



Original Research

The Reality of Hypoparathyroidism After Thyroidectomy: Which Risk Factors are Effective? Single-Center Study

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Abstract

Objectives: One of the most common complications of thyroidectomy is hypoparathyroidism and that complication has a multifactorial etiology. The etiology of post-operative hypoparathyroidism is multifactorial, some factors affecting hypoparathyroidism have been revealed in the literature, and there are some conflicting results about this complication. In the present study, we aimed to evaluate pre-operative and intraoperative factors affecting development of hypoparathyroidism.

Methods: Data of 542 patients underwent thyroidectomy±central dissection (±lateral dissection) and whose post-operative parathormone values could be obtained, between 2012 and 2020 were collected prospectively and evaluated retrospectively. A parathyroid hormone (PTH) value of <15 pg/mL at the post-operative 4th h was defined as hypoparathyroidism, and a calcium (Ca) value of <8 mg/dl on the 1st post-operative day was defined as biochemical hypocalcemia. Patients were divided into two groups as post-operative hypoparathyroidism (Group 1) and non-hypoparathyroidism (Group 2). In addition, PTH value below the reference value at the post-operative 6th month and/or still needing calcium treatment was defined as permanent hypoparathyroidism. Demographic data of the patients, pre-operative biochemical values, surgical indications, intraoperative findings, post-operative 4th h PTH values, post-operative 1st day calcium values, and pathological examination of the specimen whether there was an unintentionally resected parathyroid gland or not were evaluated as risk factors for hypoparathyroidism. A logistic regression model was used to determine independent risk factors for the development of hypoparathyroidism.

Results: Hypoparathyroidism was determined in 124 (22.9%) and hypocalcemia was determined in 120 (22.1%) patients. According to 6-month follow-up period; 110 (20.3%) patients were transient, 7 (1.3%) patients were permanent, and 7 (1.3%) patients data could not be obtained. The hypocalcemia rate was higher in Group 1 (39.3% vs. 14.3%, $p<0.0001$), also the post-operative 1st day calcium values were lower (8.2 ± 0.7 mg/dl vs. 8.5 ± 0.6 mg/dl; $p=0.000$). The rate of parathyroid autotransplantation, the rate of parathyroid gland in pathological specimen, and the rate of central dissection were significantly higher in Group 1 compared to group 2 (15.8% vs. 8%; $p=0.006$; 20% vs. 10.6%; $p=0.003$; 16.4% vs. 5.3%, $p<0.0001$, respectively). The difference between the two groups was significant in terms of the number of remaining parathyroids, and the rate of the number of patients with four remaining parathyroids in place was higher in Group 2 than in Group 1 (84.1% vs. 67.9; $p=0.000$). In the logistic regression analysis, only central dissection is an independent risk factor affecting the development of hypoparathyroidism, and central dissection increases the risk of hypoparathyroidism approximately 2.3 times ($p=0.014$; OR: 2.336). The other factors were not determined as independent risk factor.

Conclusion: Performing central neck dissection with total thyroidectomy may increase the risk of hypoparathyroidism development. The risk of hypoparathyroidism should be considered when evaluating the indications and dissection extent in the central dissection. Maximum effort should be made to preserve the parathyroid glands and their vascularization during central dissection, and if there is a removed parathyroid gland, it should be autotransplanted.

Keywords: Hypocalcemia, hypoparathyroidism, parathyroid autotransplantation, thyroidectomy

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Thyroidectomy is the most common endocrinological surgery for both malign and benign thyroid diseases and hypocalcemia is the most often complication of bilateral thyroidectomy.^[1-3] Although the etiology of hypocalcemia is multifactorial, the most common and most basic cause is hypoparathyroidism.^[3]

Post-operative hypoparathyroidism is occurred by a decrease in parathyroid hormone (PTH) in circulation due to the reduced functional total parathyroid parenchym volume related to inadvertently resection or devascularization and injury of one or more parathyroid glands by mechanical or thermal trauma during surgery.^[4,5]

In the surgical literature, post-operative transient hypoparathyroidism after total thyroidectomy is demonstrated between 1 and 60%, and permanent hypothyroidism is between 1% and 34%.^[4,5] Such a wide range of incidence may be affected by many factors such as heterogeneity of the studies, various definitions and clinical or biochemical criteria used in the studies, treatment criteria, extent of the thyroid surgery, type of the surgical technique, surgeon's experience, patient population, and diagnosis of the surgical disease.^[6,7]

These factors indicate that the etiology of post-surgical hypoparathyroidism is multifactorial. In some studies, pre-operative and intraoperative factors that may be effective on hypoparathyroidism have been evaluated and discussions about the effect of these factors still continue.^[7]

In the present study, we aimed to evaluate the effect of pre-operative and intraoperative factors on hypoparathyroidism after thyroidectomy.

