Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Comparison of clinical characteristics and outcome measures of PCR-positive and PCR-negative patients diagnosed as COVID-19: Analyses focusing on the older adults

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ABSTRACT

Purpose: While the definitive diagnosis of COVID-19 relies on PCR confirmation of the virus, the sensitivity of this technique is limited. The clinicians had to go on with the clinical diagnosis of COVID-19 in selected cases. We aimed to compare PCR-positive and PCR-negative patients diagnosed as COVID-19 with a specific focus on older adults.

Methods: We studied 601 hospitalized adults. The demographics, co-morbidities, triage clinical, laboratory characteristics, and outcomes were noted. Differences between the PCR (+) and (−) cases were analyzed. An additional specific analysis focusing on older adults (≥65 years) ($n = 184$) was performed.

Results: The PCR confirmation was present in 359 (59.7 %). There was not any difference in terms of age, sex, travel/contact history, hospitalization duration, ICU need, the time between first symptom/hospitalization to ICU need, ICU days, or survival between PCR-positive and negative cases in the total study group and older adults subgroup. The only symptoms that were different in prevalence between PCR-confirmed and unconfirmed cases were fever (73.3 % vs. 64 %, $p = 0.02$) and fatigue/myalgia (91.1 % vs. 79.3 %, $p = 0.001$). Bilateral diffuse pneumonia was also more prevalent in PCR-confirmed cases (20 % vs. 13.3 %, $p = 0.03$). In older adults, the PCR (−) cases had more prevalent dyspnea (72.2 % vs. 51.4 %, $p = 0.004$), less prevalent fatigue/myalgia (70.9 % vs. 88.6 %, $p = 0.002$).

Conclusion: The PCR (+) and (−) cases displayed very similar disease phenotypes, courses, and outcomes with few differences between each other. The presence of some worse laboratory findings may indicate a worse immune protective response in PCR (−) cases.

1. Introduction

At the end of 2019, atypical pneumonia cases have been reported in Wuhan city, China (Huang et al., 2020). The pathogen was an RNA virus previously unknown. It was a positive sense single-stranded and enveloped virus. It was a positive sense single-stranded and enveloped virus. Owing to its close similarity to SARS-CoV, it was called SARS-CoV-2 (Zheng, 2020), and the new disease was called Coronavirus disease 2019 (COVID-19). COVID-19 continues to affect the world, representing a challenge to the health care systems and a global emergency by August 2020. A second wave is further expected in late autumn.

The definitive diagnosis of COVID-19 relies on PCR confirmation of the pathogen. However, this technique is limited with relatively low sensitivity. The sensitivity of the PCR method has been reported between 60 % and 95 % from different centers (Caliendo and Hanson, 2020; Weissleder et al., 2020). As such, the clinicians had to go on with

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clinical diagnosis of COVID-19 in selected cases provided that they apply during the pandemic period and similar characteristics suggesting this new disease. Another factor contributing to the introduction of clinical diagnosis was the lack of enough and available PCR analysis in the crowded centers. To our knowledge, the comparison of COVID-19 patients confirmed vs. unconfirmed has currently not been studied. It is very well documented that older adults are at higher risk for COVID-19 related adverse outcomes (Wu and McGoogan, 2020; Richardson et al., 2020; L. Wang et al., 2020). It is surprising that specific information about older patients is limited (L. Wang et al., 2020; Li et al., 2020; Lian et al., 2020; T. Guo et al., 2020; Niu et al., 2020; Liu et al., 2020; Chen et al., 2020). Older adults have significant differences from the others e.g., with their impaired immune system, contact characteristics, accompanying co-morbidities, and drugs. The clinical characteristics and early outcomes of the older COVID-19 patients confirmed by PCR analysis that needed hospitalization have been reported before (Medetalibeyoğlu et al., n.d.). Here, we aimed to compare the features of PCR positive and PCR negative patients diagnosed as COVID-19 with a specific focus on older adults.

2. Material and methods

We designed a retrospective observational study that involved hospitalized patients aged ≥18 years with the confirmed or clinical diagnosis of COVID-19 from March 11, 2020, to May 11, 2020. Confirmed COVID-19 was defined as identification of SARS-CoV-2 pathogen by PCR analysis of the naso/oropharyngeal swabs, and clinical diagnosis was defined as the clinical presentation compatible with COVID-19 disease in the pandemic period but lacked PCR confirmation. The study participants were composed of hospitalized adults between March 11 and May 11, 2020.

The study hospital is a major teaching hospital which has reported the first COVID-19 case in Turkey in Istanbul city on March 11, 2020. It became a pandemic hospital with the emergence of the pandemic. The city, Istanbul, has been the main center of the pandemic, with the highest number of COVID-19 cases having many international links. Istanbul is the greatest city in the country, more crowded than many European countries with a population number of about 15 million (http://tuik.gov.tr/UstMenu.do?metod=temelist, 2020). This city had half (50.0 %) of all cases in the country by August 2, 2020 (https://dosyamerkez.saglik.gov.tr/Eklenti/37743,covid-19-situation-report-v4pdf.pdf?0, 2020). Our center has been one of the busiest centers in the pandemic era.

