
| | Nonselective beta-AA | 0/11 (0.0) | 1.00 | 0/11 (0.0) | .20 | 0/11 (0.0) | .49 | 0/11 (0.0) | .21 |
| | Beta-1-selective | 5/91 (5.5) | | 17/91 (18.7) | | 6/89 (6.7) | | 15/89 (16.9) | |
| 2016 Guidelines | Not followed | 3/23 (13.0) | .11 | 4/23 (17.4) | 1.00 | 3/23 (13.0) | .17 | 4/23 (17.4) | 1.00 |
| | Followed | 3/86 (3.5) | | 16/86 (18.6) | | 4/83 (4.8) | | 12/83 (15.7) | |

Abbreviations: ATD, antithyroid drug; beta-AA, beta-adrenergic receptor antagonist; CS, corticosteroid; KI, potassium iodide; MMI, methimazol; PTU, propylthiouracil.
[a]Patients with sequelae or who died were defined as having poor prognosis.

to register in this study, while, in the previous nationwide survey, we targeted hospital departments of emergency medicine, internal medicine, and cardiology as well as endocrinology and thyroidology. Therefore, it is highly possible that we might have missed registrants from the members of emergency medicine, internal medicine, and cardiology. In fact, the most common department of the first visit was the emergency department (32.7%), followed by general internal medicine (28.2%), endocrinology (18.6%), and cardiology (10.6%). Furthermore, the fact that general internal medicine was much more frequently the first department visited than endocrinology suggests that this disorder might be overlooked or diagnosis delayed.

Basic thyroid diseases, triggers, and thyroid hormone levels in this study were similar to those in the previous survey. While the incidence of CNS and gastrointestinal/hepatic symptoms were similar to those of the earlier survey, the incidence and severity of CHF appeared to be higher in this study (Table 1). Moreover, the pattern of manifestations also suggested a higher incidence of CHF (Supplementary Table S3) (16). These findings suggest that this cohort is characterized by more severe cardiac manifestations than in the previous survey.

The medians of APACHE II and SOFA scores in this study were higher than those in the previous nationwide survey (Table 1). APACHE II scores were correlated with the fatality rate at day 30 (Table 2) and day 180 (Table 3), like in the previous survey (4). Nonetheless, the mortality rate among patients with TS at day 30 (5.5%) and day 180 (6.6%) tended to be lower than the mortality rate in the previous survey (10.7%) (Table 1). This finding suggests that treatment and management had improved with the JTA and JES guidelines.

In the crude analyses, age, BMI, fever, CNS symptoms, LVEF, shock, APACHE II score, and SOFA score were significantly correlated with prognosis (Tables 2 and 3). In the multivariate analyses, BMI, shock, fever, and LVEF were independently related to poor prognosis, but APACHE II and SOFA scores were excluded due to the large number of missing values (Tables 4). Poor prognosis in the elderly has also been reported in previous studies (6-8, 17). Lower BMI is thought to be associated with mortality in severe disorders (18). The lack of high fever in TS was observed in some patients, including patients with diabetic ketoacidosis (19, 20) and the elderly (4). Low LVEF (< 44%) is a key indicator of heart failure with reduced ejection fraction (21). Considering that this cohort is characterized by severe cardiac manifestations, the strong association between LVEF and prognosis is highly understandable. Even mildly low LVEF (44 to < 60) tended to correlate with prognosis.

Although MMI was administered as a single ATD to most patients (101 of 105, 96.2%) in this study, which was more often than in the previous study (276 of 323, 85.4%), the fatality rate did not increase. This finding suggests that MMI as well as PTU can be used as first-line treatment for hyperthyroidism in TS. In a recent comparative effectiveness study involving a multicenter cohort of adult patients with TS, no significant differences were found in mortality or adverse events among patients who were treated with MMI vs PTU (22). Inorganic iodide was used in almost all patients (108 of 109, 99.1%), of whom 82 (75.9%) received it at least within 1 hour after ATD administration and 21 patients received inorganic iodide more than 1 hour after ATD administration. In the late KI administration group, 3 of 21 patients (14.3%) died by day 30, while the fatality rate tended to be lower in the early KI administration group (3 of 82 3.7%) ($P = .2$). This finding suggests that early KI administration might be favorable by reducing thyroid hormone levels more quickly than

