

Research Article

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Activated partial thromboplastin time maybe associated with the prognosis of papillary thyroid carcinoma

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Abstract

Objective – Hemostasis markers associated with tumors have been widely studied. However, the associations between the coagulation factors and papillary thyroid carcinoma (PTC) prognosis remain unclear. The aim of the present study was to investigate these associations.

Patients and methods – PTC patients treated at Shengjing Hospital between 2013 and 2019 were retrospectively analyzed and divided into three groups. Clinical, ultrasound, and pathological patient characteristics were recorded. The blood routine, coagulation factors, and thyroid function data were compared.

Results – A total of 50 patients were selected and divided into Group 1 [complicated with second primary malignancies (SPMs)], Group 2 (with postoperative cervical lymph node metastasis), and Group 3 (control group). The ages of patients in Group 2 were significantly higher than those in the control group. The neutrophil ratio (%) in Group 1 was significantly higher than that in Groups 2 and 3, while its lymphocyte ratio (%) was significantly lower. The coagulation factor activated partial thromboplastin time (APTT) in the first and second groups was statistically significantly

lower than that in the control group. There were no statistical differences in APTT between the first and second groups. Shorter APTT was associated with SPM and postoperative cervical lymph node metastasis.

Conclusions – Coagulation indicators, especially APTT, may be a new biomarker for predicting PTC prognosis and may provide a new molecular target, especially in combination with SPM and postoperative cervical lymph node metastasis.

Keywords: papillary thyroid carcinoma, prognosis, coagulation factors, APTT

1 Introduction

Thyroid cancer (TC) is the most prevalent endocrine malignancy and about 80–85% of all cases are papillary thyroid carcinomas (PTCs) [1]. In view of the highly increased prevalence of PTC over the years, it is of great importance to explore its outcomes and influencing factors [2]. While well-differentiated PTC patients generally have good outcomes, the 5-year survival rate in patients with advanced PTC is only 59% [3,4]. In addition, the recurrence of PTC after thyroidectomy is over 5%, which manifest as true soft tissue local recurrence, cervical lymphadenopathy, or distant metastasis [5–7]. The increased risk of a second primary malignancy (SPM) in PTC has been reported [8]. SPMs include salivary gland, bone, kidney, ureter, and hematologic malignancies [8]. Identifying the risk factors for PTC recurrence, metastasis, and SPM can help to identify new molecular targets and guide the expansion of surgical scope, early postoperative aggressive chemotherapy and close follow-up [3].

The last decades have delineated many interactions of the hemostatic system with tumor occurrence, progression, metastasis, and recurrence. Different coagulation factors play different roles in TCs [9]. The relationships between coagulation function and TC gained more and more attention. Sagripanti et al. [10] have measured

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plasma concentration of fibrinopeptide A and D-dimer in 21 thyroidectomized patients and 27 control subjects. They have found that fibrinolysis was enhanced in TC patients with distant metastases and that plasma D-dimer levels are useful biomarkers to monitor this condition. Franchini et al. [11] have analyzed the hemostatic balance in different thyroid disorders using literature reviews and concluded that hyperthyroidism is generally accompanied by hypercoagulable states, whereas the hemostatic profile in hypothyroidism and TC depends on the severity of the disease. Nielsen et al. [12] have reported a case undergoing removal of a malignant thyroid tumor, whose hypercoagulability was mediated by hemoxygenase-1. Ordoorkhani et al. [13] have reviewed studies on venous thromboembolism and TC and concluded that further studies are necessary, as the results would influence clinical practice for the necessity of anticoagulants use in some TC groups.

These studies have suggested that clotting factors may be potential biomarkers for TC prognosis. However, the relationship between coagulation dysfunction and PTC prognosis, especially the influence on recurrence, metastasis, and complications with SPM remains unclear. The present study aimed to reveal it.

2 Patients and methods

2.1 Patients

Patients with PTC after surgery who were followed up routinely with ultrasound and computed tomography (CT) were retrospectively analyzed between January 2013 and December 2019. The present study was approved by the Ethical Review Board of Shenzhen Samii Medical Center (Grant no. SSMC-202103-19).

