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Effect of Euthyroid Sick Syndrome Development on Prognosis in COVID-19 Patients

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ABSTRACT

Thyroid function tests may deteriorate as a result of coronavirus infection. Low free triiodothyronine (FT3) levels are related to a poor prognosis in patients with coronavirus disease 2019 (COVID-19) presenting with euthyroid sick syndrome (ESS). In this study, it was aimed to examine the mortality and other events that developed in the hospital and within the 2-year follow-up in patients who developed ESS.

In this retrospective study, 170 patients who were hospitalized as a result of COVID-19 were included. The patients were divided into two groups, as those with ESS and those without (non-ESS), according to the reference range of thyroid-stimulating hormone (TSH), FT3, or free thyroxine (FT4) levels. Secondary events that developed during the hospitalization and/or long-term follow-up (mean 24 months) were analyzed from the hospital registry system. Differences in the demographic, radiologic, clinical, and laboratory statistics were also compared.

ESS developed in 97 of a total of 170 patients. Of those, 84 died during hospitalization or within the 2-year follow-up. The FT3 and FT4 hormone levels were significantly lower in the ESS group ($P < 0.001$ for both). The COVID-19-associated mortality ratio was significantly higher in the ESS group ($P < 0.001$). Moreover, the occurrence of acute respiratory distress syndrome and acute renal failure was higher in the ESS group ($P < 0.05$). The frequency of complications, such as acute myocardial infarction, acute heart failure, and atrial fibrillation, was similar between the groups.

The development of ESS with low FT3 levels was associated with disease severity, increased mortality, and risk of complications in COVID-19 patients. The development of ESS is an important prognostic indicator in the course of COVID-19 in long-term follow-up.

Keywords: Euthyroid sick syndrome, Free T3, COVID-19, Mortality

Introduction

Coronavirus disease 2019 (COVID-19) is a contagious infection that first appeared in Wuhan, China and caused a worldwide pandemic (1). The first case in Turkey was detected on March 11th, 2020, and in the events that followed, it caused a pandemic here, as well as all over the world. Coronavirus is a systemic disease that can damage all organs in the human body, especially the respiratory system. Its effects on the immune system are not yet fully understood. It binds to angiotensin-converting enzyme (ACE) II receptors in the mucosa and organs and causes inflammation in the relevant organs. ACE II receptors are expressed in many organs. It is known that there are high levels of ACE II receptors in the thyroid gland (2).

Euthyroid sick syndrome (ESS) is described as low triiodothyronine (T3) and free triiodothyronine (FT3) with normal, low, or inappropriate thyroxine (T4) and free T4 (FT4) and/or thyroid-stimulating hormone (TSH) levels (3). ESS is a temporary decrease in thyroid hormones that can be seen with non-thyroidal systemic diseases and is currently defined as being euthyroid. This variability in thyroid function is proportional to disease prevalence and is associated with poor prognosis in critically ill patients (4).

The effects of COVID-19 on the endocrine system have been shown as similar to its effects on other body systems (5). There are different levels of influence and deterioration on thyroid function tests due to COVID-19 (6, 7). Impairment on thyroid function tests is important in predicting the course of the disease (8). ESS may be a result of COVID-19 infection (9) and these patients face higher rates of morbidity and mortality (10, 11). No studies could be found about the long-term effects of the disease on morbidity and mortality in patients with primary thyroid disease and thyroid involvement that may

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develop due to thyroid involvement. The current study aimed to evaluate whether COVID-19 patients with ESS have a more severe course of the disease, duration of hospitalization, need for oxygen support, or a greater percent of lung involvement, as revealed by computed tomography (CT) scans of the chest. It was also aimed to determine whether they have a higher risk of death and other developing complications. The lengthy 2-year follow-up period of our study is another aspect that sets it apart from other studies.

Materials and Methods

Population and Inclusion Criteria: A total of 334 patients who were followed-up with the diagnosis of COVID-19 in the internal medicine service of Necmettin Erbakan University, Meram Faculty of Medicine and the Internal Medicine Intensive Care Unit, between March 26th and November 28th, 2020, were included in the study. A total of 164 patients were excluded, including 116 patients with missing data, 29 with known hypothyroidism, 11 with known hyperthyroidism, 4 with COVID-19 PCR-negative results, 3 who were pregnant, and 1 with chronic lymphocytic leukemia. Thus, finally, 170 patients were included in the study (Figure 1).

