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Investigation of the disease process and drug combinations in patients with suspected/confirmed COVID-19 using favipiravir

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Abstract

Aims: It is aimed to investigate the disease processes and drug combinations in patients who received favipiravir treatment.

Methods: This cross-sectional, analytical and retrospective study included all patients aged ≥18 years (n = 502) who were hospitalised in Samsun, Turkey, for COVID-19 and were given favipiravir from the date between 25 March 2020 and 3 June 2020.

Results: In total, 58.6% (n = 294) of the patients were male and 24.5% (n = 123) were between the ages of 71 and 80 years. During the first case process, the mortality rate was 19.9%, whereas the rate of those who were discharged as is/followed up at home for 14 days was 37.3%. During the second case process, the mortality rate was 6.2%, and the rate of those who was discharged as is/followed up at home for 14 days was 65.6%. The mean length of hospital stay was 10.61 ± 8.17 days for the first and 7.97 ± 4.16 days for the second hospitalisation; this difference was significant. Mortality risk of those who used Tocilizumab or vitamin C beside Favipiravir was higher than those who did not. The length of hospital stay was higher in patients using tocilizumab than in those who did not ($P < .001$).

Conclusion: Administration of favipiravir later in the course of the disease makes it difficult to achieve the true efficacy expected from the drug and also makes it difficult for other combination drugs to contribute to survival. Favipiravir may also be effective in case of recurrence.

What's known

- There is still no drug that has exhibited excellent effectiveness against COVID-19.
- Favipiravir has been used in the later stages of the pandemic.
- Many drugs and combinations are still in the process of being tested.

What's new

- Administration of favipiravir later in the course of the disease makes it difficult to achieve the true efficacy expected from the drug.
- It has been observed that any drug combined with favipiravir does not contribute to the healing process.
- Favipiravir may also be effective in case of recurrence.

1 | INTRODUCTION

The battle of humanity is continuing at full speed against coronavirus disease (COVID-19), which has taken the world by storm since December 2019 and caused approximately 95 million cases and 2.0 million deaths as of 18 January 2021.[1] Various vaccine studies are being conducted in many countries, wherein several drugs such as remdesivir, interferon α-β, lopinavir, ritonavir, ribavirin, chloroquine/hydroxychloroquine, umifenovir, oseltamivir, azithromycin, favipiravir, nitazoxanide, ivermectin, vitamin C, tocilizumab and teicoplanin are being tested.[2-7] There is still no drug that has exhibited excellent effectiveness. Preliminary results and results of clinical studies have shown that favipiravir has promising potential in the treatment of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[8]

In the "Management and Treatment Guide for Patients with Covid-19," which was revised by the Turkish Ministry of Health on 25 March 2020, favipiravir was included in the treatment regimen for patients who have severe disease and do not respond to initial treatment.[9] This treatment, which was given only to critically ill patients during this period, was then administered to asymptomatic outpatients with a definitive diagnosis at 2 × 1600 mg loading dose for 5 days and 2 × 600 mg maintenance dose in the following days owing to the revised guidelines in the recent months.[10]

Favipiravir triphosphate is a broad-spectrum antiviral molecule. It is a purine nucleoside analogue that functions as a competitive inhibitor of RNA-dependent RNA polymerase. It was developed for influenza virus resistant to neuraminidase and M2 inhibitors.[11] Favipiravir is a prodrug and acts by converting in the cell to the ribofuranosyl 5′ triphosphate metabolite.[12] It has reduced efficacy in the presence of purine nucleotides such as ATP and GTP. It is metabolised by aldehyde oxidase enzyme.[13] It has an inhibitory effect against oseltamivir and zanamivir-resistant influenza A, B, C viruses and alpha/arena/bunya/ebola/entero/phlebo/flavi/filo/hanta/noro/paramyxo viruses.[2,14-17]

Favipiravir has been approved in Japan for new epidemic influenza strains that do not respond to standard antiviral treatments.[18] In China, it was approved for COVID-19 treatment in March 2020.[6]

In this study, we aimed to investigate the disease processes and drug combinations in patients who received favipiravir treatment.