**Table 6. Relationships between therapeutic modalities and prognosis in subjects with APACHE II score ≥ 12**

| | | Death at day 30 | *P* | Poor prognosis[a] at day 30 | *P* | Death at day 180 | *P* | Poor prognosis[a] at day 180 | *P* |
|---|---|---|---|---|---|---|---|---|---|
| ATD | Without | 0/1 (0.0) | 1.00 | 0/1 (0.0) | 1.00 | 0/0 | NC | 0/0 | NC |
| | With | 5/48 (10.4) | | 15/48 (31.3) | | 6/48 (12.5) | | 13/48 (27.1) | |
| | PTU only | 0/2 (0.0) | 1.00 | 0/2 (0.0) | 1.00 | 0/2 (0.0) | 1.00 | 0/2 (0.0) | 1.00 |
| | MMI only | 5/45 (11.1) | | 15/45 (33.3) | | 6/45 (13.3) | | 13/45 (28.9) | |
| KI | Without | 0/0 | NC | 0/0 | NC | 0/0 | NC | 0/0 | NC |
| | With | 5/49 (10.2) | | 15/49 (30.6) | | 6/48 (12.5) | | 13/48 (27.1) | |
| | Timing related to ATD administration | | .12 | | .73 | | .32 | | .47 |
| | After 1 hour | 3/13 (23.1) | | 5/13 (38.5) | | 3/13 (23.1) | | 5/13 (38.5) | |
| | Pre, simultaneous or within 1hr | 2/34 (5.9) | | 10/34 (29.4) | | 3/34 (8.8) | | 8/34 (23.5) | |
| CS | Without | 0/5 (0.0) | 1.00 | 1/5 (20.0) | 1.00 | 0/5 (0.0) | 1.00 | 1/5 (20.0) | 1.00 |
| | With | 5/44 (11.4) | | 14/44 (31.8) | | 6/43 (14.0) | | 12/43 (27.9) | |
| | Insufficient dosage | 3/8 (37.5) | **.03** | 4/8 (50.0) | .24 | 3/8 (37.5) | .07 | 4/8 (50.0) | .19 |
| | Sufficient | 2/36 (5.6) | | 10/36 (27.8) | | 3/35 (8.6) | | 8/35 (22.9) | |
| Beta-AA | Without | 0/3 (0.0) | 1.00 | 1/3 (33.3) | 1.00 | 0/3 (0.0) | .66 | 1/3 (33.3) | 1.00 |
| | With | 5/46 (10.9) | | 14/46 (30.4) | | 6/45 (13.3) | | 12/45 (26.7) | |
| | Oral or patch | 3/17 (17.7) | .34 | 5/17 (29.4) | 1.00 | 3/17 (17.7) | .66 | 4/17 (23.5) | 1.00 |
| | Intravenous | 2/29 (6.9) | | 9/29 (31.0) | | 3/28 (10.7) | | 8/28 (28.6) | |
| | Nonselective beta-AA | 0/4 (0.0) | 1.00 | 0/4 (0.0) | .30 | 0/4 (0.0) | 1.00 | 0/4 (0.0) | .56 |
| | Beta-1-selective | 5/42 (11.9) | | 14/42 (33.3) | | 6/41 (14.6) | | 12/41 (29.3) | |
| 2016 Guidelines | Not followed | 3/6 (50.0) | **.01** | 4/6 (66.7) | .06 | 3/6 (50.0) | **.02** | 4/6 (66.7) | **.04** |
| | Followed | 2/43 (4.7) | | 11/43 (25.6) | | 3/42 (7.1) | | 9/42 (21.4) | |

Bold letters show that *P* value is < .05, which is considered statistically significant.
Abbreviations: ATD, antithyroid drug; beta-AA, beta-adrenergic receptor antagonist; CS, corticosteroid; KI, potassium iodide; MMI, methimazol; NC, not calculated; PTU, propylthiouracil.
[a]Patients who died or survived with sequelae are defined as poor prognosis group.

late administration. Furthermore, patients who received insufficient doses of CS had poorer prognosis than those who received sufficient doses, indicating the importance of CS treatment. Regarding beta-AA therapy, the frequencies of intravenous beta-AAs (53.9%) and beta-1-selective-AAs (88.8%) use in this study were much higher than those in the previous nationwide study. The use of propranolol was only 10.8% in this study, which was much lower than that in the previous nationwide study, 66.8% ($P < .0001$). Moreover, 91.3% of patients with an APACHE II score of ≥12 received a beta-1-selective-AA. This preferential use of intravenous beta-AAs and beta-1-selective-AAs might have contributed to better prognosis in this study. Finally, patients for whom the JTA and JES guidelines were followed tended to have lower fatality rates than patients for whom the guidelines were not followed (Table 5). Among patients with an APACHE II score of ≥ 12, this tendency became statistically significant, strongly suggesting that our guidelines are appropriate for the treatment and management of TS (Table 6).

This study had several limitations. First, the number of registrants was still too small to obtain sufficient statistical power, although several significant associations were detected. Second, selection bias should be mentioned. As mentioned above, this study asked only the members of JTA and JES to register, although the departments of emergency medicine and internal medicine are thought to be the most common departments of the first visits. In addition, a low participation rate could be partly ascribed to the fact that the present registration process was cumbersome due to a large questionnaire with 176 items that spanned 6 months, although it was internet-based. Third, severe signs and symptoms of CHF in this study were more common than in the previous study. This might be related to patients having features of this disorder that were different than those in the previous survey. Nonetheless, considering that CHF and arrhythmia were the most frequent causes of death in the previous study, this study strongly suggests the importance of treatment and management of CHF and arrhythmia. Fourth, this study only covered the Japanese population. Racial and environmental differences, such as in iodine intake, might have affected the findings. Finally, other clinical questions have not been answered. For example, no young children were included. Further studies might be needed to best standardize the diagnosis and management of TS in children. TS in children, albeit very rare, can lead to serious problems (23).

In summary, the prognosis of TS in Japan seems to have improved. Multiple findings suggest that the JTA and JES guidelines might have contributed to this improvement. In particular, appropriate administrations of ATDs, inorganic iodide, CS, and beta-AAs might have been critical. Above all, fatal TS still occurred in 5.5% of patients in this study. Further improvement in the prognosis of this disorder is needed.

## Acknowledgments

We thank the members of the Japan Thyroid Association and the Japan Endocrine Society, as well as the participating physicians in hospitals and clinics for their valuable and kind cooperation in the registration process.

## Funding

This study was supported by a grant for Rare and Intractable Diseases from the Ministry of Health, Labor and Welfare of Japan (21FC1010, Nanchitou [Nan]–Ippan–004, Nanchitou [Nan]–Ippan–031).

## Disclosures

The authors declare that they have no conflicting interests.

## Data Availability

The data that support the findings of this study are available from the corresponding author (T.A.), upon reasonable request.

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