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Association among CO-RADS score, co-morbid diseases, and short-term prognosis in COVID-19 infection

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Abstract. – OBJECTIVE: CO-RADS scoring system is used as a diagnostic tool. However, the data about its association with co-morbid diseases and effectiveness in predicting intensive care need and short-term mortality are lacking. In our study, we aimed to investigate the association among CO-RADS score, co-morbid diseases, intensive care need, and 28-day-mortality.

PATIENTS AND METHODS: The study included 665 patients with COVID-19 infection suspicion between 30 May 2020 and 30 October 2020.

RESULTS: The sensitivity of CT was 77%, and specificity was 52%. A higher CT score was associated with the rate of positive PCR test results (p<0.001), and older patients had higher CO-RADS scores than younger patients (p<0.001). Hypertension (OR: 7.956; p=0.005) and diabetes mellitus (OR: 5.902; p=0.015) were associated with significantly higher CO-RADS scores. Most patients treated in the intensive care unit (ICU) had a CO-RADS score of 5. The CO-RADS score was 4 and above in 115 (89.2%) patients who were transferred to the intensive care unit due to worsening of clinical condition (p<0.001). The 28-day mortality was significantly higher in patients with a CO-RADS score of 4 and above than in patients with a score of 3 and below (97.3% *vs*. 2.7%) (p<0.001).

CONCLUSIONS: Irrespective of PCR results, a higher CO-RADS score gives us useful information about ICU need or mortality risk and alerts us for early treatment to reduce the risk of further transmission, intensive care need, and mortality particularly in patients with co-morbid diseases.

Key Words:
COVID-19, CO-RADS score, Co-morbid diseases, Intensive care, Mortality.

Introduction

Since late 2019, the world has been struggling with COVID-19, first identified as the causative agent after the emergence of pneumonia cases of unknown origin in China and then spreading rapidly to the rest of the world, including the USA[1-3]. The number of cases worldwide has reached more than 213 million, with approximately 4,5 million deaths[4].

We know that the virus affects many systems in the body, especially the immune, cardiovascular, respiratory, gastrointestinal, and central nervous systems, and it may cause sudden deterioration in liver and kidney functions that may result in death[5-7]. Great progress has been made regarding vaccines, but there are concerns about their long-term effects and safety [8]. Even if it is asymptomatic or mildly symptomatic, early diagnosis is still crucial to prevent the spread and disease progression[9]. Due to the possibility that clinical examination and polymerase chain reaction (PCR) may not detect less symptomatic patients, evaluation with computed tomography (CT) within a certain systematic framework is more valuable when used in combination to diagnose the patient, and it reduces the possibility of misdiagnosis[10,11].

The COVID-19 Reporting And Data System (CO-RADS) has been shown to provide excellent performance in the diagnostic algorithm for COVID-19; the inter-observer agreement was moderate to significant[12].

Studies are investigating the diagnostic performance of the CO-RADS scoring system in

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COVID-19 infection-suspected adults, but limited data about its association between co-morbid diseases and effectiveness to predict prognosis in COVID-19 diagnosed adults.

Patients and Methods

Study Design and Clinical Parameters

This retrospective study was approved by the Adiyaman University Ethics Committee (Decision number: 2020/7-32). The study included 665 patients admitted to Besni State Hospital and Gölbasi State Hospital (Adiyaman, Turkey) between May 30, 2020, and October 30, 2020. Clinical and medical history and radiological data were retrospectively obtained through the electronic patient database.

Patients who exhibited signs and symptoms of acute respiratory disease or clinical symptoms that could not be explained by any other cause/disease were included; individuals with symptoms, who had spent more than 15 minutes with or had been less than one meter apart from COVID-19-positive patients were also included. Patients who were asymptomatic, pregnant, and younger than 18 years of age were excluded.

A combination of nasopharyngeal and oropharyngeal swabs was taken. PCR results were considered the reference standard.

Thorax Computed Tomography Imaging

All patients were imaged at presentation with multidetector computer tomography (CT) using the TOSHIBA Alexion/Advance Edition (Toshiba Medical Systems Corporation, Ōtawara, Tochigi, Japan, 1.25 mm section thickness) with 64-detector rows. All scans were acquired without an intravenous contrast agent, with the patient in a supine position during end inspiration. CT indications were as follow: test negative on RT-PCR with normal/indeterminate chest X-ray but have moderate-to-severe respiratory symptoms and high index of clinical suspicion, COVID-19 patients showing unexplained clinical deterioration and/or where other concurrent lung pathology needs exclusion, COVID-19-positive patients with associated co-morbidities (age >65 year, diabetes, hypertension, obesity, cardiovascular disease, chronic respiratory disease, immune-compromise, etc.) who, despite having mild symptoms and normal/indeterminate CXR, record oxygen saturation of <93 percent at rest while breathing room air or de-saturate on six-minute walk test.