Methods

Approval was obtained from the Local Ethics Committee for this study with the decision number 3254, dated April 19, 2022. Data of the patients who underwent thyroidectomy between 2012 and 2020 were collected prospectively and evaluated retrospectively. 542 patients over 18 years of age, who underwent total thyroidectomy and/or central and/or lateral neck dissection, and whose pre-operative and early post-operative data were able to be obtained, have been included in the study. During this period, the patients with lobectomy, completion thyroidectomy, and secondary surgery due to recurrent disease and patients who have hyperparathyroidism with thyroid disease and whose pre-operative and early post-operative data were not able to be obtained have been excluded from the study.

Thyroidectomy technique: In our clinic, thyroidectomy surgery is performed under general anesthesia and dissection of the recurrent laryngeal nerve and external branch of the superior laryngeal nerve is routinely performed with intra-

operative nerve monitoring; and the technical details of the surgical procedure are given in other studies.^[8-10]

A surgical loop is routinely used during the surgery. During the lateral and posterior dissection of the lobe, the tertiary branches of the inferior thyroid artery were ligated close to the thyroid capsule; and parathyroid glands were tried to be determined with inspection in normal localizations.^[11]

If they were not able to be visualized in the dissection area, no extra dissection was performed to detect the parathyroid glands.

It was investigated whether there was an unintentionally resected parathyroid gland on the thyroid or central neck dissection material. If there was an unintentionally resected parathyroid gland in the dissection material, it was kept in physiological saline. If the parathyroid glands were not able to be protected with vascularization in situ or were resected unintentionally during thyroidectomy and/or central neck dissection; the parathyroid glands were chopped into 1 mm three pieces and buried into in two or three different pockets in the ipsilateral sternocleidomastoid muscle and marked with prolene suture.^[12]

Central neck dissection was performed in patients with preoperatively diagnosed medullary thyroid cancer and the patients with clinical indications among papillary thyroid cancer patients.

Parathyroid glands visualized during the surgery and autotransplanted ones were recorded on the operation note. When parathyroid was detected in the surgical specimen, it was stated on the pathology report.

The number of remaining parathyroid glands in their normal localization was calculated using the formula created with data from operative note and pathology report. The number of remaining parathyroid glands in their normal localization: 4-(parathyroid glands autografted + parathyroid glands found in the specimen).^[13]

Demographic data of the patients, pre-operative biochemical values, surgical indications, intraoperative findings, post-operative 4th h PTH values, post-operative 1st day calcium values, and pathological examination of the specimen whether there was an unintentionally resected parathyroid gland or not were evaluated. Pre-operative 25(OH) vit D3 levels were separated and compared with four 25% quartiles. A PTH value of <15 ng/L at the post-operative 4th h was defined as hypoparathyroidism.^[14,15]

It was defined as biochemical hypocalcemia if calcium (Ca) level was <8 mg/dL and defined as symptomatic hypocalcemia if there were symptoms of hypocalcemia accompanying biochemical hypocalcemia.^[16]

"Permanent hypoparathyroidism" was defined as a PTH val-

ue below normal reference values and/or need for calcium treatment at the post-operative 6th month.^[17]

According to the post-operative 4th h PTH value, the patients were divided into two groups as those with hypoparathyroidism (PTH<15 ng/L) (Group 1) and those without hypoparathyroidism (PTH>15 ng/L). Demographic, pre-operative biochemical, and intraoperative factors affecting hypoparathyroidism were evaluated.