We noted demographics, co-morbidities, triage clinical, and laboratory characteristics and outcomes from the electronic medical records. Policy of our center on suspected COVID-19 cases has been outlined elsewhere (A Medetalibeyoğlu N Senkal M Kose E Bilge Caparali M Erelel et alOlder adults hospitalized with Covid-19: clinical characteristics and early outcomes from a single center in Istanbul, Turkey, n.d.). We performed nasopharyngeal and oropharyngeal swab specimen collection for real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) examination. Till March 30, 2020, the laboratory confirmation (RT-PCR examination) of SARS-CoV-2 was performed at the official public health care laboratory. Afterward, our institution performed the analyses which have been certified in this technique. RT-PCR assays were performed according to the WHO protocol (World Health Organization, 2020). Remarkably, we imaged the chest with low dose pulmonary computerized tomography (CT) on admission provided that the patient has no individual contraindication such as pregnancy. The radiology experts evaluated the pulmonary CT images in a structured manner. They classified the COVID-19 related CT findings as mild to moderate or severe, as described elsewhere (Ooi et al., 2004). Clinically, we assessed the severity of COVID-19 pneumonia on admission, regarding the respiration rate, peripheral oxygen saturation, and dyspnea identified by the examining physician. Accordingly, the patients that had resting respiration rate ≥ 30/min or room air peripheral oxygen saturation < 90 % or objectively identified dyspnea (by the use of accessory respiration muscles at rest) were classified as clinically severe pneumonia in line with the diagnostic and treatment guidelines for SARS-CoV-2 issued by the Turkish Scientific Committee (https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf, 2020). We measured body temperature by a noncontact infrared thermometer from the forehand. We noted fever as a temperature > 38.3 °C. We designated the cut-offs of the laboratory parameters by the local laboratory thresholds or as recommended by the Turkish scientific committee.

Institutional review board approved the study with the number of 2020/747. They waived the need for informed consent due to the global urgent data requirement. We collected the data which were made available for routine clinical practice and handled them anonymously.

2.1. Statistical analysis

We presented the continuous variables as medians and minimum-maximum ranges. We presented categorical variables as counts and percentages. We compared two groups with the Mann-Whitney *U* test as necessary and used the Chi-square test with Yates correction and Fisher's exact test for 2 × 2 contingency tables when appropriate for categorical data. We used SPSS (statistical package for social sciences) for Windows 15.0 program for data analyses.

3. Results

There were 601 subjects hospitalized with COVID-19 diagnosis in the study period. The PCR confirmation was present in 359 (59.7 %). The median age was 56 years (18–98 years), and 59.6 % was male. The median duration of hospitalization was eight days. ICU admission was required in 85 patients (14.1 %). The median time between hospitalization and ICU need was two days, and time between first symptom and ICU need was seven days. The median ICU days was 21 days. In total, 55 subjects died (9.2 %). The most common triage symptoms were fatigue/myalgia (86.4 %), dry cough (80.7 %), fever (69.6 %), and dyspnea (44.4 %). The most common co-morbidities were hypertension (40.6 %), diabetes (22.6 %), and chronic obstructive pulmonary disease (COPD)/asthma (14.1 %). In triage physical examination, the respiratory rate was ≥30/min in 7 %. The peripheral oxygen saturation was <90 % in 15 %.

One hundred ninety subjects (31.6 %) were clinically dyspneic, as identified by the physician. Severe pneumonia was present in 193 (32.1 %), and there was bilateral diffuse pneumonia in 103 subjects (17.3 %). The most common abnormal triage laboratory findings were CRP > 40 mg/l (56.9 %), pro-BNP > 125 (46.3 %), D-dimer > 1000 (39.9 %), lymphocytes < 1000/mm^3 (39.6 %). The details of the study population are outlined in Table 1.

Table 2 shows the comparison of participants with PCR confirmation and without PCR confirmation for triage characteristics. There was not any difference in terms of age, sex, travel/contact history, hospitalization duration, ICU need, time between first symptom/hospitalization to ICU need, ICU days, survival. The only symptoms that were different in prevalence between PCR-confirmed and unconfirmed cases were presence of fever (73.3 % vs. 64 %, $p = 0.02$), fatigue/myalgia (91.1 % vs 79.3 %, $p = 0.001$). Among accompanying co-morbidities, COPD/asthma, congestive heart failure and solid malignancies were more prevalent in the PCR unconfirmed cases (13.2 % vs. 10.3 %, $p = 0.01$; 9.5 % vs. 5.3 %, $p = 0.047$; 11.2 % vs. 4.5 %, $p = 0.002$). There was not any difference in triage physical examination parameters. The laboratory findings that were significantly different between the PCR (+) and (−) cases were D-dimer > 1000 (34.3 % vs. 48.3 %, $p = 0.001$), increased BUN > 20 mg/l (23.4 % vs. 33.5 %, $p = 0.007$), pro-BNP > 125 (40.4 % vs. 55 %, $p < 0.001$), troponin T > 14 (23.1 % vs.35.5 %, p = 0.001), increased leukocytes > 10,000/mm^3 (12.5 % vs. 24.4 %, p = 0.001), neutrophilic leukocytosis (14.8 % vs. 24 %), increased ALP >

Table 1
Triage characteristics of the study population ($n = 601$).