Image Evaluation with CO-RADS, the Coronavirus Disease 2019 (COVID-19) Reporting and Data System

Two experienced cardiothoracic radiologists reviewed the CT examinations retrospectively. Reviewers were blinded to symptom status and the PCR results of patients. The CO-RADS classification system was used to categorize the level of COVID-19 suspicion. According to that system, the degree of suspicion is classified into five levels from very low (CO-RADS 1) to very high (CO-RADS 5). The CO-RADS levels are summarized as follows: CO-RADS 1 (no suspicion: normal findings); CO-RADS 2 (low level of suspicion: absence of ground-glass opacities [GGO], the presence of tree-in-bud signs or endobronchial spread or bronchiolitis); CO-RADS 3 (indeterminate: unifocal GGO); CO-RADS 4 (high level of suspicion: unilateral multifocal GGO); and CO-RADS 5 (very high level of suspicion: multifocal bilateral GGO) (Figure 1).

Patients with a CO-RADS score of 1 were considered negative, and those with a CO-RADS score of 2 and above were considered positive CT findings.

Statistical Analysis

Statistical analyses were applied using NCSS 12 (NCSS, LLC. Kaysville, UT, USA) and SPSS 23 (SPSS Inc., Chicago, IL, USA) statistical software for Windows. The distribution of data was examined using the Kolmogorov-Smirnov test. Continuous variables, having normal distribution or not, were presented as mean ± standard deviation or median (quartile deviation), respectively. Categorical variables were demonstrated as percentages.

Using PCR results as the reference, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of chest CT imaging were determined. Confidence intervals were calculated by the Wilson score method.

In the comparison of CT-PCR groups and CO-RADS score groups, the Chi-square and the Kruskal-Wallis tests were used. The chi-square test was also used with post hoc test in the comparison of low CO-RADS score (<3) and high CO-RADS score (>4).

Additionally, effects of chronic diseases and symptoms, which found out significant, on the event of CT+, PCR+ were examined with forward stepwise binomial logistic regression analyses. In the analyses, patients with CT-, PCR- was set