2 | MATERIALS AND METHODS

Permission was obtained from the Turkish Ministry of Health for this cross-sectional, analytical and retrospective study, and ethical approval was obtained from the Noninvasive Research Ethics Committee of Samsun Training and Research Hospital (GOKA/2020/9/3).

The study included all patients aged ≥18 years (n = 502) who were hospitalised in Samsun (the most important city of Turkey in the North) for COVID-19 and were given favipiravir from the date when favipiravir was first allowed for use, ie, 25 March 2020, until 3 June 2020. Archives of 13 hospitals that could procure this drug and administer it to their patients were reviewed from the data pool of the Turkish Ministry of Health.

Demographic data, symptoms, contact history, presence of chronic diseases, lung computed tomography (CT) findings, polymerase chain reaction (PCR) positivity, intensive care needs, intubation needs, length of hospital stay, rehospitalisation history, other COVID-19 drugs administered at the hospital and current health conditions were analysed in patients who used favipiravir.

Data were analysed using SPSS version 20.0 (IBM, USA). Risk factors affecting mortality and rehospitalisation were examined by logistic regression analysis. Analysis results were expressed with frequency (percentage) values. $P < .05$ was considered significant.

3 | RESULTS

In total, 58.6% (n = 294) of the patients included in the study were male and 24.5% (n = 123) were between the ages of 71 and 80 years. During the first case process, the mortality rate was 19.9%, whereas the rate of those who were discharged as is/followed up at home for 14 days was 37.3%. The rate of cases those who had a CT scan was 92.2%. The rate of those whose CT results were compatible with those of viral pneumonia and/or COVID-19 was 80.6%, and the rate of those whose CT results were normal was 4.2%. The rate of those who needed intensive care was 26.9%, the intubation rate was 14.9%, the contact rate was 21.9% and the rate of patients with at least 1 positive PCR result was 38.2%. Considering the symptoms that led to admission to the hospital, it was determined that the rate of respiratory distress was 53.6%, that of cough was 46% and that of fever was 36.5%. The rate of those with a chronic illness was 54.4%. With respect to chronic diseases, hypertension (HT) was found in 37.2% of the cases, diabetes mellitus (DM) in 27.7% and chronic obstructive pulmonary disease (COPD) in 18.2% of the patients. The rate of those who were admitted for the second time was 6.4%. During the second case process, the mortality rate was 6.2%, and the rate of those who were discharged as is/followed up at home for 14 days was 65.6%. Considering the symptoms at the second hospitalisation, respiratory distress was observed in 61.5%, cough in 34.6% and fever 26.9% of the patients. In addition to favipiravir, the most commonly used drug was hydroxychloroquine (n = 452), with 90% success (Table 1). The mean length of hospital stay was 10.61 (8.17) days for the first and 7.97 (4.16) days for the second hospitalisation, and the difference was significant ($P < .001$).

The risk factors affecting mortality were analysed for the first case process. As a result of the univariate analysis, it was found that the risk of death was 708-fold higher in those who were admitted to intensive care than in those who were not ($P < .001$). Increased risk of death was also observed in patients who were at a more advanced age, intubated patients and those with chronic diseases. According to the multivariate analysis, admission to the intensive care unit, being intubated and at least one positive PCR result were found to be potential risk factors. Considering the drugs that were