PCR result (+)/(−), n (%)	359 (59.7 %)/242 (40.3 %)
Age (years) (mean ± SD, IQR)	56 (18–98)
Sex (female vs. male), n (%)	243 (40.4 %) vs. 358 (59.6 %)
Hospitalization duration (days)[b], (mean ± SD, IQR)	8 (1–60)
Follow-up data	
ICU need, n (%)	85 (14.1 %)
Days between hospitalization and ICU need[b] (mean ± SD, IQR)	2 (0–17)
Days between first symptom and ICU need[b] (mean ± SD, IQR)	7 (1–24)
ICU days[b] (mean ± SD, IQR)	21 (1–70)
Discharged alive/exitus, n (%)	540 (89.9 %)/55 (9.2 %)
Travel history, n (%)	6 (1 %)
Contact history, n (%)	205 (34.1 %)
Symptoms, n (%)	
Fever (by history)	418 (69.6 %)
Dry cough	485 (80.7 %)
Sputum	16 (2.7 %)
Dyspnea (declared by patient)	267 (44.4 %)
Fatigue/myalgia	519 (86.4 %)
Nausea ($n = 573$)	95 (16.6 %)
Diarrhea ($n = 573$)	70 (12.2 %)
Anosmia (n = 573)	42 (7 %)
Body temperature (°C)	37.3 ± 0.9
Fever (>38.3 °C)	106 (17.6 %)
Systolic blood pressure < 90 mmHg	5 (0.8 %)
Dyspnea (clinical diagnosis)	190 (31.6 %)
Co-morbidities, n (%)	
Hypertension	244 (40.6 %)
Diabetes mellitus	136 (22.6 %)
Chronic obstructive pulmonary disease/asthma	85 (14.1 %)
Coronary heart disease	69 (11.5 %)
Congestive heart failure	42 (7 %)
Atrial fibrillation	19 (3.2 %)
Solid malignancy	43 (7.2 %)
Hematologic malignancy	19 (3.2 %)
Triage-physical examination, n (%)	
Respiratory rate (/min)[b]	18 (12–36)
Respiratory rate ≥ 30/min	42 (7 %)
SaO^2 (%)[b]	96 (65–100)
Peripheral oxygen saturation < 90 %	90 (15 %)
Clinical dyspnea	190 (31.6 %)
Severe pneumonia[a]	193 (32.1 %)
Bilateral diffuse pneumonia ($n = 596$)	103 (17.3 %)
Triage-laboratory examination	
Hb < 10 g/dl, n (%)	53 (8.8 %)
Thrombocytes < 100,000/mm^3	21 (3.5 %)
Leukocytes > 10,000/mm^3	104 (17.3 %)
Leukocytes < 4000/mm^3	75 (12.5 %)
Neutrophilic leukocytosis (>7700/mm^3)	111 (18.5 %)
Lymphocytes < 800/mm^3	160 (26.6 %)
Lymphocytes < 1000/mm^3	238 (39.6 %)
CRP > 40 mg/l	342 (56.9 %)
Ferritin > 500 (ng/ml)	206 (34.3 %)
D-dimer > 1000 (ug/l)	240 (39.9 %)
BUN ≥ 20 mg/l	165 (27.5 %)
pro-BNP > 125 (pg/ml)	278 (46.3 %)
Increased AST (>200 U/l)	5 (0.8 %)
Increased ALT (>200 U/l)	5 (0.8 %)
Increased GGT (>300 U/l)	6 (1 %)
Increased ALP (>300 U/l)	9 (1.5 %)
Increased LDH (>400 U/l)	185 (30.8 %)
Increased creatinine (>1.4 mg/dl)	66 (11 %)
Neutrophilic leukocytosis (>7700/mm^3)	185 (30.8 %)
Leukopenia (<4000/mm^3)	75 (12.5 %)
Leukocytosis (>10,000/mm^3)	104 (17.3 %)
Leukocytes (/mm^3), (mean ± SD, IQR)	6250 (280–97,110)
Neutrophils (/mm^3)	4450 (20–27,490)
Hb (g/dl)	13 (4.2–17.7)
Thrombocytes (/mm^3)	211,000 (20900–638,000)
Lymphocytes (/mm^3)	1100 (110–81,150)
BUN (g/dl)	14 (3–185)
Creatinine (mg/dl)	0.9 (0.3–18)
Glucose (mg/dl)	115 (63–633)
AST (U/l)	27 (7–421)
ALT (U/l)	22 (3–610)
GGT (U/l)	28 (5–1825)
ALP (U/l)	71 (19–1653)
LDH (U/l)	254 (105–1664)
Albumin (g/dl)	4 (1.2–5.1)
CRP (mg/l)	47 (1–460)
Procalcitonin (ng/ml)	3.58 (0.02–57)
Ferritin (ng/ml)	910 (6–8516)
D-dimer (ug/l)	2322 (210−20,000)
Troponin (pg/ml)	6 (3–3417)
Pro-BNP (pg/ml)	106 (5–35,000)
Regular drugs, n (%)	
Angiotensin receptor blocker	107 (17.8 %)
Angiotensin converting enzyme	57 (9.5 %)
Metformin	102 (17 %)
Sulfonylurea/glinides	34 (5.7 %)
Glitazone	13 (2.2 %)
DPP-4 inhibitors	37 (6.2 %)
SGLT-2 inhibitors	13 (2.2 %)
Insulin	48 (8 %)

Data are given as number (percentage) or median (minimum-maximum).
[a] Severe pneumonia was defined by presence of two of the followings: clinical dyspnea, respiratory rate > 30/min, peripheral saturation O^2 < 90 %.
[b] Data given as median (minimum-maximum).

300 U/l (0.3 % vs. 3.3 %), increased creatinine > 1.4 mg/dl (8.1 % vs. 1.5 %) levels. Contrary to the total study population, bilateral diffuse pneumonia was not different between the PCR-confirmed and unconfirmed cases (27.6 % vs 17.7 %, $p = 0.1$). There was not any difference between the cases in terms of antihypertensive or antidiabetic drugs.