Hypocalcemia treatment: In our clinic, patients with PTH values of 10–15 pg/mL were treated with elemental calcium (1–2 g × 3/day) according to the severity of symptoms and calcium level; also if the PTH value <10 pg/mL or with symptomatic hypocalcemia, the patients were treated with calcitriol (0.25–1 × 2–3 mcg/day) and elemental calcium (1–2 g × 3/day). In addition to oral calcium and calcitriol treatment, intravenous calcium (10 mL 10% calcium gluconate ampoule) treatment was given to patients with a calcium level of <7 mg/dL and/or severe hypocalcemia symptoms. Intravenous calcium therapy was terminated in patients whose symptoms of severe hypocalcemia improved and/or the albumin-adjusted total serum calcium value increased above 7.5 mg/dL. Patients with mild symptoms with a calcium value of 7.5 mg/dl or asymptomatic patients with a calcium values above 7 mg/dl were discharged.

Statistical Analysis

The data were evaluated using the IBM SPSS Statistics V22 program (IBM, Armonk, NY, USA). Number and percentage for categorical variables; for numerical variables, mean, standard deviation, minimum, and maximum were given. In the comparison of the groups, differences between the ratios of categorical variables were made with the Pearson Chi-square test, and non-parametric comparisons were made with the Mann–Whitney U test. To evaluate the independent factors affecting hypoparathyroidism, the formula formed from the features that were significant in pairwise comparisons was evaluated by binary logistic regression analysis. P<0.05 was accepted statistically significant.

Results

The mean age of 542 patients enrolled in the study was 48.2±23.4 years. Hypoparathyroidism was observed in 165 (30.4%) and hypocalcemia was observed in 120 (22.1%) among these patients (Table 1). Demographic and characteristics of the patients are given in Table 1. Hypoparathyroidism was permanent in 151 (27.8%) of 165 patients, in the 7 (1.3%) patients, it was transient according to 6th month results. The 6-month follow-up of seven patients (1.3%) was not able to reached.

Table 1. Demographic and characteristics of study patients

Characteristic	
Age mean±SD (min-max)	48.2±23.4 (18–82)
Gender (n) (%)	
Female	418 (77.1%)
Male	124 (22.9%)
Pre-operative diagnose (n) (%)	
MNG	366 (67.5%)
Malignancy or Suspicious for malignancy	112 (20.7%)
Graves Disease	64 (11.8%)
Performed Surgery (n) (%)	
TT	495 (91.3%)
TT+UCND	14 (2.6%)
TT+UCND+SLND	1 (0.2%)
TT+BCND	19 (3.5%)
TT+BCND+SLND	13 (2.4%)
Pre-operative Ca (mg/dl) (mean±SD) (min-max)	9.5±0.44 (7.6–10.69)
Pre-operative P (mg/dl) (mean±SD) (min-max)	3.35±0.59 (1.4–5.3)
Pre-operative Mg (mg/dl) (mean±SD) (min-max)	1.95±0.22 (1.2–2.7)
Pre-operative (ng/L) (mean±SD) (min-max)	56.5±28.9 (19–193)
Pre-operative ALP (U/L) (mean±SD) (min-max)	81.8±33.9 (15–232)
Pre-operative 25(OH)vitD3 (ng/ml) (mean±SD) (min-max)	16.8±12.3 (2–94.3)
Pre-operative Cr (mg/dl) (mean±SD) (min-max)	0.7±0.2 (0.33–1.82)
Pre-operative hyperthyroidism (n) (%)	147 (27.1%)
Central Neck Dissection (n) (%)	47 (8.7%)
Parathyroid Autotransplantation (n) (%)	56 (10.4%)
Parathyroid Gland on Pathological Specimen (n) (%)	73 (13.5%)
Hypoparathyroidism (n) (%)	165 (30.4%)
Hypocalcemia (n) (%)	120 (22.1%)

SD: Standard deviation; min: minimum; max: maximum; MNG: Multinodular goiter; TT: Total thyroidectomy; UCND: Unilateral central neck dissection; BCND: Bilateral central neck dissection; SLND: Selective lateral neck dissection; Ca: calcium; P: Phosphorus; Mg: Magnesium; PTH: Parathyroid hormone; ALP: Alkaline phosphatase; Cr: Creatinine.

There was no significant difference between the two groups in terms of age, gender, presence of pre-operative hyperthyroidism, and pre-operative biochemical parameters, except for 25 (OH) vitD3. Pre-operative 25(OH)vitamin D3 levels were present in 321 of the patients in the study. Although the mean pre-operative 25(OH)vitamin D3 level was higher in Group 1 (p=0.019); when the pre-operative 25(OH)vitamin D3 values of the patients were divided into four separate 25% quartiles, there was no significant difference between the two groups (p=0.118) (Table 2).