Pregnancy, diagnosed thyroid disease, adrenal and pituitary disease, chronic renal failure, and malignancy, and being <18 and >85 years of age were exclusion criteria for the study. Demographic, laboratory, and imaging data of patients were assessed from hospital records. The patients included in the study were followed-up for 24 months, and events and deaths during the follow-up period were recorded. Thyroid function tests of the patients were the values of the patients without steroid treatment at first visit. Since the majority of the patients received steroid treatment, baseline values unaffected by steroid treatment were included in the study. This study was approved by the Ethics COVID-19 Clinical Board and adhered to the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Necmettin Erbakan University, Meram Medical Faculty Ethics Committee on February 5th, 2021, under approval number 2021/3090.

Laboratory and Radiologic Analysis: At admission, all eligible patients underwent a baseline assessment of thyroidal function, including circulating TSH, FT4, and FT3. Thyroid hormonal panels were assessed using chemiluminescent methods with a Cobas 8000 analyzer series (Roche Diagnostics, Basel, Basel-Stadt, Switzerland). Reference ranges of the thyroidal function tests were: TSH 0.27–4.20 μUI/mL, FT4 0.93–1.7 ng/dL, and FT3 2–4.4 ng/L. In addition to the results of the thyroid function tests, C-reactive protein (CRP), pro-calcitonin, creatinine, aspartate aminotransferase (AST), glucose, hemogram, sodium, potassium, sedimentation, creatinine kinase, creatinine kinase-myocardial band, troponin, and ferritin, D-dimer levels were also recorded.

The degree of lung involvement was determined by classifying the patient's thorax images (such as no lung involvement, minimal involvement, lobar-moderate involvement, and diffuse involvement).

Definition and Outcomes: ESS is defined as low T3 and FT3 with normal, low, or inappropriate T4 and FT4 and/or TSH levels (3). Patients with FT3 levels <2 ng/L were included in the ESS group.

The following events were noted during hospitalization and within the 2-year follow-up: death, acute respiratory distress syndrome (ARDS), acute renal failure (ARF), acute myocardial infarction (AMI), acute heart failure, atrial fibrillation, newly developed diabetes mellitus, newly developed hypertension, cerebrovascular accident, pulmonary thromboembolism, peripheric arterial embolism, subacute thyroiditis, and malignancy.

Statistical Analysis: Data were analyzed with IBM SPSS Statistics for Windows 25.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine whether the variables were normally distributed. Categorical data were expressed as numbers and percentages (%). Numerical variables with parametric distribution were presented as the mean ± standard deviation, and non-parametric distributed numerical variables were presented as the median and interquartile range (IQR: 25th–75th percentile). The chi-square test with Yate's correction was used to compare the categorical variables between two groups. The independent samples t-test and the Mann-Whitney U test were used to compare the numerical variables with and without parametric distribution between the groups. Spearman correlation analysis was performed to identify associations between FT3 and other variables. Receiver operating characteristic (ROC) analysis was used to determine the cut-off value of FT3 associated with mortality. Binary logistic regression analysis was applied to predict factors associated with

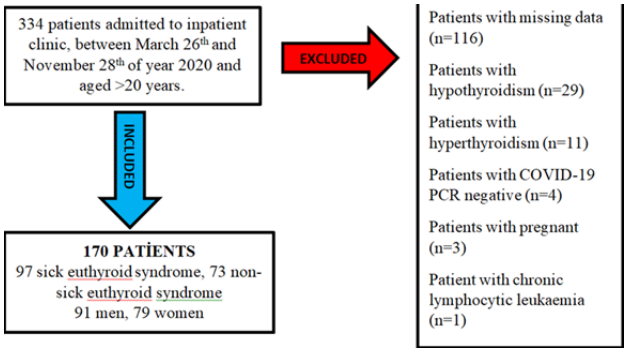

Fig. 1. Flow diagram of the study

mortality. Statistical significance was accepted as P < 0.05.