We presented the comparison of the 184 older patients (≥65 years) for triage characteristics between those PCR (−) vs. PCR (+) in Table 3 and Fig. 1. The PCR confirmation was present in 57.1 %, a figure not significantly lower than the general population ($p = 0.4$). Similarly, there was not any difference between demographic characteristics, ICU need, and survival. Among triage symptoms, the PCR (−) cases had more prevalent dyspnea (72.2 % vs 51.4 %, $p = 0.004$), less prevalent fatigue/myalgia (70.9 % vs 88.6 %, $p = 0.002$). Similar to the total study population, COPD/asthma was more prevalent in PCR (−) cases (31.6 % vs. 15.2 %). However, there was not any difference in regard to congestive heart failure or malignancies. There was also no difference in triage physical examination parameters. The laboratory findings that were significantly different between the PCR (+) and (−) cases were increased BUN > 20 mg/l (44.8 % vs. 62 %, $p = 0.02$), pro-BNP > 125 (77.1 % vs. 91.1 %, $p < 0.001$), troponin $T > 14$ (55.2 % vs. 74.7 %, $p = 0.007$), increased leukocytes > 10,000/mm^3 (17.1 % vs 39.2 %, $p = 0.001$), neutrophilic leukocytosis (22.9 % vs 39.2 %, $p = 0.03$), increased creatinine > 1.4 mg/dl (10.4 % vs. 25.3 %, $p = 0.008$) levels. Bilateral diffuse pneumonia was also more prevalent in the PCR-confirmed cases (20 % vs. 13.3 %, p = 0.03). On the contrary to the total study population, there was not any difference in the prevalence of bilateral diffuse pneumonia in the older subgroup (27.6 % in PCR (+) cases vs. 17.7 %, in PCR (−) cases, $p = 0.1$). There was also no difference between the cases in terms of antihypertensive or antidiabetic drugs.

4. Discussion

False-negative nucleic acid amplification tests (NAATs), including reverse transcriptase-PCR from upper respiratory specimens, have been well documented (Caliendo and Hanson, 2020). The accuracy and predictive values of SARS-CoV-2 NAATs have not been systematically evaluated. While they are highly specific (Nalla et al., 2020; Lieberman et al., 2020), the clinical performance regarding sensitivity is variable. The false-negative rates have been reported between <5 % and 40 %. One should consider that the accuracy and predictive values of SARS-CoV-2 NAATs have not been systematically evaluated because there is no perfect reference standard for comparison (Weissleder et al., 2020).

Table 2
Comparison of the participants for triage characteristics between those PCR (−) vs PCR (+).

