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Case Report

Persistence of Elevated Procalcitonin in a Patient with Coronavirus Disease 2019 Uncovered a Diagnosis of Medullary Thyroid Carcinoma

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ABSTRACT

Objective: During the ongoing coronavirus disease 2019 pandemic, procalcitonin (PCT) levels have proven useful in assisting clinicians to diagnose bacterial superinfection. However, in the absence of signs of infection or at the resolution thereof, inappropriately and persistently high PCT levels may suggest and reveal the presence of other pathologies. We report a patient with severe acute respiratory syndrome coronavirus 2 pneumonia with initially elevated PCT levels that persisted during recovery, prompting the diagnosis of medullary thyroid carcinoma (MTC).

Methods: A 43-year-old man presented with a 2-day history of fever, sneezing, sore throat, and dry cough. His PCT was 94 ng/mL (normal value, 0.00-0.10 ng/mL), and he was positive for severe acute respiratory syndrome coronavirus 2 RNA.

Results: Empirical antibiotic therapy was administered for 7 days, but despite a clinical improvement, serum PCT remained high (84 ng/mL). Serum calcitonin (CTN) was 2120 pg/mL (normal, ≤12 pg/mL). Cytologic examination of thyroid nodules and CTN measurement of the aspiration needle washout confirmed MTC. The patient underwent total thyroidectomy with bilateral cervical lymph node dissection. Lowered CTN (986 pg/mL) and PCT (16 ng/mL) levels were observed 48 hours after surgery. A close follow-up was planned following the results of *RET* gene analysis.

Conclusion: PCT can be a useful biochemical marker of MTC suspicion in patients with inflammatory conditions and persistently elevated PCT, even after resolution. In our case, high levels of PCT in a patient with coronavirus disease 2019 pneumonia without signs of bacterial infection led to MTC diagnosis.

Introduction

Medullary thyroid carcinoma (MTC) is neuroendocrine neoplasia derived from thyroid parafollicular or C-cells, accounting for about 5% of all thyroid cancers. Its peak incidence is during early adulthood.[1,2] Calcitonin (CTN), a peptide that results from the cleavage and posttranslational processing of procalcitonin (PCT), is the main product of the C-cells of the thyroid gland and acts to reduce blood calcium, thereby opposing the effects of parathyroid hormone. CTN measurement is, to date, the most sensitive diagnostic test for identifying patients with MTC and C-cell hyperplasia, and it is a marker for residual or recurrent disease in MTC.[2]

PCT, the CTN precursor, is found in low concentrations in the serum of healthy individuals, whereas the production and release into circulation from extrathyroidal sources, such as immune cells or the liver, increases during severe systemic inflammation, bacteremia, and sepsis, as do concentrations of proinflammatory cytokines (Table).[3] PCT was first described as a marker of bacterial infection in 1993 when high concentrations of CTN-like

Abbreviations: CTN, calcitonin; MTC, medullary thyroid carcinoma; PCT, procalcitonin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Table
Hypercalcitoninemia and Hyperprocalcitoninemia in Nonmedullary Thyroid Carcinoma Conditions

Causes	Hypercalcitoninemia	Hyperprocalcitoninemia
Physiologic conditions	Sex, age, physical activity, pregnancy, and lactation	None
Pathologies	Hypergastrinemia, hyperparathyroidism, chronic kidney disease, neuroendocrine tumors, thyroid carcinoma (follicular and papillary carcinoma), chronic autoimmune thyroiditis, systemic mastocytosis, and leukemia	Bacterial infections, massive inflammatory states (major surgery, early postoperative state, trauma, severe burns, heatstroke, inhalation injury, acute pancreatitis, and postcardiac arrest induction of hypothermia), end-stage renal disease, acute decompensated congestive heart failure, and neuroendocrine tumors
Drugs	PPIs, glucocorticoids, beta-blockers, glucagon, CGRP inhibitors, and GLP-1	None

Abbreviations: CGRP = calcitonin gene-related peptide; GLP-1 = glucagon-like peptide 1; PPI = proton pump inhibitors.

immunoreactivity were detected in the blood of patients with extrathyroid diseases, and it is now commonly used in clinical practice as a biochemical marker of sepsis.[4] Thus, it is potentially useful in raising suspicion of bacterial infection and guiding the duration of antibiotic therapy in both sepsis and lower respiratory tract infections.[4–6] PCT has also been proposed by some authors[7,8] as a suitable marker, together with CTN, in the MTC diagnostic workup. Here, we report the case of a man affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia with persistently high PCT levels, despite his recovery from the infectious disease, who was subsequently diagnosed with MTC.