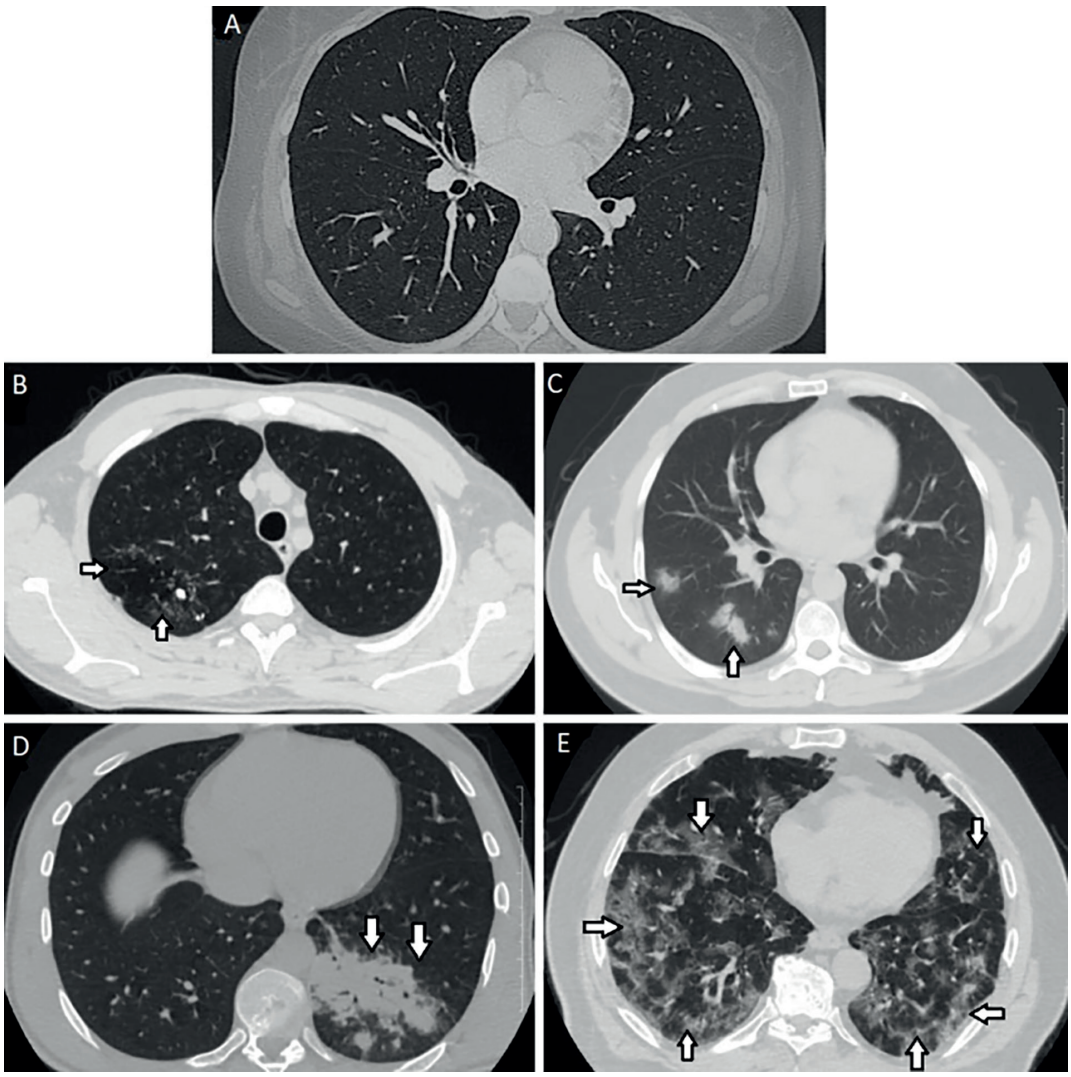

Figure 1. CT Images of COVID-suspected patients. **A,** CT image of a 28-year-old mildly symptomatic patient (CO-RADS 1). **B,** CT image of a 35-year-old patient with complaint of dry cough showing centrilobular nodular infiltration in the posterior segment of the upper lobe of the right lung and accompanying tree-in-bud sign (CO-RADS 2)**. C,** CT image of a 45-year-old patient with hypertension showing focal consolidation in the right lung lower lobe superior segment with surrounding ground-glass opacities (CO-RADS 3). **D,** CT image of a 65-year-old patient with diabetes mellitus showing multifocal consolidation in the left lung lower lobe superior segment with surrounding ground-glass opacities (CO-RADS 4). **E,** CT image of a 72-year-old patient with a history of coronary artery disease showing bilateral multifocal patched ground-glass opacities (CO-RADS 5).

as the reference category (because of their conflicting results CT+, PCR- and CT-, PCR+ groups were eliminated in these analyses). Similarly, the effects of significant chronic diseases and symptoms on CO-RADS score were examined with forward stepwise ordinal logistic regression analyses. In ordinal logistic regression analyses, CO-RADS score 1 was set as the reference category.

In all analyses, two-tailed $p < 0.05$ was accepted statistically significant (except for the table where Bonferroni adjustment was used).

Results

Basic Demographic Profile

Table I provides data about the characteristics of the 665 patients included in this study. The age of patients ranged from 20 to 95 (median, IQR; 55, 37-68) with 359 (54%) males and 306 (46 %) females. All clinically COVID-19 infection suspected patients underwent PCR tests at least one time. PCR test results were positive in 225 (33.8%) and negative in 440 (66.2%) patients.

Table I. Patient demographics and baseline characteristics.

	All (n = 665)	Control: CT-, PCR- (n = 230)	CT+, PCR- (n = 210)	CT-, PCR+ (n = 52)	CT+, PCR+ (n = 173)	*p*-value
Age (years)	55 (15.75)	49 (20)	59 (13.63)	36.5 (12.75)	55.54 ± 15.64	[a]< 0.001*
Sex (n, %)						
Female	306 (46%)	92 (40%)	105 (50%)	25 (48.1%)	84 (48.6%)	[b]0.156
Male	359 (54%)	138 (60%)	105 (50%)	27 (51.9%)	89 (51.4%)	
Smoking (n, %)	291 (43.8%)	108 (47%)	87 (41.4%)	18 (34.6%)	78 (45.1%)	[b]0.346
Comorbidity (n, %)						
Hypertension	227 (34.1%)	66 (28.7%)	75 (35.7%)	5 (9.6%)	81 (46.8%)	[b]< 0.001*
Diabetes Mellitus	97 (14.6%)	21 (9.1%)	35 (16.7%)	2 (3.8%)	39 (22.5%)	[b]< 0.001*
Asthma	29 (4.4%)	5 (2.2%)	7 (3.3%)	2 (3.8%)	15 (8.7%)	[b]0.012*
COPD	82 (12.3%)	27 (11.7%)	35 (16.7%)	1 (1.9%)	19 (11%)	[b]0.026*
CAD	78 (11.7%)	13 (5.7%)	30 (14.3%)	3 (5.8%)	32 (18.5%)	[b]< 0.001*
Heart Failure	63 (9.5%)	11 (4.8%)	25 (11.9%)	3 (5.8%)	24 (13.9%)	[b]0.007*
CKD	51 (7.7%)	11 (4.8%)	19 (9%)	1 (1.9%)	20 (11.6%)	[b]0.024*
Cancer	7 (1.1%)	2 (0.9%)	3 (1.4%)	-	2 (1.2%)	[b]0.941
Intensive care (n, %)	103 (15.5%)	-	53 (25.2%)	1 (1.9%)	49 (28.3%)	[b]< 0.001*
Symptom (n, %)						
Fever	253 (38%)	31 (13.5%)	115 (54.8%)	2 (3.8%)	105 (60.7%)	[b]< 0.001*
Cough	581 (87.4%)	198 (86.1%)	180 (85.6%)	47 (90.4%)	156 (90.2%)	[b]0.464
Shortness of breath	311 (46.8%)	105 (45.7%)	113 (53.8%)	9 (17.3%)	84 (48.6%)	[b]< 0.001*
Tiredness	255 (38.3%)	33 (14.3%)	102 (48.6%)	19 (36.5%)	101 (58.4%)	[b]< 0.001*
Headache	93 (14%)	11 (4.8%)	39 (18.6%)	8 (15.4%)	35 (20.2%)	[b]< 0.001*
Myalgia	124 (18.6%)	21 (9.1%)	56 (26.7%)	12 (23.1%)	35 (20.2%)	[b]< 0.001*
Diarrhea	20 (3%)	6 (2.6%)	9 (4.3%)	1 (1.9%)	4 (2.3%)	[b]0.615
Loss of smell	22 (3.3%)	4 (1.7%)	8 (3.8%)	3 (5.8%)	7 (4%)	[b]0.360
Loss of taste	20 (3%)	7 (3%)	6 (2.9%)	2 (3.8%)	5 (2.9%)	[b]0.985

Abbreviations: [a] Kruskal-Wallis Test; [b]Chi-square Test; *Means statistically significant; COPD: Chronic Obstructive Pulmonary Disease; CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease.