	PCR negative (n = 242)	PCR positive (n = 359)	p value
Age (years) (mean ± SD, IQR)	56 (18–98)	57 (21–90)	0.35
Sex (male), n (%)	136 (56.2 %)	222 (61.8 %)	0.2
Travel history, n (%)	none	6 (1.7 %)	0.09
Contact history, n (%)	72 (29.8 %)	133 (37 %)	0.06
Hospitalization duration (days)[b], (mean ± SD, IQR)	7 (1–52)	9 (1–60)	0.09
Follow-up data			
ICU need, n (%)	32 (13.2 %)	14.8 (14.8 %)	0.6
Time hospitalization and ICU need[b] (mean ± SD, IQR)	2 (0–17)	2 (0−11)	0.6
Days between first symptom and ICU need[b] (mean ± SD, IQR)	7 (1–24)	8 (1–16)	0.9
ICU days[b] (mean ± SD, IQR)	17 (1–64)	26 (1–70)	0.09
Discharged alive/exitus, n (%)	216 (89.3 %)/22 (9.1 %)	324 (90.3 %)/33 (9.2 %)	0.7/1
Symptoms, n (%)			
Fever (by history)	155 (64 %)	263 (73.3 %)	0.02*
Dry cough	186 (76.9 %)	299 (83.3 %)	0.05
Sputum	6 (2.5 %)	10 (2.8 %)	0.8
Dyspnea (declared by patient)	108 (44.6 %)	159 (44.3 %)	0.9
Fatigue/myalgia	192 (79.3 %)	327 (91.1 %)	0.001*
Nausea (n = 573)	36 (15.3 %) (n = 236)	59 (17.5 %) (n = 337)	0.5
Diarrhea (n = 573)	24 (10.2 %) (n = 236)	46 (12.8 %) (n = 337)	0.2
Anosmia (n = 573)	17 (7.2 %) (n = 236)	25 (7.4 %) (n = 337)	0.9
Fever (>38.3 °C)	35 (14.5 %)	71 (19.8 %)	0.09
Systolic blood pressure < 90 mmHg	4 (1.7 %)	1 (0.3 %)	0.2
Dyspnea (clinical diagnosis)	76 (31.4 %)	114 (31.8 %)	0.9
Co-morbidities, n (%)			
Hypertension	106 (43.8 %)	138 (38.4 %)	0.2
Diabetes mellitus	51 (21.1 %)	85 (23.7 %)	0.5
Chronic obstructive pulmonary disease/asthma	45 (18.6 %)	40 (11.1 %)	0.01*
Coronary heart disease	32 (13.2 %)	37 (10.3 %)	0.3
Congestive heart failure	23 (9.5 %)	19 (5.3 %)	0.047*
Atrial fibrillation	6 (2.5 %)	13 (3.6 %)	0.4
Solid malignancy	27 (11.2 %)	16 (4.5 %)	0.002*
Hematologic malignancy	9 (3.7 %)	10 (2.8 %)	0.5
Triage-physical examination, n (%)			
Respiratory rate (/min)[b]	18 (12–36)	18 (12–36)	0.4
Respiratory rate ≥ 30/min	16 (6.6 %)	26 (7.2 %)	0.8
SaO^2 (%)[b]	96 (72–100)	96 (65–100)	0.8
Peripheral oxygen saturation < 90 %	41 (16.9 %)	49 (13.6 %)	0.3
Clinical dyspnea	76 (31.4 %)	114 (31.8 %)	0.9
Severe pneumonia[a]	78 (32.2 %)	115 (32 %)	0.9
Triage-laboratory examination			
Hb < 10 g/dl, n (%)	30 (12.4 %)	23 (6.4 %)	0.01*
Thrombocytes < 100,000/mm^3	8 (3.3 %)	13 (3.6 %)	0.8
Leukocytes > 10,000/mm^3	59 (24.4 %)	45 (12.5 %)	0.001*
Leukocytes < 4000/mm^3	33 (13.6 %)	42 (11.7 %)	0.5
Neutrophilic leukocytosis (>7700/mm^3)	58 (24 %)	53 (14.8 %)	0.004*
Lymphocytes < 800/mm^3	67 (27.7 %)	93 (25.9 %)	0.6
Lymphocytes < 1000/mm^3	95 (39.3)	143 (39.8 %)	0.9
CRP > 40 mg/l	138 (57 %)	204 (56.8 %)	0.9
Ferritin > 500 (ng/ml)	80 (33.1 %)	126 (35.1 %)	0.6
D-dimer > 1000 (ug/l)	117 (48.3 %)	123 (34.3 %)	0.001*
BUN ≥ 20 mg/l	81 (33.5 %)	84 (23.4 %)	0.007*
pro-BNP > 125 (pg/ml)	133 (55 %)	145 (40.4 %)	<0.001*
Increased AST (>200 U/l)	2 (0.8 %)	3 (0.8 %)	1
Increased ALT (>200 U/l)	2 (0.8 %)	3 (0.8 %)	1
Increased GGT (>300 U/l)	3 (1.2 %)	3 (1 %)	0.8
Increased ALP (>300 U/l)	8 (3.3 %)	1 (0.3 %)	0.04*
Increased LDH (>400 U/l)	72 (29.8 %)	113 (31.5 %)	0.6
Leukocytosis (>10,000/mm^3)	59 (24.4 %)	45 (12.5 %)	0.001*
Leukocytes (/mm^3), (mean ± SD, IQR)	7090 (280–28,520)	6060 (930–97,110)	0.001*
Neutrophils (/mm^3)	5100 (20–27,490)	4090 (270–18,500)	<0.001*
Hb (g/dl)	12.7 (4.2–16.3)	13.2 (5.2–17.7)	0.001*
Thrombocytes (/mm^3)	222,500 (209000–592,100)	203,000 (42500–638,000)	0.008*
Lymphocytes (/mm^3)	1095 (110–3480)	1100 (160–81,150)	0.4
BUN (g/dl)	16 (5–99)	14 (3–185)	0.001*
Creatinine (mg/dl)	0.9 (0.4–8)	0.9 (0.3–18)	0.5
Glucose (mg/dl)	116 (63–633)	114 (69–399)	0.4
AST (U/l)	25 (7–362)	29 (7–421)	<0.001*
ALT (U/l)	20.5 (4–605)	24 (3–610)	0.01*
GGT (U/l)	27.5 (5–593)	29 (5–1825)	0.8
ALP (U/l)	77 (19–764)	67 (29–1653)	<0.001*
LDH (U/l)	245 (105–1664)	256 (132–1027)	0.07
Albumin (g/dl)	4 (1.2–5.1)	4 (2–4.9)	0.07
CRP (mg/l)	48.5 (1–368)	47 (1–460)	0.9
Procalcitonin (ng/ml)	0.09 (0.02–57)	0.08 (0.02–48)	0.2
Ferritin (ng/ml)	285.5 (6–8516)	343 (6–7412)	0.16
D-dimer (ug/l)	985 (230–19,970)	750 (210–20,000)	0.002*
Troponin (pg/ml)	7 (3–3417)	6 (3–1249)	0.02*
Pro-BNP (pg/ml)	169 (5–35,000)	84 (5–35,000)	<0.001*
Bilateral diffuse pneumonia	32 (13.3 %) (n = 241)	71 (20 %) (n = 355)	0.03*
Regular drugs, n (%)			
Angiotensin receptor blocker	42 (17.4 %)	65 (18.1 %)	0.8
Angiotensin converting enzyme inhibitors	25 (10.3 %)	32 (8.9 %)	0.6
Metformin	34 (14 %)	68 (18.9 %)	0.11
Sulfonylurea/glinides	17 (7 %)	17 (4.7 %)	0.2
Glitazone	8 (3.3 %)	5 (1.4 %)	0.1
DPP-4 inhibitors	13 (5.4 %)	24 (6.7 %)	0.5
SGLT-2 inhibitors	6 (2.5 %)	7 (1.9 %)	0.7
Insulin	23 (9.5 %)	25 (7 %)	0.3

Data are given as number (percentage) or median (minimum-maximum).
[a] Severe pneumonia was defined by presence of two of the followings: clinical dyspnea, respiratory rate > 30/min, peripheral saturation O^2 < 90 %.
[b] Data given as median (minimum-maximum).
* p value ≤ 0.05.

They are highly specific tests (Nalla et al., 2020; Lieberman et al., 2020). Although NAATs have high analytic sensitivity in ideal settings (i.e., they are able to accurately detect low levels of viral RNA in test samples known to contain viral RNA), clinical performance is more variable. The

Table 3
Comparison of the older patients (≥65 years) for triage characteristics between those PCR (−) vs. PCR (+).