Case Report

A 43-year-old man of Caucasian origin was admitted to the Emergency Department of a hub hospital in Piedmont, Italy, in March 2020 because of a 2-day history of fever, sneezing, fatigue, sore throat, and dry cough with no dyspnea. He had a medical history of mild cognitive impairment since birth and arterial hypertension. Systemic lupus erythematosus with lupus nephritis was diagnosed at the age of 27, and he was receiving mycophenolate and prednisone. His family history was negative for cancer, endocrinopathy, and inflammatory diseases. His parents were dead, and neither he nor his sister had children.

Physical examination on admission showed fever (38 °C) and oxygen saturation of 94% in room air, with a respiratory rate of 18 breaths/min. Chest auscultation revealed decreased breath sounds and coarse crackles in both lung bases. Laboratory evaluations revealed a white blood cell count of 7110/μL (normal range, 4000-10 000/μL) with mild lymphocytopenia 650/μL (normal value, 760-5000/μL). D-dimer was 0.73 μg/ml (normal value, <0.5 μg/mL), C-reactive protein was 62 mg/L (normal value, <5 mg/L), and PCT was 94 ng/mL (normal range, 0.00-0.10 ng/mL). Hemoglobin, platelets, serum electrolytes, creatinine, and liver function test results were within normal limits. Arterial blood gas analysis results were pH, 7.44; pO_2, 75 mm Hg; and pCO_2, 37 mm Hg. Positivity for SARS-Cov-2 RNA was detected from his nasopharyngeal and oropharyngeal swab samples, and chest computed tomography scan showed bilateral ground-glass opacities in the basilar lung zones. Additionally, hyperdense and irregular foci in the thoracic vertebral bodies were reported (Fig. 1). The patient was admitted to the coronavirus disease 2019 ward with a diagnosis of SARS-CoV-2 pneumonia.

Empirical antibiotic therapy with piperacillin/tazobactam was started and was maintained for 7 days together with oxygen support. On hospital day 12, the general condition of the patient improved, C-reactive protein normalized (3.5 mg/L), and blood and urine culture tests remained negative, but serum PCT remained elevated (84 ng/mL). Serum CTN was then tested and measured 2120 pg/mL (normal, ≤12 pg/mL). Carcinoembryonic antigen was 108 ng/mL (normal value, 0-5 ng/mL), while total and ionized calcium were 9.3 mg/dL (normal value, 8.7-10.4 mg/dL) and 1.21 mmol/L (normal value, 1.15-1.29 mmol/L), respectively. Thyrotropin and thyroxine were in the normal range (1.29 μU/mL and 13.2 pg/mL, respectively). A neck examination was notable for a painless, right laterocervical swelling, and neck ultrasound revealed inhomogeneously echogenic lymph nodes with small punctate calcifications and a nonhomogeneous thyroid with multiple nodules, the largest of which had a diameter of nearly 30 mm. Cytologic examination by fine-needle aspiration confirmed the diagnosis of MTC, with the CTN value in the aspiration needle washout fluid >2000 pg/mL. The PCT:CTN ratio calculation was 3.96. A neck, lung, and abdomen computed tomography scan was negative for lesions other than in the neck lymph nodes, while multiple sclerotic lesions were described at dorsal spine level as well as at hip bone level. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography scan showed an increased tracer uptake in the right laterocervical lymph nodes (SUVmax: 3.8), while only a slight tracer uptake was present in both the thyroid and the dorsal vertebral bodies (Fig. 2). The patient underwent total thyroidectomy with bilateral cervical lymph node dissection. The histologic examination of the surgical specimen confirmed the diagnosis of MTC. In particular, neoplastic cells from both thyroid lobes and the draining lymph nodes showed positive immunohistochemical staining for CTN, carcinoembryonic antigen, synaptophysin, chromogranin A, and thyroglobulin, leading to the diagnosis of MTC. MTC metastases were shown in 3 of 12 lymph nodes, of which the largest was 30 mm. The patient's MTC was classified as pathologic T1b-N1a, stage III, according to the TNM classification of the American Joint Committee on Cancer Staging Manual, 7th Edition.[9]