TABLE 1 Frequency distributions

	Frequency (n)	Percentage (%)
Sex		
Male	294	58.6
Female	208	41.4
Age interval		
18-30	17	3.4
31-40	32	6.4
41-50	64	12.7
51-60	81	16.1
61-70	119	23.7
71-80	123	24.5
81-93	66	13.1
Name of the hospital		
Turkish Ministry of Health SBÜ Samsun Training and Research Hospital	117	23.3
Turkish Ministry of Health Çarşamba State Hospital	103	20.5
Private Medibafra Hospital	59	11.8
Private Medicana International Samsun Hospital	55	11.0
Ondokuz Mayis University Hospital	41	8.2
Turkish Ministry of Health Bafra State Hospital	38	7.6
Turkish Ministry of Health Samsun Gazi State Hospital	29	5.8
Private Atasam Hospital	25	5.0
VM Medical Park Samsun Hospital	16	3.2
Turkish Ministry of Health Vezirköprü State Hospital	8	1.6
Private Samsun Great Anatolian Square Hospital	7	1.4
Turkish Ministry of Health Terme State Hospital	2	0.4
Turkish Ministry of Health Havza State Hospital	2	0.4
First case process		
Discharged as is/follow-up at home continues for 14 days	187	37.3
No symptoms developed—for screening purposes	136	27.1
Death	100	19.9
Eliminated COVID-19 (not COVID-19)	40	7.9
Discharged after recovery/follow-up at home continues	18	3.6
Hospital monitoring continues	14	2.8
Follow-up continues at home	5	1.0
Admitted to the hospital after home follow-up	2	0.4
CT		
Yes	463	92.2
No	39	7.8
CT result		
Compatible with viral pneumonia (COVID-19 or else)	405	80.6
None	39	7.8
Normal	21	4.2
Non-infectious CT finding	18	3.6
Compatible with mixed infection (not COVID-19)	13	2.6
Compatible with bacterial infection	6	1.2
Intensive care		

(Continues)

TABLE 1 (Continued)

	Frequency (n)	Percentage (%)
Yes	135	26.9
No	332	66.1
Unspecified	35	7.0
Intubated?		
Yes	75	14.9
No	392	78.1
Unspecified	35	7.0
Has contact?		
Yes	110	21.9
No	392	78.1
At least one positive PCR result		
Yes	192	38.2
No	310	61.8
Symptom (1st hospitalisation)		
Respiratory distress	269	53.6
Cough	231	46
Fever	183	36.5
Gastrointestinal complaints	51	10.2
Weakness	49	9.8
Poor general condition	37	7.4
Common cold complaints	33	6.6
Other	25	5
Pain	23	4.6
Sore throat	18	3.6
Chest pain	14	2.8
Headache/dizziness	13	2.6
Chronic illness		
Yes	273	54.4
No	229	45.6
Chronic illness		
HT	102	37.2
DM	76	27.7
COPD	50	18.2
Coronary artery disease	44	16.1
Other	44	16.1
Heart failure	41	15.0
Malignancy	32	11.7
Kidney failure	23	8.4
Neurological diseases	22	8.0
Asthma	21	7.7
Second hospitalisation		
No	470	93.6
Yes	32	6.4
Symptom (2nd hospitalisation)		
Respiratory distress	16	61.5

(Continues)

TABLE 1 (Continued)

	Frequency (n)	Percentage (%)
Cough	9	34.6
Fever	7	26.9
Poor general condition	3	11.5
Chest pain	2	7.7
Nausea	1	3.8
Vomiting	1	3.8
Sore throat	1	3.8
Weakness	1	3.8
Second case process		
Discharged as is/follow-up at home continues	21	65.6
Eliminated COVID-19 (not COVID-19)	4	12.5
Monitoring continues at the hospital	2	6.3
Death	2	6.3
Follow-up continues at home	1	3.1
No symptoms developed—for screening purposes	1	3.1
Discharged after recovery/follow-up at home continues	1	3.1
Drug use		
Favipiravir	502	100.0
Hydroxychloroquine	452	90.0
Anticoagulant	346	68.9
Oseltamivir	222	44.2
Azithromycin	217	43.2
Vitamin c	127	25.3
Tocilizumab	32	6.4
Lopinavir/ritonavir	5	1.0

administered, tocilizumab use yielded statistically significant results in the univariate analysis ($P = .004$); the risk of death was found to be 3.012 times higher in those who used this drug than in those who did not use. Similar results were obtained for vitamin C, wherein the mortality risk of those who used vitamin C was 1.614 times higher than those who did not ($P = .049$; Table 2).

Analysing the factors affecting rehospitalisation in the univariate analysis, the risk of rehospitalisation of those who used oseltamivir was 3.146 times higher than those who did not ($P = .005$). In the multivariate analysis, the use of the same drug was found to be a risk factor affecting rehospitalisation, and the risk was increased by 4.291-fold. Other drugs and demographic data were not found to have a significant effect on re-hospitalisation (Table 3).

