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The Urine Foaming Test in COVID19 as a Useful Tool in Diagnosis, Prognosis and Follow-up: Preliminary Results

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INTRODUCTION

Analytical tests for the COVID-19 are very important for management of disease and prevent to spread. A positive real-time reverse-transcriptase polymerase chain reaction (RT-rtPCR), in combination with medical and epidemiologic data, is the present classic for identification, but numerous difficulties still occur. Serological assays help to know epidemiology improved and to assess vaccine responses but they are unpredictable for diagnosis in the acute phase of infection (1). Prospective and comparative assessments of rapid, simple, reliable tests for COVID-19 infection in clinically applicable locations are immediately required (2). The features for optimal testing for diagnosis of COVID19 should contain a short turnaround time, low equipment requirements, high accuracy, low cost to let admission to testing, also considering testing priorities to diagnose vulnerable populations. RT rt-qPCR on nasopharyngeal specimens have some of these features, thus signifying the current gold standard in the diagnosis of COVID19 (3). Nevertheless, many reasons, both procedural and virus-related, may damage its reliability (4) such as a one-time sampling (5) and lack of procedural standardization (sample collection, swab types, processing) (6). Also, it remains difficult by lacks of personnel and supplies (7). These recent concerns for the laboratory diagnosis of COVID-19 must be understood by clinicians, microbiology laboratories, public health authorities and, policymakers (8). Therefore, new rapid tests, point-of-care (POC) assays, would support infection recognition and prevention in in communities without infrastructure, also in low- and middle-income locations. With this need in mind, we planned to develop a test to identify metabolites excreted specifically for COVID19 in urine, which is the most easily taken biological sample. In current studies on COVID-19 patients, some urine biochemical parameters such as blood, protein are different between patients with severe COVID19 and healthy controls (9, 10). Proteinuria is a cardinal sign of diverse renal diseases and can result in foamy urine. Foaming occurs because albumin has a soap-like effect that reduces the surface

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tension of urine (11). Foam forms by trapping pockets of gas in liquid with the help of surfactant. A surfactant is an organic compound that is amphiphilic (or amphipathic), meaning containing both hydrophilic and hydrophobic ends. A surfactant diffuses in water and adsorb at interfaces between air and water where the water insoluble hydrophobic ends aggregate to form a foam. In general, proteins or polypeptides have amphiphilic properties that can function as a surfactant and form foam in the urine. On the other hand, certain free amino acids share this property and potentially can also contribute to foam formation (12). After suspicious contact or exposure with the COVID19, if transmission has occurred, as the viral load increases, the peptides of the virus and the metabolites of chemical reactions caused by the virus are excreted in the urine. The onset time and amount of excretion in the urine is related to the virulence of the causative pathogen, the amount of viral load at the time of first exposure, individual immunity, metabolism and existing comorbid diseases. Reagent in a foaming test tube specially prepared in the R&D Laboratory (MSK®) reacts with both COVID19-specific metabolites and metabolic degradation products secondary to the virus found in urine. At this stage, the urine sample foams by shaking the test tube for 15 seconds. The foaming rate increases in direct proportion to the virus load in the body. Less foam in the urine of patient with a low virus load, and more foam occurs in patients with more. Calibration studies were carried out in the R&D laboratory with urine samples taken from patients diagnosed with COVID-19 and healthy individuals known to have not had COVID-19. As a result of the data obtained, the color scale has been set on the test tube. Urine Foaming Test (UFT) results are evaluated according to this color scale; Green Zone: No virus-specific metabolites in urine, negative or mild clinical features (Figure 1). Yellow Zone: The presence of a low amount of virus-specific metabolites in the urine, requiring further investigation and follow-up. Orange Zone: Increased virus-specific metabolite in urine, adverse clinical picture, requiring further investigation and follow-up. Red Zone: Presence of intense viral metabolites in urine (and/or substances that should not

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be in urine), severe clinical picture. Although there are no symptoms and signs of Covid-19, people who have been detected in the especially Orange Zone or Red zone should be evaluated in terms of urinary system pathologies.