Blood tests performed 48 hours after surgery showed a lowering of CTN (986 pg/mL) and PCT (16 ng/mL). On hospital day 22, nasopharyngeal and oropharyngeal swabs were repeated and were reported as negative. The patient was discharged with oral therapy of prednisone (5 mg/die), ramipril (10 mg/die), levothyroxine (50 μg/die), cholecalciferol (800 IU/die), and calcium carbonate (1 g/die). A 6-month follow-up was scheduled, and (18)F-fluorodihydroxyphenylalanine positron emission tomography was performed. No suspicious fixations at the thyroid lodge and cervical lymph node stations were described, while multiple osteoblastic foci in the skeletal area (dorsal vertebral metameres, sternum, and right scapula) with low fixation were present and considered as secondary lesions of bones. Laboratory tests showed CTN levels of 921 pg/mL, and PCT level was 16 ng/mL (Fig. 3). Considering the good clinical condition of the patient, a close follow-up was planned following the results of *RET* gene analysis.

Discussion

We report the case of a patient in whom the persistence of elevated PCT levels after resolution of SARS-CoV-2 infection, together with the presence of a painless right laterocervical

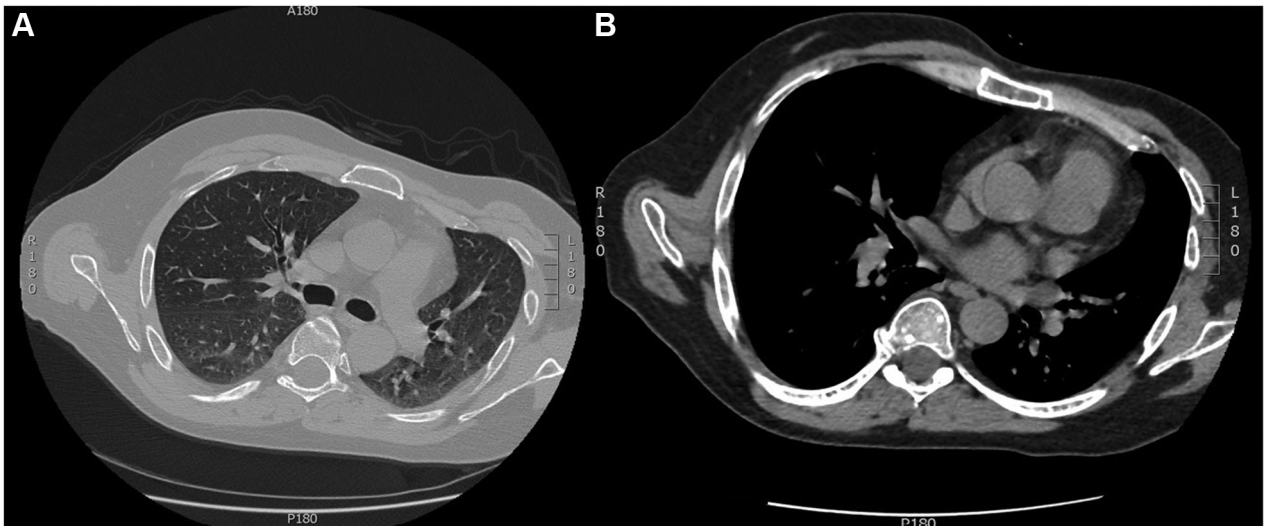

Fig. 1. Computed tomography scan of the chest. *A*, Bilateral ground-glass opacities in the basilar lung zones. *B*, Hyperdense and irregular foci in the thoracic vertebral bodies suspected as metastatic lesions were also reported.