Table 2. Comparison of patients with post-operative hypoparathyroidism and those without

	Group 1 Hypoparathyroidism (+)	Group 2 Hypoparathyroidism (-)	p
Age	48±13.7	48.3±12.8	0.774
Gender			0.956
Female n (%)	127 (77%)	291 (77.2%)	
Male n (%)	38 (23%)	86 (22.8%)	
Pre-operative Hyperthyroidism (%)	40 (%24.2)	107 (%28.4)	0.319
Pre-operative Parathyroid Hormone mean±SD (ng/L) Min-max	56.7±29.1 (23–197)	56.5±27 (19–193)	0.517
Pre-operative Calcium mean±SD (mg/dl) Min-max	9.5±0.4 (7.6–10.69)	9.5±0.4 (8–10.69)	0.573
Pre-operative Phosphorus mean±SD (mg/dl) Min-max	3.4±0.6 (1.8–5.3)	3.3±0.6 (1.4–5.3)	0.136
Pre-operative Magnesium mean±SD (mg/dl) Min-max	1.9±0.2 (1.2–2.4)	1.9±0.2 (1.2–2.7)	0.641
Pre-operative ALP mean±SD (U/L) Min-max	76±26 (35–173)	82±34 (15–232)	0.198
Pre-operative Cr mean±SD (mg/dl) Min-max	0.69±0.15 (0.35–1.1)	0.73±0.19 (0.33–1.82)	0.121
Pre-operative 25(OH)vitD3 ort±SD (ng/ml) Min-max	19.7±13.6 (3–89.7)	16.7±12.3 (2–94.3)	0.019
Categorical Pre-operative 25(OH)vitD3 (n:321)			0.118
<8.6	21 (19.8%)	59 (27.4%)	
8.7–14.9	22 (20.8%)	59 (27.4%)	
15–23.7	31 (29.2%)	49 (22.8%)	
>23.8	32 (30.2%)	48 (22.3%)	
Total (n)	106	215	
The number of parathyroid glands identified during surgery n (%)			0.462
0	2 (1.2%)	8 (2.1%)	
1	6 (3.6%)	15 (4%)	
2	16 (9.7%)	56 (14.9%)	
3	40 (24.2%)	88 (23,3%)	
4	101 (61.2%)	210 (55.7%)	
Total	165	377	
PT AT n (%)	26 (15.8 %)	30 (8%)	0.006
PT on Pathological Specimen n (%)	33 (20%)	40 (10.6%)	0.003
PGRIS n (%)			0.000
0	0	1 (0.3%)	
1	3 (1.8%)	0	
2	10 (6.1%)	5 (1.3%)	
3	40 (24.2%)	54 (14.3%)	
4	112 (67.9%)	317 (84.1%)	
Total	165	377	
Central Neck Dissection n (%)	27 (16.4%)	20 (5.3%)	0.000
Post-operative 1. day hypocalcemia	64 (39.3%)	56 (14.9%)	0.000
Post-operative 1. day Calcium mean+SD (mg/dl) Min-max	8.2±0.7 (6.2–9.7)	8.5±0.6 (6.5–10.5)	0.000

SD: Standard deviation; min: minimum; max: maximum; PT: parathyroid; AT: Autotransplantation; PGRIS: The number of parathyroid glands remaining in situ; ALP: Alkaline phosphatase; Cr: Creatinine.

Central neck dissection (16.4% vs. 5.3%; $p<0.0001$), parathyroid autotransplantation (15.8% vs. 8%; $p=0.006$), and rate of parathyroid gland detected in pathological sample (20% vs. 10.6%; $p=0.003$) were significantly higher in Group 1. The difference between the two groups was significant in terms of the number of remaining parathyroid glands in place, and the rate of the number of patients with four remaining parathyroids in place was higher in Group 2

than in group 1 (84.1% vs. 67.9%, $p=0.000$). There was no significant difference between two groups in terms of the number of the parathyroid glands that were observed intraoperatively ($p=0.462$).