	PCR negative (n = 79)	PCR positive (n = 105)	p value
Age (years) (mean ± SD, IQR)	74 (65–98)	73 (65–90)	0.3
Sex (male), n (%)	47 (59.5 %)	64 (61 %)	0.8
Contact history, n (%)	13 (29.8 %)	29 (37 %)	0.07
Hospitalization duration (days)[b], (mean ± SD, IQR)	9 (1–52)	10 (1–60)	0.09
Follow-up data			
ICU need, n (%)	20 (25.3 %)	31(29.5 %)	0.5
Days between first symptom and ICU need[b] (mean ± SD, IQR)	7 (1–24)	8 (1–16)	0.9
ICU days[b] (mean ± SD, IQR)	17.5 (1–64)	36 (1–70)	0.1
Discharged alive/exitus, n (%)	61 (77.2 %)/15 (19 %)	81 (77.1 %)/22 (21 %)	0.9/0.7
Symptoms, n (%)			
Fever (by history)	43 (54.4 %)	66 (62.9 %)	0.25
Dry cough	51 (64.6 %)	76 (72.4 %)	0.25
Sputum	2 (2.5 %)	2 (1.9 %)	0.8
Dyspnea (declared by patient)	57 (72.2 %)	54 (51.4 %)	0.004*
Fatigue/myalgia	56 (70.9 %)	93 (88.6 %)	0.002*
Nausea (n = 573)	7 (9.3 %)	11 (17.5 %)	0.6
Diarrhea (n = 573)	7 (8.9 %)	12(12.8 %)	0.6
Anosmia (n = 573)	1 (1.3 %)	3 (3.2 %)	0.6
Fever (>38.3 °C)	10 (12.7 %)	18 (17.1 %)	0.4
Dyspnea (clinical diagnosis)	44 (55.7 %)	53 (31.8 %)	0.5
Co-morbidities, n (%)			
Hypertension	55 (69.6 %)	66 (62.9 %)	0.3
Diabetes mellitus	26 (32.9 %)	35 (33.3 %)	0.9
Chronic obstructive pulmonary disease/asthma	25 (31.6 %)	16 (15.2 %)	0.008*
Coronary heart disease	23 (29.1 %)	26 (24.8 %)	0.5
Congestive heart failure	19 (24.1 %)	16 (15.2 %)	0.1
Atrial fibrillation	6 (7.6 %)	10 (9.5 %)	0.6
Solid malignancy	8 (10.1 %)	8 (7.6 %)	0.5
Hematologic malignancy	3 (3.8 %)	7 (6.7 %)	0.4
Triage-physical examination, n (%)			
Respiratory rate (/min)[b]	20 (14–36)	22 (16–36)	0.5
Respiratory rate ≥ 30/min	9 (11.4 %)	15 (14.3 %)	0.6
SaO^2 (%)[b]	93 (72–98)	94 (65–99)	0.3
Peripheral oxygen saturation < 90 %	27 (34.2 %)	28 (26.7 %)	0.3
Clinical dyspnea	44 (55.7 %)	53 (50.5 %)	0.1
Severe pneumonia[a]	45 (57 %)	53 (50.5 %)	0.4
Triage-laboratory examination			
Hb < 10 g/dl, n (%)	16 (20.3 %)	12 (11.4 %)	0.1
Thrombocytes < 100,000/mm^3	3 (3.8 %)	4 (3.8 %)	1
Leukocytes > 10,000/mm^3	31 (39.2 %)	18 (17.1 %)	0.001*
Leukocytes < 4000/mm^3	7 (8.9 %)	11 (10.5 %)	0.7
Neutrophilic leukocytosis (>7700/mm^3)	31(39.2 %)	24 (22.9 %)	0.03*
Lymphocytes < 800/mm^3	30 (38 %)	43 (41 %)	0.4
Lymphocytes < 1000/mm^3	40 (50.6 %)	60 (57.1 %)	1
CRP > 40 mg/l	48 (60.8 %)	69 (65.7 %)	0.5
Ferritin > 500 (ng/ml)	26 (32.9 %)	43 (41 %)	0.3
D-dimer > 1000 (ug/l)	52 (65.8 %)	63 (60 %)	0.4
BUN ≥ 20 mg/l	49 (62 %)	47 (44.8 %)	0.02*
pro-BNP > 125 (pg/ml)	72 (91.1 %)	81 (77.1 %)	<0.001*
Troponin T > 14 (pg/ml)	59 (74.7 %)	58 (55.2 %)	0.007*
Increased AST (>200 U/l)	5 (0.8 %)	2 (1.9 %)	1
Increased ALT (>200 U/l)	5 (0.8 %)	2 (1.9 %)	1
Increased GGT (>300 U/l)	6 (1 %)	3 (2.9 %)	0.7
Increased ALP (>300 U/l)	9 (1.5 %)	1 (1 %)	0.6
Increased LDH (>400 U/l)	185 (30.8 %)	36 (34.3 %)	0.9
Increased creatinine (>1.4 mg/dl)	20 (25.3 %)	11 (10.4 %)	0.008*
Leukocytes (/mm^3), (mean ± SD, IQR)	7090 (280–28,520)	6100 (930–97,110)	0.004*
Neutrophils (/mm^3)	5100 (20–27,490)	4440 (270–18,300)	<0.005*
Hb (g/dl)	12.3 (4.2–15.5)	12.5 (6.1–16.2)	0.08
Thrombocytes (/mm^3)	220,000 (209000–515,000)	216,000 (67700–638,000)	0.8
Lymphocytes (/mm^3)	990 (110–2800)	1100 (160–81,150)	0.9
BUN (g/dl)	22 (8–99)	18 (5–74)	0.02*
Creatinine (mg/dl)	1 (0.5–8)	0.9 (0.5–10)	0.02*
Glucose (mg/dl)	131 (63–390)	118 (69–399)	0.3
AST (U/l)	23 (12–362)	29 (9.8–421)	0.2
ALT (U/l)	19 (6–605)	19 (5–610)	0.8
GGT (U/l)	25 (6–445)	25 (6–1825)	0.4
ALP (U/l)	81 (19–662)	72 (31–1653)	0.03*
LDH (U/l)	264 (130–1664)	254 (136–1027)	0.5
Albumin (g/dl)	3.6 (1.2–4.8)	3.7 (2.1–4.6)	0.8
CRP (mg/l)	51 (1–368)	59 (3–254)	0.4
Procalcitonin (ng/ml)	0.15 (0.02–57)	0.12 (0.02–7.8)	0.3
Ferritin (ng/ml)	261 (7–8516)	420 (16–5083)	0.1
D-dimer (ug/l)	1380 (340–10,850)	1260 (270–20,000)	0.5
Troponin (pg/ml)	28 (3–3417)	18 (3–1249)	0.02*
Pro-BNP (pg/ml)	911 (8–29,462)	577 (5–35,000)	<0.001*
Bilateral diffuse pneumonia	14 (17.7 %)	29 (27.6 %)	0.1
Regular drugs, n (%)			
Angiotensin receptor blocker	18 (22.8 %)	36 (34.3 %)	0.8
Angiotensin converting enzyme inhibitors	13 (16.5 %)	9 (8.6 %)	0.6
Metformin	16 (20.3 %)	28 (26.7 %)	0.11
Sulfonylurea/glinides	11 (13.9 %)	8 (7.6 %)	0.2
Glitazone	2 (2.5 %)	1 (1 %)	0.1
DPP-4 inhibitors	4 (5.1 %)	13 (12.4 %)	0.5
SGLT-2 inhibitors	3 (3.8 %)	2 (1.9 %)	0.7
Insulin	14 (17.7 %)	8 (7.6 %)	0.3