MATERIAL AND METHOD

The study which was designed as a prospective, randomized, single-blind (evaluator), was carried out in a tertiary training and research hospital of the Ministry of Health in Istanbul. This research was approved by the local Clinical Research Ethics Committee on October 5, 2020 (2011-KAEK-40 no:2020-437) and, permission was obtained from the Ministry of Health (2020-09-29T19_05_46). Also, written informed consent for the study was obtained from each participant included. In this study, consecutively, admitted to outpatient and/or hospitalized patients with a suspected case of COVID-19 from October 8, 2020, to October 15, 2020, were identified at a single tertiary care referral hospital and followed up to the end of November 2020. All suspected COVID-19 patients were included in this cohort study, but patients with diabetes and nephrotic disease were excluded. All suspected COVID-19 patients were evaluated in the infectious diseases clinic of the hospital. Then, suspected patients experienced physical examinations with routine blood tests, RT-PCR and chest CT scans. According to the inclusion and exclusion criteria 171 patients subjects was included in this study divided into three groups; group A: outpatients with suspected COVID19 (n=80), group B: inpatients for follow-up and treatment (57), group C: patients in intensive care unit (n=34). In addition, 30 healthy volunteers were included as the control group D (n = 30).

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Mild symptoms are low-grade fever (not more than 38 degrees celsius), dry cough, fatigue, sore throat, headache, the new loss of taste, and smell. Moderate symptoms are fever of about 38,5-39 degrees celsius, chills, deep cough, fatigue and body aches, muscle pain, the general feeling of being unwell. Severe symptoms are shortness of breath, chest discomfort, confusion/unresponsiveness, possible gastrointestinal issues, like diarrhea or nausea, cardiovascular or central nervous system findings. All data of the patients were obtained from the hospital information management system (HIMS) and the physician caring for the patient.

Specimen collection and handling: 10 ml of urine samples were taken from all patients and the control group into a sterile urine glass and transferred to the laboratory as soon as possible. All urine samples, as soon as accepted by the laboratory, were analyzed by the same technician with a urine foaming test tube and evaluated by the same biochemist according to the color scale. Urine was added to the test tube with foaming urine with the help of a pasteur pipette to the black line of the tube (approximately 2.5 ml) and shaken for 15 seconds. The foam level formed was recorded as one of the green, yellow, orange and red zones indicated on the tube.

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Statistical Analysis: All analyses were performed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In the evaluation of the data, in addition to descriptive statistical methods (mean, standard deviation), Shapiro - Wilk normality test was used to examine the distribution of variables, Kruskal Wallis test for subgroup comparisons of variables that did not show normal distribution, Dunn's multiple comparison test for comparison of paired groups, Mann Whitney U test for comparison of paired groups, Chi-square test was used to qualitative data. Areas under the Curve (ROC) were calculated for differential diagnosis according to the results of the UFT / clinical status, patient group, RT-PCR test and CT, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood- ratio LR (+) values were determined. The results were evaluated at the significance level of $p < 0.05$ in the 95% confidence intervals (CI)

RESULTS

The number of patients in each group and the distribution of the results of UFT, RT-PCR and CT are given in **Table 1**. A statistically significant difference was observed between the clinical situation, UFT results, RT-PCR results and CT image features distributions of control, outpatient, inpatient and intensive care patients (all of them p = 0.0001). The results of UFT test orange and red, positive RT-PCR and positive CT in inpatients and intensive care patients was statistically significantly higher than in the outpatient and control groups **(Table 2).** A statistically significant differences were observed between the biochemical parameters and the results of UFT green, yellow, orange and red region in inpatient and intensive care patients (p<0,01). All biochemical parameters increased from green to red according to the color scale of the UFT test in inpatients and intensive care patients.The comparison of the results of C-RP, D-Dimer, ferritin, procalcitonin, interleukin-6 with the results obtained according to the UFT color scale is given in **Table 3.** The diagnostic accuracy of UFT was determined in all group, the pooled sensitivity was 92% (95% CI: 87–95%) and specificity was 89% (95% CI: 80–98%) **(Table 4).**