Not only, the rate of hypocalcemia was higher in Group 1 than Group 2 (39.3% vs. 14.3%; $p<0.0001$) but also the mean value of post-operative 1st day calcium was significantly lower (8.2 + 0.7 mg/dl vs. 8.5 + 0.6 mg/dl; $p=0.000$,

respectively) (Table 2). The formula formed from the terms of central dissection, parathyroid autotransplantation (PT AT: Parathyroid autotransplantation), presence of parathyroid in the specimen, and preserved parathyroid number in situ (PGRIS) (PGRIS: Number of parathyroid glands in situ remaining) was evaluated by binary logistic regression analysis and significant difference was found in pairwise comparison of these terms. Central dissection is the only independent risk factor affecting the development of hypoparathyroidism, and central dissection increases the risk of hypoparathyroidism approximately 2.3 times ($p=0.014$; OR:2.336). Other factors were not found as independent risk factors.

Discussion

The certain incidence of hypoparathyroidism which is the most common complication of thyroidectomy is still debatable.^[3]

In this study, the rates of early hypoparathyroidism and permanent hypoparathyroidism were calculated 30.4% and 1.3%, respectively; and only central dissection was demonstrated as the independent risk factor affecting the development of hypoparathyroidism. Performing central neck dissection increases the risk of hypoparathyroidism approximately 2.3 times.

To prevent hypoparathyroidism during thyroidectomy; it is important to preserve both the parathyroid glands and their vascularization which is delicate and complex.

We believe that central dissection is an important factor that increases the risk of hypoparathyroidism by increasing both the risk of removal of the inferior parathyroids within the central tissue and the risk of impaired arterial and venous vascularization of the parathyroids.

Although the development of hypoparathyroidism is multifactorial, in our study, in Group 1 compared to Group 2, in pairwise comparisons; the rate of performing parathyroid autotransplantation (15.8% vs. 8%; $p=0.006$, respectively) and parathyroid glands unintentionally removed (20% vs. 10.6%; $p=0.003$, respectively) is higher, and the PGRIS rates are different but these factors were not identified as inde-

pendent risk factors. The effect of parathyroid autotransplantation on hypoparathyroidism is still controversial. At the present time, there is a widespread consensus that performing parathyroid autotransplantation increases the risk of early hypoparathyroidism.^[3,6,13,18,19] There is a positive correlation between the number of autografted parathyroid glands and the rate of hypoparathyroidism; the higher the number of autografted parathyroid glands, the higher the rate of hypoparathyroidism.^[19,20]

At the present time, it is one of the most debated issue if there is a positive effect of parathyroid autotransplantation over preventing hypoparathyroidism. In some studies, liberal or routine parathyroid autotransplantation is recommended for preventing hypoparathyroidism.^[18,19,21] However, in some other studies, it has been revealed in that parathyroid autotransplantation was not able to prevent hypoparathyroidism.^[22,23] Even recently; it has been reported that the rate of permanent hypoparathyroidism may increase in patients who have undergone parathyroid autotransplantation.^[24]

Lorento et al. revealed that the rate of permanent hypoparathyroidism in patients who underwent parathyroid autotransplantation through the technique of fragmented tissue buried into sternocleidomastoid muscle was three times higher compared to the patients who did not (9.8% vs. 3.1%; $p<0.002$).^[13,25,26]

Although the rate of unintentionally parathyroidectomy was demonstrated approximately 10% in the previous studies, it was reported that it did not result in symptomatic transient and permanent hypoparathyroidism.^[27,28] It has also been reported that the effect of accidentally removed parathyroid glands is one of the main factors in the development of hypoparathyroidism.^[29]

Both recent clinical studies and meta-analyses have demonstrated that inadvertent removal parathyroidectomy increases both transient and permanent hypoparathyroidism.^[5,30-32] In fact, in the last decade, there has been consensus that accidental parathyroidectomy increases the prevalence of persistent hypoparathyroidism by up to 8%.^[29]

The proofs of the current studies suggest that the critical factor in post-operative parathyroid failure is the number of parathyroid glands in situ preserved.^[29] Although it was not demonstrated as an independent factor in our study, the rate of in situ preserved parathyroid glands was higher in Group 2 compared to Group 1 (84.1% vs. 67.9%, $p=0.000$).