Of patients, 291 (43.8%) were smokers and 183 (27.5%) of them were evaluated as positive according to PCR and/or CT test results. In terms of comorbid diseases, 227 (34.1%) patients had hypertension, 97 (14.6%) diabetes mellitus, 29 (4.4%) asthma, 82 (12.3%) COPD, 78 (11.7%) CAD, 63 (9.5%) heart failure, 51 (7.7%) CKD, and 7 (1.1%) cancer. Clinical presentations included fever (n=253; 38%), cough (n=581; 87.4%), shortness of breath (n=311;46.8%), tiredness (n=255; 38.3%), headache (n=93; 14%), myalgia (n=124; 18.6%), diarrhea (n=20; 3%), loss of smell (n=22; 3.3%) and loss of taste (n=20; 3%). One-hundred-three (15.5%) patients needed intensive care.

PCR test and CO-RADS Score Characteristics

Of patients, 230 (34.5 %) had negative PCR results with negative CT findings, 210 (31.5 %) negative PCR results with positive CT findings, 52 (7.8%) positive PCR test results with negative CT findings, 173 (26.2%) positive PCR test result and positive CT findings. As we used PCR as the reference test, the sensitivity of CT was 77% and specificity was 52% (Table II).

Table III provides the data of the patients evaluated with the CO-RADS scoring system and grouped according to their scores. Patients with higher CT scores had a significantly higher rate of positive PCR test results (p<0.001) and older patients had higher CO-RADS scores than younger patients (p<0.001).

In our study, we evaluated the patients with negative CT and PCR tests as the control group, and found that the likelihood of both CT (score 2 and above) and PCR being positive was significantly higher in patients with diabetes mellitus (OR:2.207; 95% CI, 1.207-4.038, p=0.010), asthma (OR: 3.968; 95% CI, 1.379-11.409, p=0.011) and CAD (OR:3.100; 95% CI, 1.530-6.275, p=0.002). Similarly, fever (OR:9.217; 95% CI, 5.334-15.924, p<0.001), tiredness (OR:6.247; 95% CI, 3.622-10.771, p<0.001), headache (OR:6.011; 95% CI, 2.588-13.968, p<0.001), and myalgia (OR:2.433; 95%

Table II. The performance of chest CT for COVID-19 infection with RT-PCR result as reference.

	Results (n)				Diagnostic Performance (%)				
	TP	TN	FP	FN	Sensitivity [95% CI]	Specificity [95% CI]	PPV [95% CI]	NPV [95% CI]	Accuracy [95% CI]
Overall	173	230	210	52	0.77 [71, 82]	0.52 [47, 57]	0.45 [40, 50]	0.82 [77, 86]	0.61 [57, 64]

TP: True Positive, TN: True Negative, FP: False Negative, FP: False Positive, PPV: Positive Predictive Value, NPV: Negative Predictive Value, CI: Confidence Interval.

CI, 1.192-4.965, p=0.015) were associated with the likelihood of both positive CT and PCR test results (Table IV).

CO-RADS Score, Symptoms and Co-Morbid Diseases

As symptoms, fever, shortness of breath, tiredness, headache, and myalgia were more frequently seen in patients with higher CO-RADS scores. Patients with hypertension (p<0.001), diabetes mellitus (p<0.001), coronary artery disease (p<0.001), heart failure (p=0.001), chronic kidney disease (p<0.001) had higher CO-RADS scores, and it was statistically significant. Gender, smoking status, asthma, COPD, and cancer were not associated with higher CO-RADS scores (Table III).

As seen in Table V, the presence of hypertension (OR:1.604; 95% CI, 1.155-2.231, p=0.005) and diabetes mellitus (OR:1.716; 95% CI, 1.111-2.651,

Table III. Demographic and clinical characteristics of 665 patients according to CO-RADS Score.