2.2 Inclusion and exclusion patient criteria

Inclusion criteria were as follows: (1) PTC patients confirmed by pathology; (2) patients who had undergone radical surgery of the thyroid for the first surgery and took different doses of thyroxine tablets orally according to the result of thyroid function analysis; (3) no postoperative radiation or chemotherapy was administered; and (4) the follow-up period was ended upon when the ultrasound or CT examination of the patient was suspected abnormal. Patients with diabetes mellitus, hypertension,

autoimmune disease, acute or chronic infection, hematologic disease, heart failure, myeloproliferative disorders, hepatic or renal disorders, and bleeding or thrombotic disease were excluded from the study.

2.3 Groups

The patients were divided into three groups according to the different prognoses. Group 1 included patients complicated with SPM. Group 2 consisted of patients with postoperative cervical lymph node metastasis. Group 3 patients served as control group that included those suspected to have postoperative cervical lymph node metastasis or recurrence in the thyroidectomy bed based on the routine ultrasonography examination during the follow-up but were confirmed to be normal by pathology analysis after the second surgery.

2.4 Examining and analyzing the indicators

Epidemiological characteristics of all patients at the first diagnosis with PTC were recorded, including gender, age, blood type, and ultrasound and pathological tumor characteristics. Routine laboratory parameters of all patients before the second surgery were recorded, including data on blood routine examination, thyroid function, and coagulation indicators. All blood samples were obtained in the morning between 7:00 and 8:00 o'clock 3 or 4 days before the second surgery, without any physical exercise after overnight fasting. The same standardized blood tubes were used for sampling. All blood samples were analyzed within 1 h after venipuncture and measured using standard laboratory methods on a biochemistry autoanalyzer (Sysmex XN-9000 automated hematology analyzer, ACLTOP700 automatic coagulation analyzer, and ARCHITECT i2000SR immunoassay analyzer) with the company's original kits.

The routine blood indicators included white blood cell (WBC) count, neutrophil (NEUT%) ratio, lymphocyte (LYM%) ratio, monocyte (MONO%) ratio, eosinophil (EOS%) ratio, basophil (BASO%) ratio, red blood cell (RBC) count, hemoglobin (HGB) count, and platelet (PLT) count. The thyroid function indicators included triiodothyronine (FT3), thyroxine (FT4), thyroid-stimulating hormone (TSH), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TgAb). The coagulation factors included prothrombin time (PT), prothrombin time activity (PTA), prothrombin

international normalized ratio (INR), prothrombin ratio (PTR), activated partial thromboplastin time (APTT), fibrinogen (FIB), thrombin time (TT), and D-dimer.

2.5 Statistical analysis

All analyses were conducted using the SPSS software version 27.0. Continuous variables were expressed as mean \pm SD. One-way analysis of variance (ANOVA) was used to compare intergroup differences. Multiple comparisons between groups were compared with LSD. Categorical variables were compared using the Chi-square test (Monte Carlo Sig. T2). A *P*-value of <0.05 was considered significant.

3 Results

3.1 Epidemiological and clinical characteristics

A total of 5077 PTC patients who underwent surgery and follow-up at the ShengJing Hospital of China Medical University between 2013 and 2019 were retrospectively analyzed. A total of 50 cases were selected to participated in the present study based on the inclusion and exclusion

criteria, including 11 in Group 1 (patients complicated with SPM), 16 in Group 2 (patients with postoperative cervical lymph node metastasis), and 23 in Group 3 (control group). The mean intervals of TC and second malignancies were 33 months (7–66 months) and 28 months (11–61 months) in Group 2 with postoperative cervical lymph node metastasis, respectively. For the 11 cases complicated with SPM, there was one case of pancreatic cancer, two of gastric cancer, four of breast cancer, two of lung cancer, one of cervical cancer, and one of intestinal cancer. Figure 1 is a flow diagram of the standards for the patient inclusion and exclusion criteria.