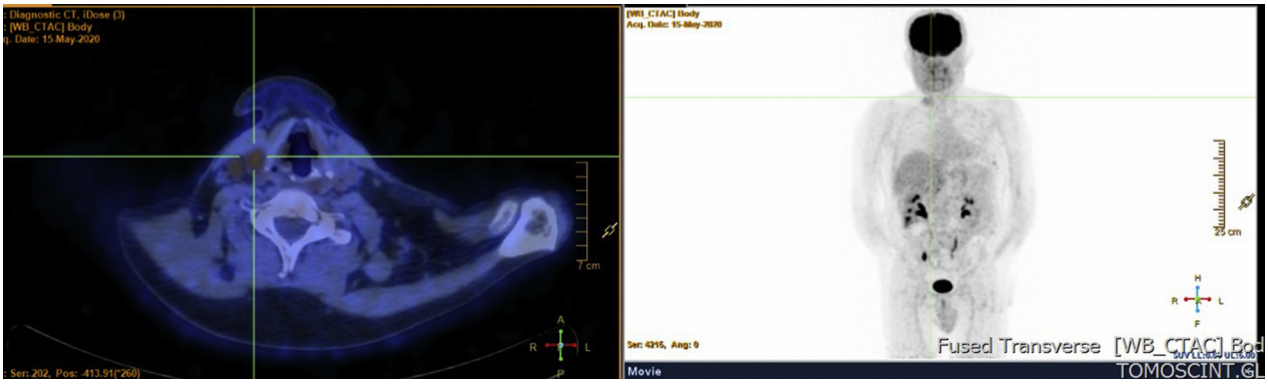

Fig. 2. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography scan showed an increased tracer uptake in the right laterocervical lymph nodes (SUVmax: 3.8) with no significant tracer uptake either in the thyroid or in the dorsal vertebral bodies.

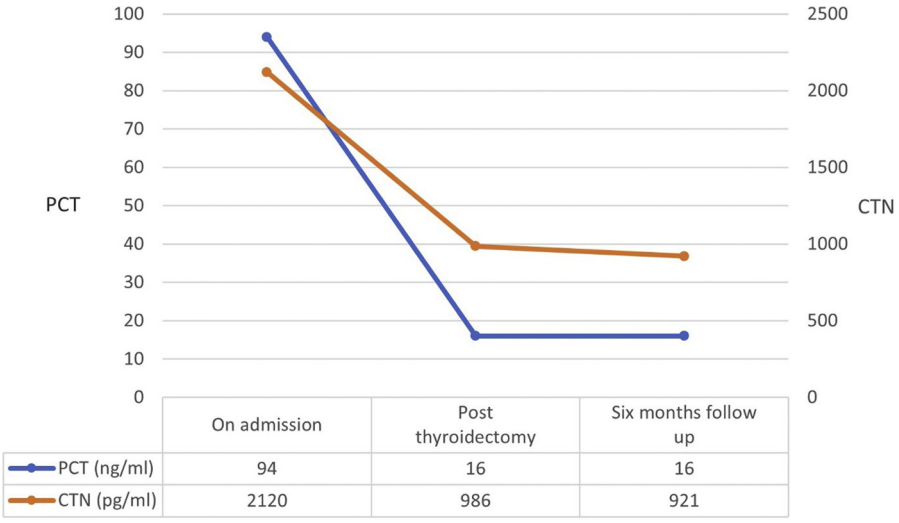

Fig. 3. Blood tests performed 48 hours after total thyroidectomy showed a reduction of calcitonin (986 pg/mL) and PCT (16 ng/mL). At 6-month follow-up, calcitonin was 921 pg/mL, and PCT was 16 ng/mL. *CTN* = calcitonin; *PCT* = procalcitonin.

swelling, uncovered a diagnosis of MTC. Sporadic MTC typically occurs between the fourth to sixth decades of life, and the most common presentation is a painless solitary thyroid nodule, whereas patients with hereditary disease present earlier multifocal and bilateral lesions. MTC prognosis depends on early detection and treatment, and elevated CTN levels are mandatory for the diagnostic workup. However, diagnosing MTC is still a challenge in clinical practice, and over the past few decades, there has been no significant trend toward detecting the disease at an earlier stage, with no significant increase in patient survival.[2]