	CO-RADS 1 (n = 282)	CO-RADS 2 (n = 30)	CO-RADS 3 (n = 82)	CO-RADS 4 (n = 92)	CO-RADS 5 (n = 179)	*p*-value
PCR + (n, %)	52 (18.4%)	15 (50%)	40 (48.8%)	35 (38%)	83 (46.4%)	[b]< 0.001*
Age (years)	44 (19)	46.43±23.2	48.83±17.6	55.76±15.84	62 (20)	[a]< 0.001*
Sex (n, %)						
Female	117 (41.5%)	13 (43.3%)	38 (46.3%)	43 (46.7%)	95 (53.1%)	[b]0.197
Male						
Smoking (n, %)	126 (44.7%)	10 (33.3%)	44 (53.7%)	43 (46.7%)	68 (38%)	[b]0.114
Comorbidities (n, %)						
Hypertension	71 (25.2%)	7 (23.3%)	27 (32.9%)	33 (35.9%)	89 (49.7%)	[b]< 0.001*
Diabetes Mellitus	23 (8.2%)	3 (10%)	15 (18.3%)	11 (12%)	45 (25.1%)	[b]< 0.001*
Asthma	7 (2.5%)	-	4 (4.9%)	6 (6.5%)	12 (6.7%)	[b]0.121
COPD	28 (9.9%)	4 (13.3%)	12 (14.6%)	14 (15.2%)	24 (13.4%)	[b]0.519
CAD	16 (5.7%)	5 (16.7%)	8 (9.8%)	12 (13%)	37 (20.7%)	[b]< 0.001*
Heart Failure	14 (5%)	2 (6.7%)	7 (8.5%)	10 (10.9%)	30 (16.8%)	b0.001*
CKD	12 (4.3%)	-	8 (9.8%)	4 (4.3%)	27 (15.1%)	[b]< 0.001*
Cancer	2 (0.7%)	-	1 (1.2%)	-	4 (2.2%)	[b]0.457
Intensive care (n, %)	1 (0.4%)	-	18 (22%)	18 (19.6%)	66 (36.9%)	[b]< 0.001*
Shift to intensive care (n, %)	-	2 (1.5%)	12 (9.3%)	29 (22.5%)	86 (66.7%)	[b]< 0.001*
Death (n, %)	-	-	1 (2.7%)	2 (5.4%)	34 (91.9%)	[b]< 0.001*
Symptom (n, %)						
Fever	33 (11.7%)	6 (20%)	43 (52.4%)	47 (51.1%)	124 (69.3%)	[b]< 0.001*
Cough	245 (86.9%)	28 (96.6%)	77 (93.9%)	80 (87%)	150 (83.8%)	[b]0.111
Shortness of breath	114 (40.4%)	12 (40%)	44 (53.7%)	39 (42.4%)	102 (57.7%)	[b]0.005*
Tiredness	52 (18.4%)	13 (43.3%)	42 (51.2%)	46 (50%)	102 (57%)	[b]< 0.001*
Headache	19 (6.7%)	5 (16.7%)	11 (13.4%)	18 (19.6%)	40 (22.3%)	[b]< 0.001*
Myalgia	33 (11.7%)	5 (16.7%)	21 (25.6%)	26 (28.3%)	39 (21.8%)	[b]0.001*
Diarrhea	7 (2.5%)	1 (3.3%)	1 (1.2%)	5 (5.4%)	6 (3.4%)	[b]0.495
Loss of smell	7 (2.5%)	-	4 (4.9%)	5 (5.4%)	6 (3.4%)	[b]0.477
Loss of taste	9 (3.2%)	-	4 (4.9%)	3 (3.3%)	4 (2.2%)	[b]0.744

Abbreviations: [a]Kruskal-Wallis Test; [b]Chi-square Test; *Means statistically significant; COPD: Chronic Obstructive Pulmonary Disease; CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease.

Table IV. The binomial logistic regression analysis results of the factors for being both positive RT-PCR and CT.

	β estimates with standard errors	Odds Ratio [95% CI]	[c]*p*-value
Diabetes Mellitus (β_1)	0.792 ± 0.308	2.207 [1.207-4.038]	0.010*
Asthma (β_2)	1.378 ± 0.539	3.968 [1.379-11.409]	0.011*
CAD (β_3)	1.131 ± 0.360	3.100 [1.530-6.275]	0.002*
Fever (β_1)	2.221 ± 0.279	9.217 [5.334-15.924]	< 0.001*
Tiredness (β_2)	1.832 ± 0.278	6.247 [3.622-10.771]	< 0.001*
Headache (β_3)	1.794 ± 0.430	6.011 [2.588-13.968]	< 0.001*
Myalgia (β_4)	0.889 ± 0.364	2.433 [1.192-4.965]	0.015*

Abbreviations: [c]Binomial logistic regression analysis; *Means statistically significant; CAD: Coronary Artery Disease; CI: Confidence Interval.

p=0.015) were particularly correlated with higher CO-RADS scores. Similarly, patients with symptoms of fever (OR: 7.071; 95% CI, 5.107-9.790, *p*<0.001), shortness of breath (OR:1.597; 95% CI, 1.178-2.164, *p*=0.002), tiredness (OR:2.746; 95% CI, 2.010-3.750, *p*<0.001), and headache (OR:2.757; 95% CI, 1.781-4.268, *p*<0.001) were correlated with higher CO-RADS score.

The data of PCR negative patients categorized according to their CT score were presented in Table VI. There were 210 patients with PCR negative but positive CT findings. In that group, age (*p*=0.001), CAD (*p*=0.008), heart failure (*p*=0.009), and CKD (*p*=0.010) were significantly associated with higher CO-RADS scores. As symptoms, fever (*p*=0.001), headache (*p*=0.001), myalgia (*p*=0.001) were associated with higher CO-RADS scores.