The epidemiological and clinical characteristics of the three groups are shown in Table 1. Of the 50 cases included, 76% were female, which was consistent with the epidemiological PTC trend. The proportion of women in Group 1 was slightly higher than that in the other groups but showed no statistically significant difference. The ages of patients in Group 2 (54.1 ± 14.7 years) were significantly higher ($P < 0.05$) than those in Group 3 (43.7 ± 11.8 years). Patients in Group 1 (51.5 ± 10.2 years) were also older than those in Group 3, but there was no statistically significant difference among them. There was one case of peripheral tissue invasion in both Group 1 and Group 2 after the first surgery, but not in Group 3. The rate of lymph node metastasis in Groups 1 and 2 was approximately 1.5 and 2 times that in Group 3, respectively, but there were no significant differences among the three groups. The proportion of tumor calcification

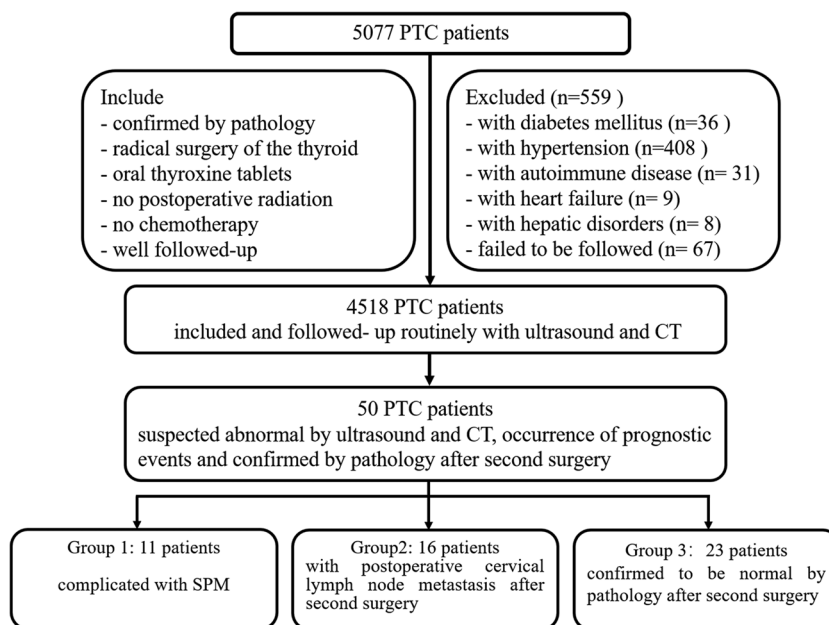


Figure 1: Flow diagram of standards for patient inclusion and exclusion criteria.

Table 1: Epidemiological and clinical characteristics of the patients

Groups	Total (N = 50)	Group 1 (N = 11)	Group 2 (N = 16)	Group 3 (N = 23)	
Gender: female (n, %)	38 (76.0)	9 (81.8)	12 (75.0)	17 (73.9)	
Age (years)	48.7 ± 13.2	51.5 ± 10.2	54.1 ± 14.7*	43.7 ± 11.8	
Peripheral tissue invasion (n, %)	2 (4.0)	1 (9.1)	1 (6.3)	0 (0)	
Lymphatic metastasis after first surgery (n, %)	17 (34.0)	4 (36.4)	8 (50.0)	5 (21.7)	
Calcification (n, %)	Microcalcification	23 (46.0)	6 (54.5)	6 (37.5)	11 (47.8)
	Coarse calcification	3 (6.0)	0 (0)	3 (18.8)*	0 (0)
	Mixed calcification	2 (4.0)	0 (0)	0 (0)	2 (8.7)
	Without calcification	22 (44.0)	5 (45.5)	7 (43.8)	10 (43.5)
Blood type (n, %)	A	10 (20.0)	3 (27.3)	2 (12.5)	5 (21.7)
	B	18 (36.0)	3 (27.3)	6 (37.5)	9 (39.1)
	O	16 (32.0)	5 (45.5)	5 (31.3)	6 (26.1)
	AB	6 (12.0)	0 (0)	3 (18.8)	3 (13.0)
RH+ (n, %)	50 (100.0)	11 (100.0)	16 (100.0)	23 (100.0)	
Tumor size (cm)	1.5 ± 1.1	1.7 ± 1.3	2.1 ± 1.2**	1.1 ± 0.7	

Group 1: patients complicated with SPM. Group 2: patients with postoperative cervical lymph node metastasis. Group 3: control group. Chi-square test, one-way ANOVA, * $P < 0.05$, ** $P < 0.01$, compared with Group 3.