Among the available diagnostic tests are thyroid ultrasound, cytologic examination by fine-needle aspiration, and serum CTN, which represents a highly sensitive method for the diagnosis of MTC. It has been shown that the positive predictive values for basal CTN levels in the preoperative diagnosis of MTC ranges from 8% to 25% for values ≥20 pg/mL and <100 pg/mL and 100% for values >100 pg/mL, while 3% to 10% of subjects without thyroid disease have CTN levels >10 pg/mL. In fact, CTN is also affected or influenced by physiologic and other pathologic conditions (Table). Furthermore, there is still no agreement in the literature on the CTN cutoff to exclude MTC, with some CTN-negative MTC cases also having been described.[8,10,11] Additionally, CTN presents other analytical problems, including susceptibility to relatively rapid degradation owing to serum proteases, which can lead to altered test results if blood samples are not quickly processed.[11,12] The hook effect may also occur, which can lead to false negatives when very high serum CTN saturates antibodies used in immunoradiometric and chemiluminescent assays. This effect can be unmasked by repeating the assay using progressive serum dilutions.[12] The presence of different immunoreactive isoforms and fragments of CTN has also been considered to potentially lead to erroneous results. Additionally, there is a lack of comparability of results obtained using different assays.[11,12]

In an effort to exceed these limits and to attain a higher degree of diagnostic accuracy with higher specificity, PCT is increasingly regarded as a potential marker of MTC.[7,8] PCT, a propeptide cleaved to CTN by a specific protease, is normally produced in the C-cells of the thyroid gland. Under physiologic conditions, PCT levels are undetectable, but during severe systemic bacterial infections, it is produced by extrathyroid tissues in large amounts (≥100 ng/mL). Remarkably, in contrast to the short half-life of CTN (10 minutes), PCT has a long half-life (22-35 hours) in serum. Furthermore, PCT assays are exempt from preanalytic flaws and produce consistent results across different analytical methods.[13–15] According to the U.S. Food and Drug Administration and the current international 2016 Surviving Sepsis Campaign guidelines, PCT is employed in clinical practice as an aid, in conjunction with other laboratory tests and clinical assessments, to begin or shorten antibiotic treatment duration in patients with sepsis and lower respiratory tract infections as well as to distinguish bacterial infections from other causes of infection or inflammation.[4,16] Recommendations differ as to the timing and cutoff points used to discontinue antibiotics on the basis of PCT measurement. Values ranging from 0.25 to 0.1 mg/L in patients in emergency departments and medical wards, from 0.5 to 0.25 mg/L in intensive care unit patients, or an 80% reduction from peak levels in patients with sepsis are considered markers of sepsis resolution and antibiotic discontinuation.[17,18] During this ongoing coronavirus disease 2019 pandemic, a meta-analysis has shown that increased PCT values, probably due to bacterial coinfection and an acute state of inflammation, are often associated with a higher risk of evolution toward a more severe form of the disease.[19] Recently, PCT has also been regarded as a potential marker of MTC in patients with thyroid nodules. In patients with MTC, PCT levels have been correlated with the extent of distant metastasis and the number of lymph nodes affected, whereas a high PCT:CTN ratio has been correlated with an increased risk of progressive disease and a shortened progression-free survival, both consequently being potentially useful parameters in predicting prognosis. In the study by Walter et al,[20] it was reported that the optimal PCT:CTN ratio cutoff for predicting progressive disease was 2.4 (sensitivity, 72.2%; specificity, 73.5%; and diagnostic accuracy, 73.2%), whereas the more stringent cutoff of 5.2 provided a sensitivity of 38.9%, a specificity of 91.8%, and a diagnostic accuracy of 77.6%. Giovanella et al[7] showed that among patients with autonomously functioning thyroid nodules and without inflammatory conditions, PCT and CTN were equally sensitive and specific in detecting MTC, being close to 100% for both markers. Nonetheless, the specificity of PCT in the diagnosis of MTC is reduced in cases of a bacterial infection or systemic inflammation. As a result, since the use of PCT is very common in clinical practice as a marker in bacterial infections, neuroendocrine neoplasia should be suspected and investigated (eg, by measuring CTN) if PCT levels remain high despite the resolution of the infection.