CO-RADS Score and Prognosis

The hospitalization rate was significantly higher in the high score group (CO-RADS≥4). Most of the patients treated in the ICU had a CO-RADS score of 5 and even almost all of them had a score of 3 and above, which was statistically significant (*p*<0.001). As seen in Table VII, the CO-RADS score was 4 and above (high score) in 115 (89.2%) patients who did not need intensive care at the first hospitalization and were transferred to the ICU due to worsening of clinical condition (*p*<0.001). Similarly, the 28-day mortality was significantly higher in patients with a CO-RADS score of 4 and above than in patients with a score of 3 and below (97.3% *vs.* 2.7%, *p*<0.001). The causes of death in all patients were respiratory system and multiorgan failure.

Discussion

According to our study, CO-RADS scoring provides important information about the need for intensive care and the prognosis of patients, regardless of the PCR result. Individuals with comorbid diseases, particularly diabetes and hypertension had higher scores on CT imaging. Pulmonary involvement was more likely in patients with diabetes, asthma, and CAD. Therefore, such diseases indirectly caused the need for

Table V. Ordinal logistic regression analysis results of risk factors associated with higher CO-RADS score.

	β estimates with standard errors	Odds Ratio [95% CI]	[d]*p*-value
Hypertension (β_1)	0.473 ± 0.168	1.604 [1.155-2.231]	0.005*
Diabetes Mellitus (β_2)	0.540 ± 0.222	1.716 [1.111-2.651]	0.015*
CAD (β_3)	0.483 ± 0.302	1.621 [0.897-2.930]	0.109
Heart Failure (β_4)	0.163 ± 0.332	1.177 [0.614-2.256]	0.623
CKD (β_5)	0.441 ± 0.298	1.554 [0.867-2.787]	0.139
Fever (β_1)	1.956 ± 0.166	7.071 [5.107-9.790]	< 0.000*
Shortness of breath (β_2)	0.468 ± 0.155	1.597 [1.178-2.164]	0.002*
Tiredness (β_3)	1.010 ± 0.159	2.746 [2.010-3.750]	< 0.000*

Abbreviations: [d]Ordinal logistic regression analysis; *Means statistically significant; CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease; CI: Confidence Interval.

Table VI. Demographic and clinical characteristics of RT-PCR negative patients according to CO-RADS Score.

	CO-RADS 1 & PCR - (n = 230)	CO-RADS 2 & PCR - (n = 15)	CO-RADS 3 & PCR - (n = 42)	CO-RADS 4 & PCR - (n = 57)	CO-RADS 5 & PCR (n = 96)	*p*-value
Age (years)	49 (20)	65 (14.35)	49±20.32	56 (12.25)	63.5 (10.5)	[a]0.001*
Sex (n, %)						
Female	92 (40 %)	5 (10 %)	22 (52.4 %)	25 (43.9 %)	53 (55.2 %)	[b]0.086
Male						
Smoking (n, %)	108 (47 %)	6 (40 %)	23 (54.8 %)	27 (47.4 %)	31 (32.3 %)	[b]0.076
Comorbidities (n, %)						
Hypertension	66 (28. 7%)	3 (20 %	15 (35.7 %)	16 (28.1 %)	41 (42.7 %)	[b]0.106
Diabetes Mellitus	21 (9.1 %)	2 (13.3 %)	7 (16.7 %)	7 (12.3 %)	19 (19.8 %)	[b]0.090
Asthma	5 (2.2 %)	-	1 (2.4 %)	3 (5.3 %)	3 (3.1 %)	[b]0.695
COPD	27 (11.7 %)	3 (20 %)	9 (21.4 %)	11 (19.3 %)	12 (12.5 %)	[b]0.250
CAD	13 (5.7 %)	2 (13.3 %)	4 (9.5 %)	6 (10.5 %)	18 (18.8 %)	[b]0.008*
Heart Failure	11 (4.8 %)	1 (6.7 %)	2 (4.8 %)	6 (10.5 %)	16 (16.7 %)	[b]0.009*
CKD	11 (4.8 %)	-	4 (9.5 %)	1 (1.8 %)	14 (14.6 %)	[b]0.010*
Cancer	2 (0.9 %)	-	-	-	3 (3.1 %)	[b]0.388
Intensive care (n, %)	-	-	10 (23.8 %)	11 (19.3 %)	32 (33.3 %)	[b]< 0.001*
Symptom (n, %)						
Fever	31 (13.5 %)	4 (26.7 %)	24 (57.1 %)	28 (49.1 %)	59 (61.5 %)	[b]< 0.001*
Cough	198 (86.1 %)	14 (100 %)	42 (100 %)	48 (84.2 %)	75 (78.1 %)	[b]0.007*
Shortness of breath	105 (45.7 %)	9 (60 %)	29 (69 %)	25 (43.9 %)	50 (52.1 %)	[b]0.051
Tiredness	33 (14.3 %)	5 (33.3 %)	18 (42.9 %)	27 (47.4 %)	52 (54.2 %)	[b]0.084
Headache	11 (4.8 %)	1 (6.7 %)	5 (11.9 %)	10 (17.5 %)	23 (24 %)	[b]< 0.001*
Myalgia	21 (9.1 %)	4 (26.7 %)	12 (28.6 %)	17 (29.8 %)	23 (24 %)	[b]< 0.001*
Diarrhea	6 (2.6 %)	-	1 (2.4 %)	4 (7 %)	4 (4.2 %)	[b]0.493
Loss of smell	4 (1.7 %)	-	1 (2.4 %)	3 (5.3 %)	4 (4.2 %)	[b]0.402
Loss of taste	7 (3 %)	-	1 (2.4 %)	2 (3.5 %)	3 (3.1 %)	[b]0.972