was similar in the three groups, but the types were different. In Group 2, the proportion of microcalcification was lower, while the proportion of coarse calcification was significantly higher than that in Group 3 (18.8% vs 0%, $P < 0.05$). Interestingly, there were obvious differences in blood type composition among the three groups. Patients with type O blood accounted for almost half (45%) of the cohort in Group 1. There were no cases with type AB blood. Patients with type B blood was dominant in Groups 2 (37.5%) and 3 (39.1%). The lowest numbers of patients in Groups 2 and 3 were those of types A (12.5%) and AB (13.0%), respectively. However, whether this difference in blood type has biological significance needs to be investigated in further studies with larger samples. Ultrasound examination revealed that the tumor length in Group 2 was significantly higher than Group 3 (2.1 ± 1.2 cm vs 1.1 ± 0.7 cm, $P < 0.01$) and tumor of Group 1

(1.7 ± 1.3 cm) was also larger than that in Group 3, but no significant difference was observed.

3.2 Blood routine test results

As shown in Table 2, the NEUT (%) in Group 1 was significantly higher than that in Groups 2 and 3 (65.5% vs 56.3% vs 57.4%, $P < 0.05$), while the LYM (%) in Group 1 was significantly lower than that in Groups 2 and 3 (25.0% vs 34.2% vs 32.1%, $P < 0.05$). Both NEUT (%) and LYM (%) in Group 2 showed no significant difference compared to Group 3. The PLT in Group 2 was significantly lower than that in Group 1 (199.4 vs 258.2, $P < 0.01$) and Group 3 (199.4 vs 234.3, $P < 0.05$). The WBC of Group 2 was lower than that in the other two groups,

Table 2: Blood routine test results of the patients

Groups	Total (N = 50)	Group 1 (N = 11)	Group 2 (N = 16)	Group 3 (N = 23)
WBC ($10^9/L$)	7.2 ± 6.0	7.4 ± 1.9	5.2 ± 1.3	8.4 ± 8.5
NEUT (%)	58.8 ± 10.8	65.5 ± 11.4* [#]	56.3 ± 10.1	57.4 ± 10.2
LYM (%)	31.2 ± 9.7	25.0 ± 9.6* [#]	34.2 ± 9.7	32.1 ± 8.7
MONO (%)	6.6 ± 2.2	6.4 ± 1.9	6.3 ± 2.2	7.0 ± 2.4
EOS (%)	2.0 ± 1.4	2.0 ± 1.3	1.8 ± 1.3	2.0 ± 1.6
BASO (%)	0.7 ± 1.6	0.3 ± 0.2	1.2 ± 2.7	0.5 ± 0.2
RBC ($10^{12}/L$)	4.4 ± 0.5	4.3 ± 0.2	4.4 ± 0.5	4.5 ± 0.5
HGB (g/L)	133.2 ± 14.5	131.3 ± 11.3	132.7 ± 16.1	134.5 ± 15.2
PLT ($10^9/L$)	228.4 ± 54.0	258.2 ± 71.1 ^{##}	199.4 ± 40.7*	234.3 ± 44.4

Group 1: patients complicated with SPM. Group 2: patients with postoperative cervical lymph node metastasis. Group 3: control group. One-way ANOVA, * $P < 0.05$ compared with Group 3. [#] $P < 0.05$, ^{##} $P < 0.01$ compared with Group 2.

while its BASO (%) was higher than that in the other two groups and exceeded the upper limit of the normal reference range, although this result was not statistically significant. There were no statistically significant differences among the three groups in items of blood routine parameters, including MONO (%), EOS (%), and RBC and HGB counts.

Furthermore, the analysis of the proportion of outliers in the above-mentioned blood routine indicators showed that BASO and RBC outliers in Group 1 were significantly higher than those in Groups 2 and 3 (Table 3).

3.3 Thyroid function test results

The mean levels of FT3, FT4, and TSH in the three groups were all within the normal range and without significant differences, which may be due to the use of drugs to control thyroid levels in all patients experiencing PTC

after surgery (Table 4). Interestingly, the mean value of TPOAb in Group 1 was within the normal range, while the mean value of TgAb in Group 1 was close to the normal range. The mean values of the two indexes in Groups 2 and 3 were very high compared to the normal range nearly 10 times higher than the upper limit. However, due to the sizeable variance, there was no significant difference between the three groups.