Results

Patients were divided into two groups according to the free T3 levels. The ESS group included 97 patients and the non-ESS group included 73 patients. The median age was significantly higher in the ESS group (P = 0.030). The groups were similar in gender. The FT3 and FT4 hormone levels were lower in the ESS group, as expected (P < 0.001 for both). Again, the TSH level was lower in the ESS group (P < 0.001) (Table 1).

Laboratory parameters of the groups are presented in Table 2. The glucose, urea, creatinine, AST, lactate dehydrogenase (LDH), CRP, pro-calcitonin, ferritin, D-dimer, neutrophils, and creatinine phosphokinase (CPK) levels were significantly higher in the ESS group (P < 0.05), while the albumin and lymphocyte levels were significantly lower (P < 0.05). No significant differences were found in the other laboratory parameters between the groups (P > 0.05) (Table 2).

The duration of hospitalization was significantly higher in the ESS group. The frequency of associated comorbidity was also higher in the ESS group (P < 0.001), but the number of comorbidities (grouped as 1, 2, 3, or 4 comorbidities) was similar between groups. The frequency of stage 2 lung involvement and non-long involvement was similar between the groups. The number of patients who did not receive O_2 support or received only nasal O_2 was higher in the non-ESS group (P < 0.05). In contrast, the number of patients who received high-flow O_2 or mechanical ventilation support was higher in the ESS group. COVID-19-associated mortality was significantly higher in the ESS group. The frequency of glucocorticoid (GC) use and complications such as ARDS and ARF was higher in the ESS group (P < 0.05). The frequency of

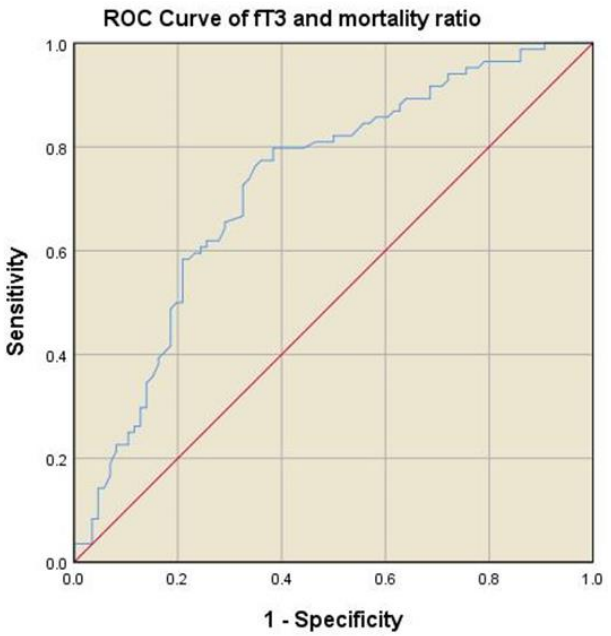

Fig. 2. ROC analysis of FT3 and mortality

complications such as AMI, acute heart failure (AHF), and atrial fibrillation (AF) was similar between the groups. No comparison could be made for other developed comorbidities because of the low number of cases (Table 3).

When all of the patients were included in the correlation analysis, there was a moderate negative correlation between FT3 and the stage of lung involvement (Rho = –0.303, P < 0.001), duration of hospitalization (–0.368, P < 0.001), and mortality (Rho = –0.391, P < 0.001). A strong negative correlation was seen between FT3 and the need for more invasive O_2 support (Rho = –0.419, P < 0.001). A negligible correlation was found between FT3 and complications such as ARDS and ARF. No correlation was found between the other complications and the FT3 level. Table 4 shows the correlation analysis of FT3 with the other variables (Table 4).

In the ESS group, FT3 was not correlated with lung involvement, the need for more invasive O_2 support, mortality, ARDS, ARF, or other complications. Therefore, there was a weak negative correlation between the FT3 level and the duration of hospitalization (Table 5).

The ROC analysis between FT3 and mortality revealed that the cut-off value of FT3 (area under the ROC curve (AUC) = 0.0726, CI: 0.649–0.803, P < 0.001) predicted mortality with 82.1% sensitivity and 50.0% specificity was 2.16 (Table 6, Figure 2).