DISCUSSION

Rapid and accurate diagnosis of COVID-19 is essential to establish an adequate therapeutic strategy to reduce morbidity and mortality, as well as pandemic control. In the pandemic, significant challenges have arisen in screening, diagnostic and follow-up testing. It is also important to identify patients who can be followed at home to reduce the burden of healthcare. Several diagnostic tools are needed to identify or rule out current infection, identify people in need of inpatient treatment or intensive care (13). For this purpose, we aimed to develop a point of care test that is evaluated with different foaming levels by a chemical reaction specific to the amino acid content of virus-specific peptides in the urine sample. Normal urine is clear, with a yellowish hue, with no blood or foam. Foamy urine is a sign of protein in the urine. This could be caused by a some of diseases that directly impact the kidneys, but can also be a symptom of a medical issue affecting other systems. The peptides of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (the cause of COVID-19 in humans) and the metabolites of specific chemical reactions caused by the virus are excreted in the urine. The

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foam level is proportional to the amount of the amino acid content of the peptide structures of the SARS-COV2 virus in the urine. Our preliminary results show that the urine foaming (UFT) test is useful and usable particularly in predicting the clinical severity of the disease. Moreover, In an unpublished study involving 112 inpatients with this test, significant results related to prognosis and mortality were obtained.

The WHO presently recommend COVID-19 diagnosis to be carried out by laboratories using molecular tests targeting SARS-CoV-2 virus RNA. Even if RT-rtPCR is the most commonly accepted method for diagnosis, it may cause false-negative results, and its use is restricted by the necessity of laboratory infrastructure (14). False-negative results can may be caused by mostly because of insufficient extraction of nucleic acid; poor sample quality; low viral load; sample collection time; inappropriate sample storage, transport, and handling; and PCR inhibition (15,16). Results of various RT-PCRs protocols have revealed difference in their performance depending on the primers and probes. In many RT- PCR tests, the primers were designed against the envelope (E) and RNA-dependent RNA polymerase (RdRp) regions (17). The E-region was used for screening, while the RdRp region was used for confirmation. Some researchers settled one-step rtPCR tests to sense open reading frame (ORF) 1b and N regions of SARS-CoV-2 (18). The N region assay was used for screening, while ORF1b testing served as a confirmatory test. On the other hand, since ORF1b and N regions are highly conserved in Sarbecoviruses, the specific primers could also bind other coronaviruses and associated viruses. The custom of specific primers provides the high specificity of result, but the possibility of false-positives cannot be excluded (13). A chest computerized tomography (CT) scan can be secondhand as a diagnostic tool that allows physicians to well identify COVID-19 infection in many RT-PCR false-negative cases. Repeat tests can be needed if the patient has a clinical feature of viral pneumonia, and/or radiographic findings likeminded with COVID-19 pneumonia (19). Some Chinese articles, explain the challenge of recognizing gold standard for

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laboratory testing. In a study of 1,014 patients with suspected COVID19 who experienced both CT and RT-PCR testing, 580 offered with positive RT-PCR and positive CT findings, while 105 were negative by both laboratory test (20). Of the 329 patients with conflicting results, only 19 were positive by RT-PCR, whereas 308 had positive CT findings. Therefore, 97% of patients with positive RT-PCR had positive chest CT, but most of patients with negative RT-PCR demonstrated viral pneumonia. Some of these patients later had positive RT-PCR. This study makes clear the challenge of developing a gold standard for diagnosis. RT-PCR results from a nasal swab are most likely to be positive in the first week after onset of symptoms, with the likelihood of a positive result dropping after that. Similarly, in our study, patients with moderate clinical findings and positive CT findings were detected in outpatients and inpatients, although RT-PCR was negative.

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Although the duration of SARS-CoV-2 viral shedding in the upper and lower respiratory tract and stool has been reported limited data are available for that in the urine. Nomoto et al investigated the detectability and duration of SARSCoV-2 RNA in the urine among patients with different severities of COVID-19 (21). In their study, SARS-CoV-2 RNA was detected in the urine of two of 20 patients (10%). Their results suggest that SARS-CoV-2 RNA may be excreted in the urine depending on the severity of COVID-19. The other 2 previous reports have evaluated the presence of this virus in urine (22,23). One of them the virüs was detected in 1 of 9 patients (11.1%) and, the other one include 72 urine specimens from patients, however, no patients tested positive for SARS CoV-2 RNA (23). In a meta-analysis examining the viral transmission of COVID-19 with urine and its clinical relationships, while COVID-19 is rarely detected in infected urine, infection transmission through urine was reported. Also, infected urine is more likely in the presence of moderate or severe disease (24).