It was observed that the length of hospital stay was higher in patients using tocilizumab than in those who did not ($P < .001$). There was no difference between the mean length of hospital stay of those who used other drugs, and these patients had a shorter length of hospital stay than the others who took tocilizumab treatment. With respect to males, there was no difference amongst tocilizumab, vitamin C and oseltamivir. The mean length of hospital stay was higher in patients using tocilizumab than in those who used any other drug. In females, however, tocilizumab led to a similar length of hospital stay as lopinavir/ritonavir but a higher mean length of hospital stay than other drugs (Table 4).

4 | DISCUSSION

This study is one of the rare studies that investigate disease processes of patients with COVID-19 from the aspect of favipiravir. The fact that the effects of drugs combined with favipiravir on the case processes were also evaluated increases the strength of the study and renders the study as a guide for further studies and treatment processes.

Favipiravir use in hospitalised patients in Samsun was initiated with the detection of the first COVID-19 positive case in March 2020. Favipiravir is supplied by the Turkish Ministry of Health and sent to the provincial health directorate. The scientific committee recommended the use of favipiravir after 72 hours of hydroxychloroquine sulphate use in the beginning but then modified the said recommendation and stated that it could be used as the first choice in severe pneumonia. PCR positivity was not sought in patients in whom favipiravir treatment was started.[10] Therefore, our data also include the patients who were started on medication without PCR.

TABLE 2 Logistic regression analysis results for the first case process

	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Hydroxychloroquine	1.148 (0.539-2.449)	.720	3.38 (0.918-12.449)	.067
Oseltamivir	0.989 (0.363-1.537)	.960	1.309 (0.475-3.606)	.603
Azithromycin	0.847 (0.543-1.324)	.467	0.434 (0.178-1.058)	.066
Tocilizumab	3.012 (1.433-6.331)	**.004**	0.845 (0.194-3.669)	.822
Anticoagulant	1.548 (0.935-2.562)	.089	0.68 (0.239-1.937)	.470
Vitamin C	1.614 (1.002-2.599)	**.049**	1.835 (0.665-5.069)	.241
Sex	0.752 (0.478-1.184)	.219	0.643 (0.279-1.484)	.301
Age	1.044 (1.027-1.062)	**<.001**	1.002 (0.971-1.034)	.895
CT	1.100 (0.994-1.218)	.065	0.669 (0.177-2.535)	.555
Intensive care (yes)	708.186 (96.223-5212.116)	**<.001**	1242.182 (115.567-13 351.735)	**<.001**
Intubated (yes)	43.515 (22.295-84.933)	**<.001**	0.326 (0.137-0.773)	**.011**
Contact (yes)	0.935 (0.547-1.597)	.805	1.782 (0.515-6.161)	.362
At least one positive PCR (yes)	0.936 (0.595-1.472)	.774	0.244 (0.068-0.878)	**.031**
Chronic illness (yes)	2.903 (1.783-4.728)	**<.001**	1.626 (0.603-4.385)	.337

Bold indicate significant values.

Favipiravir looks promising for COVID-19. Therefore, it continues to be investigated in monotherapy or combination therapy form. It is also being compared with placebo or other antiviral regimens. Combination examples of favipiravir include IFN-α, lopinavir/ritonavir, darunavir/ritonavir, chloroquine and tocilizumab therapy.[19-22]

In a nonrandomised study that included 80 patients with COVID-19 in China, patients with mild or moderate COVID-19 were enrolled within 7 days of disease onset, whereas severely or critically ill patients were excluded. A significant reduction in SARS-CoV-2 viral clearance time was detected in patients included in the study group that was treated with favipiravir compared with the control group that was treated with lopinavir/ritonavir. Radiographic improvement was seen in 91.4% of patients in the favipiravir group and 62.2% of patients in the lopinavir/ritonavir group. A significantly lower rate of side effects was observed in the favipiravir group than in the lopinavir/ritonavir group (11.4% vs. 55.6%; $P < .01$).[23]

According to a study comparing umifenovir with favipiravir, fever was decreased and cough improved faster in the favipiravir group than in the umifenovir group. No difference was found in terms of oxygen or noninvasive mechanical ventilation requirement.[24]