Data are given as number (percentage) or median (minimum-maximum).
[a] Severe pneumonia was defined by presence of two of the followings: clinical dyspnea, respiratory rate > 30/min, peripheral saturation O^2 < 90 %.
[b] Data given as median (minimum-maximum).
* p value ≤ 0.05.

sensitivity of the PCR testing depends on several factors: the type and quality of the specimen, the duration of illness at test time, and the specific assay: Lower respiratory tract specimens may have higher viral loads yielding positive tests than the upper respiratory specimens (W. Wang et al., 2020; Yu et al., 2020). The sensitivity of SARS-CoV-2 PCR may also be affected by the disease duration (L. Guo et al., 2020). The estimated false-negative result rates have been reported as 100 % percent on exposure day, 38 % on day 5 representing the first day of symptoms, 20 % on day 8, and 66 % on day 21 (Kucirka et al., 2020).

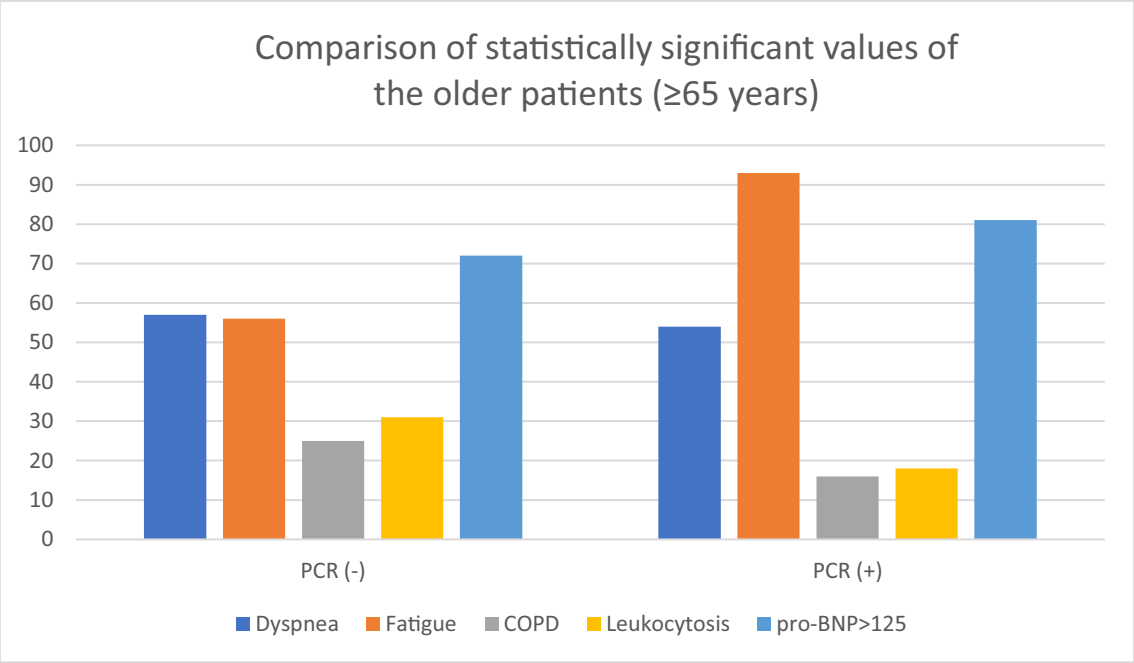

Fig. 1. Comparison of statistically significant values of the older patients (≥65 years).
COPD: Chronic obstructive pulmonary disease/asthma.

However, we should consider that heterogeneity across studies and assumptions makes the analysis doubtful. On the other hand, a standard finding from all reports so far is the more serious disease and outcomes in older adults (https://dosyamerkez.saglik.gov.tr/Eklenti/37743, covid-19-situation-report-v4pdf.pdf?0, 2020). Accordingly, our aim in this study was to compare PCR positive and PCR negative patients diagnosed as COVID-19 with a specific focus on older adults.

With aging, changes occur in the immune system. Possible mechanisms behind the behavior of SARS-CoV-2 in the elderly include immunosenescence and related impaired antiviral immunity, mature immunity and related hyper-inflammatory responses, comorbidities and their effects on the functioning of critical organs/systems, and the altered expression of angiotensin-converting enzyme 2 (ACE2) that acts as an entry receptor for SARS-CoV-2. For these reasons, PCR testing is thought to be associated with immunity (Mirbeyk et al., 2021).