Abbreviations: [a]Kruskal-Wallis Test; [b]Chi-square Test; *Means statistically significant; COPD: Chronic Obstructive Pulmonary Disease; CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease.

intensive care and 28-day mortality. In addition, individuals with comorbid diseases and higher CO-RADS scores had a higher rate of the shift to the ICU.

Although COVID-19 can be asymptomatic or mildly symptomatic, it can be complicated by severe acute respiratory distress syndrome (SARS), cardiac arrhythmia, renal/multiple organ failure and even death. Concomitant systemic diseases such as diabetes, hypertension, chronic heart failure, and coronary artery diseases affect the prognosis[13,14]. Despite the vaccine development, we still need more information about the short and long-term effects[8]. Therefore, the early detection strategy is still important to control the epidemic that causes more deaths day by day[9].

From the very beginning, PCR positivity of throat swab or nasal swab samples has been accepted as the gold standard in diagnosis[15]. Since its sensitivity in the diagnosis of COVID-19 is around 50-62%, some cases may be missed[16]. In our study, since 230 (34.5%) patients were both CT and PCR negative, these patients were considered COVID-19 negative. However, since

Table VII. CO-RADS Score and prognosis of patients.

	Low (CO-RADS < 3)	High (CO-RADS > 4)	*p*-value	*p*-value
Home treatment	292 (91%)	28 (9%)		[c]< 0.001*
Hospitalization	99 (32%)	209 (68%)	[b]< 0.001*	[c]< 0.001*
Death (within 28 days)	1 (2.7%)	36 (97.3%)		[c]< 0.001*
Transferring ICU (no)	380 (71%)	156 (29%)	[b]< 0.001*	[c]< 0.001*
Transferring ICU (yes)	14 (11%)	115 (89%)		[c]< 0.001*

Abbreviations: [b]Chi-square Test; [c]Post-hoc test; *Means statistically significant. *Bonferroni adjustment was used, *p*-value was accepted as 0.008 in the first three rows and as 0.013 in the last two rows.

210 (31.5%) patients were PCR negative, clinical symptoms were present and CT findings were consistent with COVID-19, they were considered COVID-19 positive. That group of patients comprised almost one-third of all patients included in the study and interestingly, 53 of them needed intensive care. Probably, factors such as the immature development of detection technology, low patient viral load, and improper sampling contributed to the patient's negative test results.

From previous studies, we know that the sensitivity of CT in detecting COVID-19 is around 90-98%[17,18]. It provides to manage the transmission control, screen any clinically stored case to identify and quarantine the infected patients. It also provides timely treatment and finds out all close contacts for further examination. It is important to evaluate CT findings with a specific algorithm with a low margin of error. For that reason, we used the CO-RADS scoring system which provides a standardized assessment with a five-point scale, moderate to substantial agreement among observers, high power in the diagnosis of COVID-19[19]. In that scoring system, we considered patients with a CO-RADS score of 2 as COVID-19 positive, even though the score referred to a low level of suspicion because the patients were also accompanied by clinical and laboratory findings such as lymphopenia. Although CT has a high sensitivity, it has a relatively low specificity. According to a study from Wuhan including 1014 patients, the sensitivity and specificity of CT were 97% and 25%[20]. A recent meta-analysis also suggested that a pooled sensitivity and specificity of CT were 94% and 37%[21]. In our study, the sensitivity of CT was 77% and specificity was 52%. We assumed the relatively higher specificity due to the practical and systemic algorithm of the CO-RADS scoring system. It can also be interpreted that we found the sensitivity of CT lower than expected in our findings. The reason for that relatively low rate may be since the patients in this group had a milder course of infection like an upper respiratory tract infection, or the lung findings have not yet occurred because CT was performed at the onset of symptoms. Another reason that is often forgotten is the drugs such as paracetamol, antihistaminic drugs, steroids, or non-steroid anti-inflammatory drugs being used without a doctor's recommendation when the symptoms have just started.

Recent studies have shown that people with diabetes mellitus, hypertension, a smoking habit, COPD, asthma, or heart failure are associated with increased infection risk and a severe prognosis. A study confirmed that diabetes (22%) was one of the most evident comorbidities of 32 non-survivors from a group of 52 intensive care patients with COVID-19[22-25]. In correlation with this evidence, our study showed that patients with systemic diseases have a higher risk of COVID-19 infection risk and significantly higher CO-RADS scores.