Recently, research and development (R&D) studies on urine tests in the diagnosis of Covid19 are common. Because urine is a simple and noninvasive biological sample. At the

Medical Center of Göttingen University (Germany), researchers detected pathologies in the urine samples of patients with COVID-19 who converted very sick within a few days (urine samples positive for blood, albumin, and leukocytes). They report that analysis of a urine sample on admission to hospital can be used to identify the systemic capillary leak syndrome, which can be a predictor of fluid overload, respiratory failure, need for ICU admission, and death (25). They summarized that the respiratory tract is the entry for SARS-CoV-2 infection but, COVID-19- related nephritis, which can be just screened for through a simple and low-cost urine sample analysis, might help predict complications. In another project, Chemists at Iowa State University are developing a paper-strip urine test to detect infection by the coronavirus that causes COVID-19. The test is designed to detect the presence of a coronavirus protein in a urine sample. The research group uses electric fields to boost test sensitivity. This technology, called electrokinetics, is used to concentrate, separate, isolate and manipulate charged particles (26). We also propose this method we developed in a urine sample as a cost-effective and efficient tool. We will initiate a multicentre observational study in Istanbul to confirm our findings. If validated, we believe this test could allow early anticipation of later need for ICU admission, improved allocation of patients for special therapies. The same test could be used for the risk evaluation of outpatients.

Consequently, easy-access, non-invasive, available at the point of care, with a scalable color urine foaming test will facilitate the rapid and accurate diagnosis and monitoring of COVID19 infections and greatly assist in the control of this pandemic.

We declare no competing interests.

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Table 1. The number of patients in each group and the distribution of the results of UFT, RT-PCR and CT

		n	%
Group	**A(Outpatient)**	80	39,80
	B (Inpatient)	57	28,36
	C (ICU)	34	16,92
	D (Control)	30	14,93
UFT	**Green Zone**	102	50,75
	Yellow Zone	51	25,37
	Orange Zone	33	16,42
	Red Zone	15	7,46
RT-PCR	**Negative**	114	56,72
	Pozitive	87	43,28
CT image feature	**COVID-19 negative**	15	16,48
	COVID-19 positive	76	83,51

UFT: urine foaming test RT-PCR: real-time polymerase chain reaction
CT: computerized tomography

Table 2: Comparison of Covid19 patients in outpatient, inpatient and intensive care units according to clinical status, UFT, RT-PCRand CT images

		A (outpatient)		B (Inpatient)		C (ICU)		D (Control)		
		n	%	n	%	n	%	n	%	p^{+}
Clinical Situation	**Mild**	58	72,50%	11	19,30%	1	2,94%	30	100,00%	
	Moderate	22	27,50%	46	80,70%	8	23,53%	0	0,00%	
	Severe	0	0,00%	0	0,00%	25	73,53%	0	0,00%	**0,0001**
UFT	**Green**	51	63,75%	11	19,29%	3	8,82%	30	100,00%	
	Yellow	26	32,50%	22	38,59%	10	29,41%	0	0,00%	
	Orange	3	3,75%	15	26,32%	15	44,12%	0	0,00%	
	Red Zone	0	0,00%	9	15,79%	6	17,65%	0	0,00%	**0,0001**
RT-PCR	**Negative**	64	80,00%	12	21,05%	8	23,53%	30	100,00%	
	Positive	16	20,00%	45	78,95%	26	76,47%	0	0,00%	**0,0001**
CT image features	**Negative**	76	95,00%	18	31,58%	1	2,94%	0	0,00%	
	Positive	4	5,00%	39	68,42%	33	97,06%	0	0,00%	**0,0001**

$^{+}$ Chi-Square test. UFT: urine foaming test RT-PCR: real-time polymerase chain reaction
CT: computerized tomography

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Table 3: Comparison of biochemical parameters according to color scale of urine foaming test (UFT) in inpatients and intensive care (ICU) patients