This result was further confirmed by the statistical analysis of each indicator's outliers. In Groups 2 and 3, a high proportion of patients had an abnormally high TPOAb (25.0% vs 26.1%) and TgAb (37.5% vs 39.1%) (Table 5).

3.4 Coagulation function test results

The mean values of PT and TT among the three groups were within the normal range but without significant differences (Table 6). The PTA of the three groups exceeded

Table 3: Outlier comparison of blood routine test results

Groups		Total (N = 50)	Group 1 (N = 11)	Group 2 (N = 16)	Group 3 (N = 23)
WBC (ref: $3.5\text{--}9.7 \times 10^9/\text{L}$)	Outlier ratio (n, %)	8 (16.0)	2 (18.2)	2 (12.5)	4 (17.4)
	Abnormally high ratio (n, %)	6 (12.0)	2 (18.2)	0 (0)	4 (17.4)
	Abnormally low ratio (n, %)	2 (4.0)	0 (0)	2 (12.5)	0 (0)
NEUT (ref: 43.2–71.5%)	Outlier ratio (n, %)	9 (18.0)	2 (18.2)	3 (18.8)	4 (17.4)
	Abnormally high ratio (n, %)	5 (10.0)	2 (18.2)	1 (6.3)	2 (8.7)
	Abnormally low ratio (n, %)	4 (8.0)	0 (0)	2 (12.5)	2 (8.7)
LYM (ref: 16.8–43.4%)	Outlier ratio (n, %)	11 (22.0)	2 (18.2)	5 (31.3)	4 (17.4)
	Abnormally high ratio (n, %)	6 (12.0)	0 (0)	4 (25.0)	2 (8.7)
	Abnormally low ratio %	5 (10.0)	2 (18.2)	1 (6.3)	2 (8.7)
MONO (ref: 4.6–12.4%)	Outlier ratio (n, %)	8 (16.0)	2 (18.2)	3 (18.8)	3 (13.0)
	Abnormally high ratio (n, %)	1 (2.0)	0 (0)	0 (0)	1 (4.3)
	Abnormally low ratio (n, %)	7 (14.0)	2 (18.2)	3 (18.8)	2 (8.7)
EOS (ref: 0.7–7.8%)	Outlier ratio (n, %)	10 (20.0)	2 (18.2)	3 (18.8)	5 (21.7)
	Abnormally high ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)
	Abnormally low ratio (n, %)	10 (20.0)	2 (18.2)	3 (18.8)	5 (21.7)
BASO (ref: 0.2–1.2%)	Outlier ratio (n, %)	7 (14.0)	4 (36.4)*	2 (12.5)	1 (4.3)
	Abnormally high ratio (n, %)	2 (4.0)	0 (0)	2 (12.5)	0 (0)
	Abnormally low ratio (n, %)	5 (10.0)	4 (36.4)*,###	0 (0)	1 (4.3)
RBC (ref: $3.8\text{--}5.5 \times 10^{12}/\text{L}$)	Outlier ratio (n, %)	5 (10.0)	0 (0)	2 (12.5)	3 (13.0)
	Abnormally high ratio (n, %)	1 (2.0)	0 (0)	0 (0)	1 (4.3)
	Abnormally low ratio (n, %)	4 (8.0)	0 (0)	2 (12.5)	2 (8.7)
HGB (ref: 115–150 g/L)	Outlier ratio (n, %)	8 (16.0)	1 (9.1)	3 (18.8)	4 (17.4)
	Abnormally high ratio (n, %)	5 (10.0)	0 (0)	2 (12.5)	3 (13.0)
	Abnormally low ratio (n, %)	3 (6.0)	1 (9.1)	1 (6.3)	1 (4.3)
PLT (ref: 135–350/L)	Outlier ratio (n, %)	3 (6.0)	1 (9.1)	1 (6.3)	1 (4.3)
	Abnormally high ratio (n, %)	2 (4.0)	1 (9.1)	0 (0)	1 (4.3)
	Abnormally low ratio (n, %)	1 (2.0)	0 (0)	1 (6.3)	0 (0)

Group 1: patients complicated with SPM. Group 2: patients with postoperative cervical lymph node metastasis. Group 3: control group. Chi-square test, * $P < 0.05$ compared with Group 3. ### $P < 0.01$ compared with Group 2.