The binary logistic regression analysis revealed that age (OR = 747.081, P = 0.03), FT3 (OR = 0.051, P = 0.012), creatinine (OR = 0.031, P =

Table 1. Demographic Features and Thyroid Function Tests of the Groups

		non-ESS (n = 73)	ESS (n = 97)	P-value
		Median (IQR: 25th–75th percentile) or mean ± SD		
Age		62.50 (51.25–73.00)	68.5 (61.0–75.8)	0.030
Sex (n/%)	Female	36 (49.3)	43 (44.3)	0.538
	Male	37 (50.7)	54 (55.7)	
FT3		2.46 ± 0.34	1.5 ± 0.35	0.001
FT4		1.43 ± 0.34	1.19 ± 0.35	0.001
TSH		1.35 (0.60–2.30)	0.63 (0.29–1.37)	0.001

The all values are presented as the mean ± SD or median (minimum–maximum)
ESS euthyroid sick syndrome, FT3 free triiodothyronine, FT4 free thyroxine, TSH thyroid-stimulating hormone

Table 2. Comparison of the Laboratory Parameters of the Groups

	non-ESS (n = 73)	ESS (n = 97)	P-value
	Median (IQR: 25th–75th percentile) or mean ± SD		
Glucose (mg/dL)	117.0 (98.0–152.0)	159.9 (117.8–246.3)	0.001
Urea (mg/dL)	34.0 (24.9–47.4)	53.5 (35.0–83.1)	0.001
Creatinine (mg/dL)	0.9 (0.8–1.19	1.0 (0.8–1.5)	0.045
AST (IU/L)	24.0 (17.0–39.9)	31.9 (21.0–45.5)	0.025
ALT (IU/L)	22.3 (13.0–32.5)	22.9 (15.4–37.0)	0.355
LDH (IU/L)	284.5 (221.8–404.5)	400.0 (301.8–562.5)	0.001
Sodium (mEq/L)	136.0 (133.0–138.8)	136.0 (132.3–139.0)	0.912
Potassium (mEq/L)	4.2 (4.0–4.6)	4.2 (3.8–4.6)	0.541
Albumin (mg/dL)	37.5 (32.5–40.0)	32.4 (28.1–36.9)	0.001
CRP (mg/dL)	35.9 (10.7–118.9)	73.6 (32.2–138.8)	0.001
Sedimentation (mm/h)	46.5 (28.0–73.8)	50.0 (28.0–63.3)	0.995
Pro-calcitonin (µg/L)	0.10 (0.05–0.22)	0.31 (0.12–1.07)	0.001
Ferritin (ng/mL)	341.9 (149.9–691.1)	546.2 (240.0–1056.3)	0.010
D-dimer (ng/mL)	320.5 (161.3–630.8)	541.0 (278.0–1039.5)	0.010
Fibrinogen (mg/dL)	436.0 (321.0–534.0)	440.5 (301.3–592.3)	0.604
Troponin (µg/L)	0.1 (0.1–0.1)	0.1 (0.1–0.2)	0.050
CPK (U/L)	63.0 (36.3–119.3)	90.5 (46.0–153.3)	0.046
CK-MB (µg/L)	1.3 (0.8–2.7)	1.6 (1.0–3.1)	0.052
WBC (mm3)	7555 (5225–10390)	8620 (6100–11722)	0.067
Neutrophile (mm3)	5590 (3347–8100)	7350 (4720–9887)	0.001
Lymphocyte (mm3)	1140 (822–1705)	845 (535–1145)	0.001
HGB (g/dL)	12. 6 (10.9–14.0)	11.7 (9.9–13.7)	0.140
PLT (mm3)	219500 (151000–306250)	200000 (144250–277750)	0.189
PCT (%)	22.6 (16.2–30.0)	21.7 (15.0–29.4)	0.256

The all values are presented as the mean ± SD or median (minimum–maximum).
IQR interquartile range, AST aspartate aminotransferase, ALT alanine aminotransferase, LDH lactate dehydrogenase, CRP c-reactive protein, CPK creatinine phosphokinase, CK-MB creatinine kinase-myocardial band, WBC white blood cell, HGB hemoglobin, PLT platelet, PCT plateletcrit