Our study suggested that patients with diabetes mellitus, asthma, and coronary artery had a significantly increased risk of having both positive PCR and CT results. Similarly, patients with hypertension and diabetes mellitus had an increased risk of having higher CO-RADS scores. A recent study suggested that there was a positive correlation between CO-RADS score and diabetes and hypertension[26]. That may be explained by systemic inflammation, compromised immune response, and impaired RAAS in those groups of patients. In addition, it is also suggested that hyperglycemia is a link for the association between diabetes and viral infections, which influences viral growth and inflammation, thereby exacerbating mortality and morbidity in patients[27].

Although COPD is a disease that primarily affects the respiratory tract, it is still not clear that the risk of COVID-19 is increased in that disease[28]. Çomoğlu et al[26] found that there was a positive correlation between CO-RADS score and chronic pulmonary diseases including COPD[26]. In our study, we included all the patients with COPD who present with new or worsening respiratory symptoms, fever, and/or other symptoms that may be associated with COVID-19 and found that the disease was associated with COVID-19 infection risk but not a higher CO-RADS score. We know that ACE2 receptors play an important role in the entry of the virus into the cell. In a recent study, it was shown that ACE2 levels were decreased in both bronchial and alveolar epithelial cells from COPD patients *vs.* controls, and cigarette smoke-exposed *vs.* air-exposed mice[29]. That may be one of the main reasons for the relatively low CT score of COPD, as observed in our results. We also hypothesized that inhaled corticosteroids, long-acting bronchodilators, or chronic macrolides affected the manifestation of lung findings on CT.

A recent study emphasized that the CO-RADS score was effective in triage, diagnosis, management decisions, and prognosis[30]. In support of this study, almost all patients in our study requiring treatment in intensive care had CO-RADS scores of 3 and above, 115 (89.2%) of shifted to intensive care unit had CO-RADS

scores 4 and above and 36 (97.3%) of patients died due to COVID-19 infection had CO-RADS scores 4 and above. Even in PCR negative group, we saw that approximately half of the patients with negative PCR results (n= 210) had a CO-RADS score of 2 and above, and among them, the number of patients with a score of 5 refers to a severe lung disease was considerably higher. Although the PCR was negative, 53 patients with a CT score of 3 or more needed intensive care. In CT negative and PCR positive group (52 patients), control CT was not required in the following periods, because there was no worsening in their symptoms. Whether PCR positive or not, almost all patients requiring intensive care were patients with a CO-RADS score of 3 or more which highlights the association between CO-RADS scores patient's clinical course.

Recently, most of the studies have evaluated the diagnostic performance of the CO-RADS scoring system and compared it with PCR, or other reporting and data systems such as BI-RADS, CAD-RADS, 0-RADS, RSNA chest CT scoring systems[30-32]. There are limited data about its prognostic performance and association between co-morbid diseases. Çomoğlu et al[26] investigated the diagnostic performance of the CO-RADS scoring system and its association between clinical signs and found that age, hypertension, diabetes, chronic pulmonary diseases, symptoms, and duration of symptoms were correlated with the CO-RADS score, but its association with intensive care unit need and mortality were lacking.[26] In another retrospective study involving 192 patients, CT findings were associated with a longer hospital stay, the need of intensive care unit, and 28- day mortality, but an association with co-morbid diseases was lacking [33]. Our study confirmed those findings with the larger population of patients and also found a significant association between co-morbid diseases and CO-RADS scores.

There are some limitations of our study. First, the diagnostic criteria for COVID-19 in this study were based on the results of RT-PCR, but we know that the technique of taking the swab affects the test results. In our study, swabs were not taken by the same staff. Second, even though bronchoalveolar lavage fluid (BALF) samples are more valuable than pharynx swabs, the samples in our study were pharynx swabs which may contribute false negative PCR results. Third, some patients may have received medical intervention by themselves once they suspected of having flu-like symptoms (perhaps antimicrobial therapy, non-steroid anti-inflammatory drugs, fluid administration, or steroid therapy) which may affect chest CT findings. Lastly, our study did not include the patients with the COVID-19 delta variant. Larger sample sizes and studies are required for further verification.

Conclusions

As a result, our study suggests the benefit of COVID-19 patients to make the diagnosis quickly when symptoms, PCR, and CT findings are combined. CO-RADS scoring provides important information about the need for intensive care and the short-term prognosis of patients. It may be very useful and effective for timely and intensive treatment for the patients with cardiovascular or pulmonary diseases or with risk factors related to these diseases who require much more attention to minimize the risk of transmission, reduce intensive care unit need and mortality,

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Concept – İ.H.İ, A.G., N.B.; Design – İ.H.İ., F.A.İ., C.Ş.; Supervision – İ.H.İ., A.G., M.B.; Materials – İ.H.İ., A.G., N.B., M.B.; Data Collection and/or Processing – İ.H.İ., A.G., C.Ş., M.B.; Analysis and/or Interpretation – İ.H.İ., F.A.İ., N.B.; Literature Review – İ.H.İ., F.A.İ., A.G., C.Ş.; Writing – İ.H.İ; Critical Review – C.Ş., F.A.İ., M.B.,N.B.

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