Conclusion

This case report describes the diagnosis of advanced MTC in a patient affected by SARS-CoV-2 pneumonia in which levels of PCT continued to be high despite clinical and laboratory pneumonia recovery. A complete anamnestic investigation and clinical workup, including neck palpation, CTN measurement, and thyroid ultrasound, should be performed if elevated PCT levels persist in the absence of clinical signs of infection. This case suggests that MTC should be ruled out in patients with inflammatory conditions if PCT remains elevated after resolution.

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Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Griebeler ML, Gharib H, Thompson GB. Medullary thyroid carcinoma. *Endocr Pract*. 2013;19(4):703–711.
2. Wells Jr SA, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid*. 2015;25(6):567–610.
3. Hoeboer SH, van der Geest PJ, Nieboer D, Groeneveld ABJ. The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2015;21(5):474–481.
4. Hamade B, Huang DT. Procalcitonin: where are we now? *Crit Care Clin*. 2020;36(1):23–40.
5. U.S. Food and Drug Administration. FDA clears test to help manage antibiotic treatment for lower respiratory tract infections and sepsis. U.S. Food and Drug Administration; 2017. Accessed January 15, 2021. https://www.fda.gov/news-events/press-announcements/fda-clears-test-help-manage-antibiotic-treatment-lower-respiratory-tract-infections-and-sepsis.
6. Schuetz P, Wirz Y, Sager R, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev*. 2017;10(10):CD007498.
7. Giovanella L, Imperiali M, Piccardo A, et al. Procalcitonin measurement to screen medullary thyroid carcinoma: a prospective evaluation in a series of 2705 patients with thyroid nodules. *Eur J Clin Invest*. 2018;48(6), e12934.
8. Trimboli P, Seregni E, Treglia G, Alevizaki M, Giovanella L. Procalcitonin for detecting medullary thyroid carcinoma: a systematic review. *Endocr Relat Cancer*. 2015;22(3):R157–R164.
9. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471–1474.

10. Kováčová M, Filková M, Potočárová M, Kiňová S, Pajvani UB. Calcitonin-secreting pancreatic neuroendocrine tumors: a case report and review of the literature. *Endocr Pract*. 2014;20(8):e140–e144.
11. Borget I, De Pouvourville G, Schlumberger M. Editorial: Calcitonin determination in patients with nodular thyroid disease. *J Clin Endocrinol Metab*. 2007;92(2):425–427.
12. Soh SB, Aw TC. Laboratory testing in thyroid conditions—pitfalls and clinical utility. *Ann Lab Med*. 2019;39(1):3–14.
13. Algeciras-Schimnich A, Preissner CM, Theobald JP, Finseth MS, Grebe SKG. Procalcitonin: a marker for the diagnosis and follow-up of patients with medullary thyroid carcinoma. *J Clin Endocrinol Metab*. 2009;94(3):861–868.
14. Reinhart K, Karzai W, Meisner M. Procalcitonin as a marker of the systemic inflammatory response to infection. *Intensive Care Med*. 2000;26(9):1193–1200.
15. Choi JJ, McCarthy MW. Novel applications for serum procalcitonin testing in clinical practice. *Expert Rev Mol Diagn*. 2018;18(1):27–34.
16. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13(5):426–435.
17. Branche A, Neeser O, Mueller B, Schuetz P. Procalcitonin to guide antibiotic decision making. *Curr Opin Infect Dis*. 2019;32(2):130–135.
18. Sager R, Kutz A, Mueller B, Schuetz P. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. *BMC Med*. 2017;15(1):15.
19. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chim Acta*. 2020;505:190–191.
20. Walter MA, Meier C, Radimerski T, et al. Procalcitonin levels predict clinical course and progression-free survival in patients with medullary thyroid cancer. *Cancer*. 2010;116(1):31–40.