Inpatient/ICU patients	Green zone n:14	Yellow zone n:32	Orange zone n:30	Red zone n:15	p†
C-RP	57±64,82	60,42±43,23	193,18±151,56	205,36±100,92	**0,0001†**
D-Dimer	2,48±1,21	4,74±8,04	8,14±8,21	13,47±12,63	**0,004†**
Ferritin	306,84±462,63	641,58±446,04	1322,62±1879,75	1846,91±4887,84	**0,006†**
Procalcitonin	0,64±1,32	0,99±2,19	3,89±5,12	8,61±19,72	**0,007†**
Interleukin-6	12,85±9,18	75,36±46,16	446,18±378,5	727,05±950,64	**0,01***

†Kruskal Wallis test *Mann Whitney U test

Dunn's multiple comparisons test	C-RP	D-Dimer	Ferritin	P.Kalsi.	İ.Lökin-6
Green / Yellow	0,678	0,998	**0,004**	0,629	0,164
Green / Orange	**0,002**	**0,009**	**0,008**	**0,016**	**0,047**
Green / Red	**0,005**	**0,013**	**0,001**	**0,01**	**0,001**

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Table 4: Performance of orange-red zone results of UFT test according to clinical situation, RT-PCR and CT findings. The last line shows the total performance for all color scales of the UFT with respect to the RT-PCR and / or CT positive COVID19 status. According to the table, the UFT test shows the highest sensitivity when compared to the clinical situation (in this case the CT results are also positive).

		Sensitivity	Specificity	PPV	NPV	Accuracy	LR(+)
Mild/ Moderate	**Orange/Red Zone**	0,95	0,85	0,56	0,99	0,87	6,33
Severe/ Critical	**Orange/Red Zone**	0,93	0,98	0,87	0,99	0,97	40,39
RT-PCR	**Orange/Red Zone**	*0,87*	*0,80*	*0,85*	*0,83*	*0,84*	*4,47*
CT	**Orange/Red Zone**	0,93	0,87	0,67	0,99	0,88	7,32
RT-PCR and/or CT	**UFT/ All**	*0,87*	*0,80*	*0,97*	*0,35*	*0,84*	*5,47*

PPV: Positive predictive value NPV: Negative predictive value LR: likelihood-ratio a b

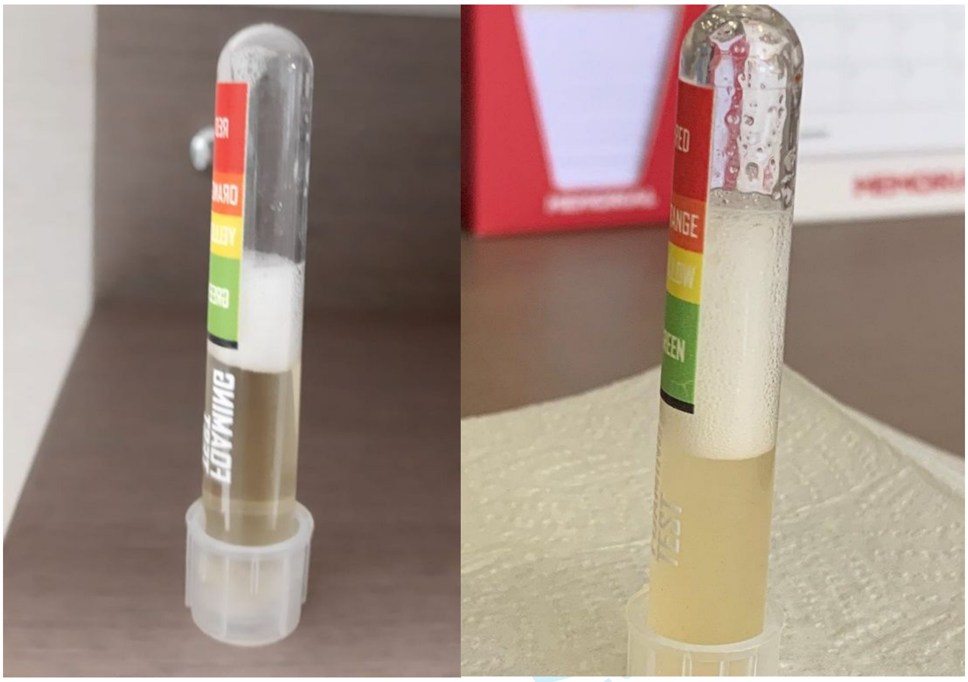

Figure 1: Two examples of urine foaming tests with foam levels in the green zone (a) and orange zone (b)