According to the prospective study by Lorenta-Posh et al., the prevalence of hypocalcemia and prevalence of protracted and permanent hypoparathyroidism were in negative correlation with the number of in situ preserved parathyroid glands (PGRIS). In addition, PGRIS score was

Table 3. Logistic regression analysis

	Odds ratio		p
Central Neck Dissection (-)	2.336	1.192–4.587	0.014
PT autotransplantation (+)	0	0	0.999
PT on Pathological Specimen (+)	0	0	0.999
PGRIS	0	0	0.999

PT: Parathyroid Gland; PGRIS: The number of parathyroid glands remaining *in situ*.

determined as the most powerful independent factor for acute and chronic parathyroid failure and it was concluded that the protection of the in situ parathyroids has a critical role in preventing permanent hypoparathyroidism after total thyroidectomy.^[13]

Similarly, in another study, a significant correlation was found between permanent hypoparathyroidism and the number of parathyroid glands preserved in situ; and protection of at least three parathyroid glands was associated with a lower rate of permanent hypoparathyroidism (2.79% vs. 13.3%, $p=0.0001$) compared to one or two in situ parathyroid protection.^[5]

In addition to that, obesity, central neck dissection, parathyroid glands in pathological specimen, and staged surgery have been determined as independent risk factor according to de León-Ballesteros et al.^[5,32]

There are some conflicting results in the literature regarding the effect of age and gender on hypoparathyroidism. In our study, mean age and gender were similar between the two groups. Although female gender was reported as a risk factor for transient hypoparathyroidism in some studies, no correlation was found between hypoparathyroidism and gender in other studies.^[33-35]

The literature include studies determining old age as a risk factor and some others determining young age as a risk factor for transient hypoparathyroidism. However, there are studies demonstrating no relationship between age and hypoparathyroidism.^[35-37]

Furthermore, pre-operative Vitamin D deficiency was found to be a risk factor for transient hypoparathyroidism.^[37]

Graves disease, malignancy, and identification of three or four parathyroid glands were defined as predictive factors for biochemical hypocalcemia by Riordan et al.^[38] In a multicentric study, Graves disease was determined as an independent risk factor for both transient and permanent hypoparathyroidism.^[33]

Villarroya-Marquina et al. described female patients younger than 45 years of age and low PGRIS score as independent variables in predicting post-operative hypocalcemia in patients with MNG.^[39]

Hypocalcemia is one of the most common results of impaired parathormone secretion.

In our study, the rate of total biochemical hypocalcemia was significantly higher in the group with hypoparathyroidism than in those without hypoparathyroidism (39.3% vs. 14.9%; $p<0.0001$, respectively). The reason why biochemical hypocalcemia cannot be detected on day 1st in all hypoparathyroid patients may be due to several factors. The PTH values of patients with PTH <15 ng/L at the 4th h can re-

cover at the 24th h in approximately 20% of the patients.^[40]

In some patients, the calcium value may decrease after the 1st day. PTH decrease rate may be a more accurate indicator than low PTH value in predicting transient hypocalcemia.^[41] In addition, in our center, hypocalcemia may not have occurred due to early replacement treatment initiated in patients with low PTH values.

The main limitations of our study are that it was retrospective and the lack of detailed evaluation of replacement treatment administered to the patients and the clinical hypocalcemia that was not evaluated in detail.

Hypoparathyroidism is one of the common complications after thyroidectomy; and although most of them are temporary, they can also occur as permanent hypoparathyroidism. The central neck dissection with thyroidectomy may increase the risk of hypoparathyroidism. The risk of hypoparathyroidism should be considered when evaluating the indications and dissection extent in the central dissection. Maximum effort should be made to preserve the parathyroid glands and their vascularization during central dissection, and if there is a removed parathyroid gland, it should be autotransplanted.

Disclosures

Ethics Committee Approval: Approval was obtained from the Local Ethics Committee of our hospital for this study with the decision number 3254, dated April 19, 2022.

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Conflict of Interest: None declared.

Authorship Contributions: Concept – M.U., I.E.A., N.A., Y.C.; Design – I.E.A., M.T.U., N.A.; Supervision – M.U., N.A., C.Y., M.K.; Data collection &/or processing – C.Y., M.K., M.T.U., A.R.T.; Analysis and/or interpretation – A.E.T., E.B., Y.C., A.Y.; Literature search – I.E.A., C.Y., A.Y., E.B., Y.C.; Writing – A.E.T., A.Y., E.B., Y.C.; Critical review – M.U., M.T.U., N.A., M.K.

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