Atypical presentation in geriatric population may include afebrile or low-grade fever, absence of cough, malaise, muscle pains, dyspnea etc. The negative PCR test of patients with atypical presentation leads to a delay in the diagnosis of the disease and thus a delay in the treatment. Due to the high fragility of the geriatric population, early diagnosis and treatment of patients who are PCR negative and diagnosed with COVID-19 by clinical and imaging are very important (Bansod et al., 2021).

In this study, composed of 601 patients with a diagnosis of COVID-19, the PCR confirmation was present in 359 (59.7 %). This figure is in line with the so far published literature, with a sensitivity at the lower end. The median day between the first symptom and hospitalization was five days, accounting roughly between 10 days and 19 days of exposure. This low sensitivity is, therefore, in accordance with the limited published studies as false-negative PCR results were reported 20 % at day 8 and 66 % at day 21. The sensitivity was lower in the older adults, albeit this was not significant (57.1 %, $p = 0.4$). The median age was 56 years, 59.6 % was male. ICU admission was required in 85 (14.1 %), and 55 subjects died (9.2 %). Between PCR (+) and (−) cases, there was not any difference in terms of age, sex, travel/contact history, hospitalization duration, ICU need, the time between the first symptom to ICU need, ICU days, or survival. There was not also any difference in triage physical examination parameters or the use of specific antihypertensive or antidiabetic drugs. The only symptoms that were different in prevalence were the presence of fever, fatigue/myalgia more prevalent in PCR-confirmed cases. Bilateral diffuse pneumonia was also more prevalent in the PCR-confirmed cases. On the other hand, COPD/asthma, congestive heart failure, and solid malignancies were more prevalent in the PCR unconfirmed cases. The laboratory findings that were significantly different between the PCR (+) and (−) cases were D-dimer > 1000, increased BUN > 20 mg/l, pro-BNP > 125 ng/ml, troponin $T > 14$ ng/ml, increased leukocytes > 10,000/mm^3, neutrophilic leukocytosis, increased ALP > 300 U/l which were more prevalent again in PCR (−) cases. Focusing on older adults, there was not any difference between demographic characteristics, ICU needs, and survival between PCR (+) and (−) cases, nor in terms of using specific antihypertensive or antidiabetic drugs or triage physical examination parameters. Among triage symptoms, the PCR (−) cases had more prevalent dyspnea, less prevalent fatigue/myalgia. Similar to the total study population, COPD/asthma was more prevalent in PCR (−) cases. The laboratory findings that were significantly different between the PCR (+) and (−) cases were increased BUN > 20 mg/l, pro-BNP > 125, troponin $T > 14$, increased leukocytes > 10,000/mm^3, neutrophilic leukocytosis which were all more prevalent in the PCR (−) group. There was no difference in the prevalence of bilateral diffuse pneumonia in the older subgroup in contrast to the finding in the general study population. The results of this study suggest that the PCR (+) and (−) cases display very similar disease phenotypes, course, and outcomes with few differences between each other. As a quick look, there were more accompanying co-morbidities and some worse laboratory findings indicating systemic involvement, such as cardiac, renal, and hepatocellular damages in the PCR (−) group. This may indicate the worse immune protective response to the infection in PCR (−) cases. A finding against this suggestion was the higher prevalence of bilateral diffuse pneumonia in PCR (+) cases. However, of note, this was not valid for the older subgroup, and the consequences of the disease were indifferent between the PCR groups.

We should note some limitations of the study. As this is a single-center retrospective study, we cannot suggest a causality relationship,

and some confounders might have been overlooked. However, to our knowledge, this is the first study that compares clinical presentation, laboratory, and imaging features of PCR positive and PCR negative patients diagnosed as COVID-19, also representing the very first study focusing on older adults in this regard. Another strength is, in line with the standard approach of our center, we introduced a structured approach to triage patients. Hence, there is no missing data except for the data on less frequent potential presenting symptoms of the infection (loss of smell/taste and gastrointestinal symptoms), which were identified later in the course of the pandemic.

5. Conclusion

In conclusion, we reported that The PCR (+) and (−) cases displayed very similar disease phenotypes, courses, and outcomes with few differences between each other. This proves the success of the COVID-19 clinical diagnoses in the pandemic era. The presence of more comorbidities and some worse laboratory findings may indicate the worse immune protective response to the infection in PCR (−) cases. Due to the diversity of immune response in the geriatric population, clinical diagnosis and early treatment are of great importance.

Further studies would help to clarify the success and role of this approach in the pandemic era.

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Informed consent

All participants agreed to participate in the study and the guardian of each subject signed written informed consent form.

Statement of ethics

Institutional review board approved the study. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

CRediT authorship contribution statement

Naci Senkal: Conceptualization, Investigation, Project administration, Resources. **Gulistan Bahat:** Supervision, Project administration, Writing – original draft. **Alpay Medetalibeyoglu:** Investigation, Resources. **Timurhan Cebeci:** Conceptualization, Investigation, Project administration. **Dilek Deniz:** Conceptualization, Investigation, Project administration. **Yunus Catma:** Conceptualization. **Meryem Merve Oren:** Conceptualization. **Emine Bilge Caparali:** Conceptualization. **Sena Bayrakdar:** Investigation. **Seniha Basaran:** Investigation. **Murat Kose:** Resources, Project administration. **Mustafa Erelel:** Conceptualization. **Mehmet Akif Karan:** Supervision, Visualization. **Tufan Tukek:** Supervision, Visualization.

Declaration of competing interest

All authors declare no competing financial disclosure. All authors declare no competing conflict of interest.

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Data availability

All data generated or analyzed during this study are included in this published article.

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