Table 4: Thyroid function indicators

Groups	Total (N = 50)	Group 1 (N = 11)	Group 2 (N = 16)	Group 3 (N = 23)
FT3 (pmol/L)	4.4 ± 0.5	4.4 ± 0.5	4.6 ± 0.6	4.4 ± 0.4
FT4 (pmol/L)	14.9 ± 2.6	14.5 ± 2.1	14.3 ± 2.4	15.6 ± 2.8
TSH (μIU/mL)	2.1 ± 1.6	1.9 ± 1.5	2.8 ± 2.1	1.8 ± 1.3
TPOAb (IU/mL)	28.6 ± 85.4	4.4 ± 13.3	36.4 ± 86.9	34.7 ± 103.2
TgAb (IU/mL)	55.8 ± 168.0	4.4 ± 7.4	113.4 ± 274.1	40.3 ± 87.4

Group 1: patients complicated with SPM. Group 2: patients with postoperative cervical lymph node metastasis. Group 3: control group. One-way ANOVA.

Table 5: Outlier comparison of thyroid function indicators

Groups		Total (N = 50)	Group 1 (N = 11)	Group 2 (N = 16)	Group 3 (N = 23)
FT3 (ref: 2.63–5.71 pmol/L)	Outlier ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)
	Abnormally high ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)
	Abnormally low ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)
FT4 (ref: 9.01–19.05 pmol/L)	Outlier ratio (n, %)	3 (6.0)	1 (9.1)	1 (6.3)	1 (4.3)
	Abnormally high ratio (n, %)	2 (4.0)	1 (9.1)	0 (0)	1 (4.3)
	Abnormally low ratio (n, %)	1 (2.0)	0 (0)	1 (6.3)	0 (0)
TSH (ref: 0.3–4.8 μIU/mL)	Outlier ratio (n, %)	7 (14.0)	2 (18.2)	2 (12.5)	3 (13.0)
	Abnormally high ratio (n, %)	3 (6.0)	1 (9.1)	2 (12.5)	0 (0)
	Abnormally low ratio (n, %)	4 (8.0)	1 (9.1)	0 (0)	3 (13.0)
TPOAb (ref: 0–5.61 IU/mL)	Outlier ratio (n, %)	11 (22.0)	1 (9.1)	4 (25.0)	6 (26.1)
	Abnormally high ratio (n, %)	11 (22.0)	1 (9.1)	4 (25.0)	6 (26.1)
	Abnormally low ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)
TgAb (ref: 0–4.11 IU/mL)	Outlier ratio (n, %)	18 (36.0)	3 (27.3)	6 (37.5)	9 (39.1)
	Abnormally high ratio (n, %)	18 (36.0)	3 (27.3)	6 (37.5)	9 (39.1)
	Abnormally low ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)

Group 1: patients complicated with SPM. Group 2: patients with postoperative cervical lymph node metastasis. Group 3: control group. Chi-square test.

the normal upper limit, and the level in Group 2 was slightly lower than that in the other two groups. Similarly, the D-dimer level in Group 2 was lower than that in the other two groups, but the difference was not statistically significant. The mean values of all three groups were within the normal

range. The INR, PTR and APTT levels in Group 1 were significantly lower than those in Group 3, and its FIB level was significantly higher than that of Group 3. INR and PTR in Group 1 were also lower than those in Group 2. For Group 2, only APTT was significantly lower than that in Group 3.

Table 6: Coagulation factors

Groups	Total (N = 50)	Group 1 (N = 11)	Group 2 (N = 16)	Group 3 (N = 23)
PT (s)	10.9 ± 1.6	10.3 ± 0.4	11.2 ± 1.1	11.1 ± 2.2
PTA (%)	110.2 ± 19.9	110.6 ± 16.2	104.5 ± 19.5	113.9 ± 21.6
INR	0.9 ± 0.1	0.9 ± 0.0 ^{**,#}	1.0 ± 0.1	1.0 ± 0.1
PTR	0.9 ± 0.1	0.9 ± 0.0 ^{**,#}	0.9 ± 0.1	1.0 ± 0.1
APTT (s)	29.0 ± 5.3	25.9 ± 4.8 ^{**}	27.1 ± 5.7 ^{**}	31.9 ± 3.6
FIB (g/L)	2.8 ± 0.7	3.3 ± 0.9 [†]	2.8 ± 0.7	2.7 ± 0.4
TT (s)	18.7 ± 18.7	16.9 ± 1.8	16.3 ± 1.8	21.2 ± 27.6
D-Dimer (μg/L)	179.2 ± 266.9	223.5 ± 437.6	119.1 ± 94.3	199.8 ± 247.9

Group 1: patients complicated with SPM, Group 2: patients with postoperative cervical lymph node metastasis; Group 3: control group. One-way ANOVA, ^{*}P < 0.05, ^{**}P < 0.01 compared with Group 3. [#]P < 0.05 compared with Group 2.