0.018), ferritin (OR = 0.958, P = 0.032), CPK (OR = 0.989, P = 0.034), HGB (OR = 0.187, P = 0.027), and PLT (OR = 0.948, P = 0.015) count, and GC use (OR = 0.057, P < 0.001) were inversely associated with mortality, while the D-dimer level (OR = 1.006, P = 0.019), neutrophil (OR = 392.881, P = 0.016), and lymphocyte (OR = 374.972, P = 0.012) count and mechanic

Table 3. Comparison of the Clinical Features of the Groups

		non-ESS (n = 73)	ESS (n = 97)	P-value
		Median (IQR: 25th–75th percentile)		
Duration of hospitalization (days) (median: IQR)		13.0 (6.0–18.8)	17.0 (10.3–27.8)	0.001
		N (%)		
Number of comorbidities	0	23 (31.5)	12 (12.3)	0.010
	1	24 (32.9)	31 (32.0)	
	2	18 (24.7)	32 (33.0)	
	3	7 (9.6)	16 (16.5)	
	4	1 (1.4)	6 (6.2)	
Lung involvement on CT	None	22 (30.1)	17 (17.5)	0.001
	Minimal	29 (39.7)	22 (22.7)	
	Moderate	19 (26.0)	26 (26.8)	
	Diffuse	3 (4.1)	32 (33.0)	
O_2 support	None	28 (38.4)	11 (11.3)	0.001
	Nasal O_2	25 (34.2)	20 (20.6)	
	High-flow	6 (8.2)	19 (19.6)	
	Non-invasive ventilation	2 (2.7)	10 (10.3)	
	Mechanic ventilation	11 (15.1)	37 (38.1)	
GC treatment		20 (27.4)	58 (59.8)	0.001
Tocilizumab treatment		-	5 (5.2)	
Mortality		19 (26.0)	65 (67.0)	0.001
Cause of mortality	COVID-19	18 (24.7)	58 (59.8)	0.001
	Other	1 (1.4)	7 (7.2)	
Developing complications				
ARDS		8 (11.0)	25 (25.8)	0.019
ARF		16 (21.9)	38 (39.2)	0.020
AMI		3 (4.1)	8 (8.2)	0.454
AHF		4 (5.5)	6 (6.2)	0.846
AF		4 (5.5)	4 (4.19)	0.962
DM		1 (1.4)	12 (12.4)	0.010
HT		1 (1.4)	1 (1.0)	
CVA		1 (1.4)	5 (5.2)	
PTE		1 (1.4)	5 (5.2)	
PAE		1 (1.4)	-	
SAT		1 (1.4)	-	
Malignity		2 (2.7)	4 (4.1)	

The all values are presented as the mean ± SD or median (minimum–maximum).

CT computed tomography, ARDS acute respiratory distress syndrome, ARF acute renal failure, AMI acute myocardial infarction, AHF acute heart failure, AF atrial fibrillation, DM newly developed diabetes mellitus, HT newly developed hypertension, CVA cerebrovascular accident, PTE pulmonary thromboembolism, PAE peripheric arterial embolism, SAT subacute thyroiditis.

Table 4. Correlation Analysis of FT3 With Mortality-associated Variables and Complications in the all of the Patients (n = 170)

		Lung involvement	Duration of hospitalization	Need for O_2 support	Mortality	ARDS	ARF
FT3	Rho	–0.303	–0.368	–0.419	–0.391	–0.167	–0.176
	P Value	0.001	0.001	0.001	0.001	0.029	0.021

Table 5. Correlation Analysis of FT3 with Mortality-Associated Variables and Complications in the Ess Patients (n = 97)

		Lung involvement	Duration of hospitalization	Need for O_2 support	Mortality	ARDS	ARF
FT3	Rho	–0.005	–0.211	–0.113	–0.089	–0.003	–0.042
	P-value	0.958	0.038	0.272	0.389	0.977	0.684

Table 6. Results of the ROC Analysis of FT3 and Mortality

Risk factor	AUC (95% CI)	Cut off According to Youden's Index	P-value	Sensitivity (%)	Specificity (%)
FT3	0.726 (0.649–0.803)	2.16	<0.001	82.1	50.0

ventilation support (OR = 6883.438, P = 0.010) were positively associated with mortality for all of the patients. Gender, FT4, TSH, glucose, ALT, LDH, albumin, sedimentation, CRP, pro-calcitonin, fibrinogen, stage of pulmonary involvement on CT, other types of O_2 support, and duration of hospitalization were not associated with mortality (P > 0.05).