Generally reviewing other types of combinations mentioned in the literature, Gautret et al showed that azithromycin significantly enhanced the efficacy of hydroxychloroquine in the treatment of 20 patients with severe COVID-19.[25] However, this combination was used less frequently due to the cardiac side effects thereof and failure to achieve the expected success.[26] Combinations of oseltamivir with favipiravir, chloroquine, darunavir and ritonavir are also being studied.[27] However, no definitive success has been achieved yet. In a randomised controlled study conducted at Shanghai Public Health Clinical Centre, the efficacy of the darunavir/cobicistat combination was evaluated in 30 patients with COVID-19, and it was shown that the said combination was not effective in alleviating the symptoms or shortening treatment duration.[28] According to a clinical research conducted with 199 severely ill patients with SARS-CoV-2 infection at Jin Yin-Tan Hospital in Wuhan, the mortality rate in patients receiving the lopinavir/ritonavir combination was not different than that of the control group receiving standard hospital care.[29] It was thought that ribavirin could be combined with IFN-α, β and lopinavir/ritonavir, and the studies are still ongoing.[30]

According to our data set, tocilizumab was not found to be superior to other drugs in combined therapy. It was even observed that the length of hospital stay was higher with tocilizumab than with other drugs. However, since the patient group generally consists of those hospitalised with severe pneumonia, the recent attempts to use tocilizumab treatment may have had an impact on this situation. Apart from this, it is also interesting that the patients who used oseltamivir were more likely to be hospitalised for the second time. Patient groups in which combinations are administered from the first day are necessary to observe the actual effects of these drugs. An experiment has been initiated at Peking University Hospital to investigate the effects of the combined use of oseltamivir and tocilizumab on COVID-19 in 150 patients.[22] In addition, there is an ongoing study investigating the combination of tocilizumab and favipiravir against tocilizumab alone and favipiravir alone.[31]

Since SARS-CoV2 induces high IL-6 levels and gradual complement activation, which contribute to the prothrombotic state of patients with COVID-19, it was reported that the use of anti-inflammatory drugs that target and inhibit the IL-6 pathway and gradual complement activation could be beneficial. Similarly, drugs that reduce endothelial dysfunction, such as statins and ACEI, may

TABLE 3 Determining the risk factors affecting the second hospitalisation

	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Hydroxychloroquine	0.702 (0.235-2.100)	.527	0.459 (0.114-1.847)	.273
Oseltamivir	3.146 (1.411-7.015)	**.005**	4.291 (1.602-11.492)	**.004**
Azithromycin	0.748 (0.348-1.606)	.456	1.228 (0.483-3.122)	.666
Tocilizumab	0.491 (0.065-3.722)	.491	0.786 (0.09-6.837)	.827
Anticoagulant	1.256 (0.547-2.887)	.591	1.681 (0.623-4.53)	.305
Vitamin C	0.574 (0.215-1.532)	.268	0.615 (0.195-1.937)	.406
Sex	0.759 (0.351-1.639)	.482	0.807 (0.346-1.885)	.621
Age	1.008 (0.985-1.032)	.491	0.997 (0.97-1.026)	.859
BT	1.017 (0.866-1.195)	.838	0.452 (0.056-3.687)	.459
Intensive care (yes)	1.942 (0.692-5.451)	.207	0.55 (0.114-2.658)	.457
Intubated (yes)	3.652 (0.962-13.862)	.057	1.089 (0.166-7.167)	.929
Contact (yes)	0.519 (0.176-1.530)	.235	2.397 (0.657-8.747)	.185
At least one positive PCR (yes)	0.663 (0.296-1.488)	.320	1.175 (0.453-3.046)	.740
Chronic illness (yes)	1.842 (0.853-3.979)	.120	0.514 (0.198-1.334)	.172

Bold indicate significant values.