Analysis of the proportion of outliers showed that the proportion of abnormally low PT values in Group 1 was significantly higher than that in the other two groups. The proportion of FIB outliers in Group 1 was significantly higher than that in the other two groups. In addition, the proportion of abnormally high PTA value in Group 1 was twice as high as that in Group 3. The proportion of abnormally high APTT value in Group 2 was twice as high as that in Group 3, but without significant differences (Table 7).

4 Discussion

Various hemostasis markers associated with tumor staging and prognosis have been previously studied [14,15]. Elevated D-dimer levels, preoperative plasma prolonged PT level, hyperfibrinogenemia, high D-dimer level, and increased fibrinogen degradation product level may function as hemostasis markers that predict overall survival in gastric cancer patients, operable colorectal cancer patients, and renal, prostate, and bladder cancer patients [14,16,17]. Jianyong *et al.* [18] have found that PTC cases with

preoperative hyperfibrinogenemia are more likely to have an advanced tumor lymph nodes' metastasis stage and higher rate of PTC recurrence, while serum fibrinogen levels may serve as a biomarker for predicting PTC recurrence, not concerning the other coagulation factors. Uysal *et al.* [19] have observed that red cell distribution width, mean platelet volumes, hemoglobin content, and plateletcrit were significantly higher in the benign multinodular goiter and PTC groups than in the healthy control group. A possible correlation between APTT and hemoglobin content and tumor size in benign multinodular goiter and PTC was also noted [20,21]. APTT and PT in the PTC group were statistically significantly higher than those in the healthy controls [20]. There is currently no literature focusing on the relationship between the hemostasis markers and different TC prognoses.

The present study evaluated the expression of coagulation factors in samples of PTC with different prognoses to investigate the associations among them. To the best of our knowledge, this is the first study focusing on the biomarkers for the prognosis of PTC with postoperative cervical lymph node metastasis and SPM.

Table 7: Outlier comparison of coagulation factors

Groups		Total (N = 50)	Group 1 (N = 11)	Group 2 (N = 16)	Group 3 (N = 23)
PT (ref: 10.5–13.5 s)	Outlier ratio (n, %)	14 (28.0)	6 (54.5)*	5 (31.3)	3 (13.0)
	Abnormally high ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)
	Abnormally low ratio (n, %)	14 (28.0)	6 (54.5)*	5 (31.3)	3 (13.0)
PTA (ref: 80–100%)	Outlier ratio (n, %)	38 (76.0)	9 (81.8)	11 (68.8)	18 (78.3)
	Abnormally high ratio (n, %)	34 (68.0)	9 (81.8)	9 (56.3)	16 (43.5)
	Abnormally low ratio (n, %)	4 (8.0)	0 (0)	2 (12.5)	2 (8.7)
INR (ref: 0.8–1.5)	Outlier ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)
	Abnormally high ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)
	Abnormally low ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)
PTR (ref: 0.8–1.2)	Outlier ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)
	Abnormally high ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)
	Abnormally low ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)
APTT (ref: 21–37 s)	Outlier ratio (n, %)	6 (12.0)	1 (9.1)	3 (18.8)	2 (8.7)
	Abnormally high ratio (n, %)	3 (6.0)	0 (0)	1 (6.3)	2 (8.7)
	Abnormally low ratio (n, %)	3 (6.0)	1 (9.1)	2 (12.5)	0 (0)
FIB (ref: 2–4 g/L)	Outlier ratio (n, %)	7 (14.0)	3 (27.3)	3 (18.8)	1 (4.3)
	Abnormally high ratio (n, %)	4 (8.0)	3 (27.3)**	1 (6.3)	0 (0)
	Abnormally low ratio (n, %)	3 (6.0)	0 (0)	2 (12.5)	1 (4.3)
TT (ref: 13.5–19.5 s)	Outlier ratio (n, %)	5 (10.0)	1 (9.1)	2 (12.5)	2 (8.7)
	Abnormally high ratio (n, %)	3 (6.0)	1 (9.1)	1 (6.3)	1 (4.3)
	Abnormally low ratio (n, %)	2 (4.0)	0 (0)	1 (6.3)	1 (4.3)
D-Dimer (ref: 0–252 µg/L)	Outlier ratio (n, %)	8 (16.0)	1 (9.1)	2 (12.5)	5 (21.7)
	Abnormally high ratio (n, %)	8 (16.0)	1 (9.1)	2 (12.5)	5 (21.7)
	Abnormally low ratio (n, %)	0 (0)	0 (0)	0 (0)	0 (0)