Discussion

The main finding of the study was that the mortality rates were significantly higher in the group of patients who developed ESS with low FT3, FT4, and TSH. In addition, lung involvement, length of hospitalization, oxygen requirement, and development of ARDS and ARF were observed at a higher rate in the ESS group. Based on the present findings, low FT3 (i.e., < 2.16 ng/L) results are strongly associated with an unfavorable outcome and with a high risk of death in hospitalized COVID-19 patients. Mortality rates were observed to be high because our study included a lengthy 2-year follow-up period.

ACE 2 and transmembrane protease serine 2, which are the receptors that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus binds to the most in the body, are found in many endocrine organs, including the thyroid, pituitary, and hypothalamus (5). For this reason, thyroid diseases and other endocrine disorders can occur during the course of COVID-19. SARS-CoV-2 can cause thyroid damage and thyroiditis, directly affecting the thyroid gland (12–14). In addition to these, it has been reported that ESS, also known as non-thyroidal illness syndrome, progresses with low FT3 and TSH levels and typically develops due to systemic inflammation (15). ESS, with temporary changes in thyroid function, can be seen together with probably any severe illness (16). It has been shown that the development of ESS in critical illness affecting any organ system is associated with poor prognosis (17, 18). Numerous factors have been identified as contributing to the development of ESS. One of them is an increase in cytokine levels, like interleukin-6 (19). The term "cytokine storm" refers to an overactive immune response with a significant release of inflammatory cytokines and chemokines, whose plasmatic levels appear to be related to the severity of COVID-19 (20).

ESS and other thyroidal disorders due to COVID-19 have been revealed in some studies. Sparano et al. prospectively evaluated 506 COVID-19 patients with mild disease at hospital admission. They found that low FT3 levels were associated with poor prognosis in patients with mild SARS-CoV-2 (21). Our study differed from theirs, in that there were patients with not only mild disease but also included moderate and severe disease, and a long follow-up period of 2 years. In a study of 100 severe COVID-19 patients, reduced FT3 levels were found to be an independent predictor of all

causes of death (22). In a study of 367 mild to moderate COVID-19 patients, the development of ESS was not infrequent and could predict clinical deterioration (23). The reason why the development of ESS was found to be high in our patient group is that the patients were treated in a tertiary hospital that included the moderate-severe COVID-19 patient group compared to other studies, and the long follow-up period. Low FT3 levels were linked to an increased risk of in-hospital mortality in a study involving 127 patients (24). The severity of the disease and inflammatory markers were observed to be related to the development of ESS in COVID-19 patients (25). It was observed that the TSH, T3 and T4 levels returned to normal levels with the improvement of the disease without any treatment (15).

In addition to hypothyroidism, COVID-19 can lead to hyperthyroidism in patients with Graves' disease (26). It has also been found that those with thyroid disease have severe COVID-19 infection (27). The benefits of T3 replacement treatment for COVID-19 patients are unknown. Even though studies on the topic have begun, they the results remain unclear (28).

According to our study results, low FT3 levels in hospitalized COVID-19 patients are prognostic indicators for mortality and other poor outcomes. Evaluating thyroid function in COVID-19 patients can be easily accessed in prognosis assessment and can be used as an independent indicator of prognosis together with other risk assessment parameters. Serial measurement of thyroid function in these patients can provide clinicians with powerful information regarding prognosis and treatment approaches. The long-term impact on prognosis may be better understood with a longer follow-up of COVID-19 patients who develop ESS.

Limitations: This study had some limitations. First, it had a relatively small sample size and included a single-center experience. There were no tests for particular antibodies, thyroid ultrasounds, or measurements of reverse T3 levels.

Compliance with Ethical Standards

Conflict of Interest: On behalf of all of the authors, the corresponding author states that there are no conflicts of interest.

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Approval of ethics committee: Necmettin Erbakan University, Meram Medical School Ethics Committee approved the study under approval no. 2021/3090 and dated 05.02.2021.

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