TABLE 4 Comparison of the length of hospital stay (days) according to drugs

	Total	Male	Female
Hydroxychloroquine	10.8 (8.3)[a]	10.6 (8.3)[a]	11.0 (8.4)[a]
Oseltamivir	11.3 (8.5)[a]	11.4 (8.3)[ab]	11.1 (8.8)[a]
Azithromycin	10 (7.6)[a]	10.2 (7.8)[a]	9.8 (7.3)[a]
Ritonavir/lopinavir	11.6 (8.1)[a]	9.0 (1.4)[a]	13.3 (11.0)[ab]
Tocilizumab	17.6 (14.2)[b]	16.2 (14.3[b]	21.9 (13.6)[b]
Anticoagulant	10.7 (8.3)[a]	10.7 (8.8)[a]	10.9 (7.6)[a]
Vitamin c	11.2 (8.7)[a]	11.0 (9.8)[ab]	11.6 (7.0)[a]
P	<.001	<.001	<.001

Note: a, b: There is no difference between drugs designated with the same letter.

also play a role. In addition, low molecular-weight heparin is widely used to prevent thrombus formation in patients with COVID-19. All of these drugs can help fight the disease in a single or combined form.[32] Amongst our patients in the said city, many patients benefited from these treatment strategies. However, according to our data set, it was observed that anticoagulants combined with favipiravir did not contribute significantly to the first or second case processes. The number of studies on this combination is very limited, and potential treatments such as nebulised tPA, heparin and nafamostat combination have also been discussed.[33]

According to the news reported in The Guardian, sources of the Japanese Ministry of Health argue that the drug is not effective in people with more severe symptoms. This suggests that the drug, which was said to be procured especially for patients in intensive care, had controversial efficacy on this patient group, whereas its use may be more effective in patients who are not severely ill and prevent these patients from getting worse.[34]

In the present study, the higher mortality rates than the COVID-19-related mortality rates (2.3%)[1] throughout the country suggest that favipiravir use may be more effective in outpatients than in hospitalised patients. The length of hospital stay was shorter, mortality rate was lower and discharge rate was higher amongst patients who were rehospitalised than those were hospitalised only once. Favipiravir may have a more potent effect at its second encounter with the virus. It should be separately studied whether this is related to the enhanced immune response in such patients.

Broadly, the rates of presenting complaints in COVID-19 were as follows: fever 80%, cough 65%, weakness 40%, sputum production 30%, myalgia 20%, dyspnoea 18%, chills 15%, sore throat 13%, headache 12%, anosmia 10%, diarrhoea 8%, nausea/vomiting 7%, nasal congestion 4% and runny nose 4%.[35] The most common symptom observed in our patient group at both first and second hospitalisation was respiratory distress. It has been shown that advanced age, male sex, smoking and chronic diseases are associated with a severe or mortal course of COVID-19.[36,37] We also found that age and presence of a chronic disease were positively correlated with mortality in our patients. In the study conducted by De Abajo et al, 1139 patients with COVID-19 and 11,390 healthy subjects were compared, and it was found that cardiovascular diseases and the associated risk factors were more prevalent amongst the patients than amongst the control group and that the comorbidities such as HT, COPD, DM and heart failure were also more common in the patient group than in the control group.[38] In this study, the most common comorbidities were HT, followed by DM and COPD. In a study by Lovato and de Filippis evaluating the data of 1556 patients, the rate of critically ill patients

with complications was 9%, the rate of those admitted to intensive care was 7.3%, the rate of those who needed mechanical ventilation was 3.4% and the mortality rate was 2.4%.[39] However, according to the meta-analysis published by Rodriguez-Morales et al, these rates were higher, wherein the rate of admission to intensive care unit was 20.3% and the overall mortality rate was 13.9%.[40] Our data are similar to the data provided by this meta-analysis.

Factors such as the fact that research articles on COVID-19 are all recently published, that there are not enough meta-analyses and even original studies on COVID-19 and that we learn something new about the disease each day are the common limitations of such research, and these limitations become obvious whilst discussing the current data.

In conclusion, administration of favipiravir later in the course of the disease makes it difficult to achieve the true efficacy expected from the drug and also makes it difficult for other combination drugs to contribute to survival. The shortened length of hospital stay, lower mortality rate and increased survival in patients who were rehospitalised due to COVID-19 show that favipiravir may also be effective in case of recurrence. It is clear that there is a need for further studies to compare the early and late effects of favipiravir in terms of the clinical picture and the effectiveness of drug combinations.

DISCLOSURES

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

RESEARCH INVOLVING HUMAN PARTICIPANTS AND/OR ANIMALS

Research involves only human participants.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Non-Invasive Research Ethics Committee of Samsun Training and Research Hospital [GOKA/2020/9/3]). and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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