Group 1: patients complicated with SPM, Group 2: patients with postoperative cervical lymph node metastasis; Group 3: control group. Chi-square test, * $P < 0.05$, ** $P < 0.01$ compared with Group 3.

The coagulation system includes endogenous and exogenous coagulation system. PT is a sensitive and commonly used screening test for exogenous coagulation, while APTT is used for the endogenous coagulation system [22]. The shorter PT and APTT may be due to the increased blood viscosity and thromboembolic diseases, while the longer PT and APTT may be due to the opposite condition, such as the lack of some coagulation factors, hyperactivity of anticoagulant and fibrinolytic system, and use of some anticoagulant drugs [23,24]. In the present study, the shortened APTT in PTC patients was associated with SPM and postoperative cervical lymph node metastasis. This indicates that the coagulation factors are related to the different PTC prognoses.

There are few studies focusing on the relationship between APTT and cancer. APTT is increased in renal cancer, but not in prostate and bladder cancers [16]. It has no prognostic value for the survival of patients with hepatocellular carcinoma [25]. APTT in healthy persons is longer compared to non-small-cell lung cancer patients [26]. A possible correlation has been observed among APTT, hemoglobin content, and tumor size in benign multinodular goiter and PTC groups. There is no current literature on the relationship between APTT and multiple cancers. The present study showed that shorter APTT is related to SPM and postoperative cervical lymph node metastasis in PTC patients.

In general, cancer is associated with an imbalance in the hemostatic system and induces a prothrombotic state. However, the molecular and laboratory features of cancer-associated thrombosis are complex and multifactorial and are difficult to assess clinically [26,27]. Several mechanisms may explain the observed impact of the hypercoagulability state. First, several procoagulant molecules, among which tumor necrosis factor is the most important, are expressed by cancer cells or are induced by them in normal vascular tissues via the release of soluble mediators and direct cancer cell host cell contact [28]. Second, the role of various components of the plasminogen activating system, especially urokinase-plasminogen activator and plasminogen activator inhibitor type 1, in TC progression, metastasis, prognosis, and progression-free survival has been established [28–30]. Finally, it is unknown to what extent TSH-suppressive thyroid hormone therapy may contribute to the hypercoagulability state in TC patients. Reports on the influence of thyroid hormones on hemostasis, while suggesting a hypercoagulable state in thyrotoxicosis, have often been inconclusive [31].

Although the present study described the APTT levels in TC patients with different prognoses, especially in patients with multiple TCs, the current investigation had some

limitations. The cohort consisted of a small number of patients in each group, without including all prognosis types of PTC, such as recurrence in the thyroidectomy bed and distant metastasis. Another shortcoming of the current study is that it could not evaluate coagulation parameters in patients with different tumor stages. The postoperative lymph node metastasis was more likely if the stage before the first surgery was advanced and lateral cervical lymph node dissection was needed, which may have affected the results. A larger study population with different tumor stages would provide a higher statistical power and data on patients' characteristics and coagulation parameters would be more homogeneous and less prone to errors.

5 Conclusion

In summary, PTC patients with different prognosis exhibited different APTTs. The shortened APTT was associated with the increased risk of SPM and postoperative cervical lymph node metastasis. The coagulation factor APTT may be associated with different PTC prognoses. Therefore, coagulation indicators such as APTT may be a new biomarker for predicting the prognosis of PTC and may provide a new molecular target for treating it, especially in combination with SPM and postoperative cervical lymph node metastasis.

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