RESEARCH ARTICLE

Fecal occult blood and urinary cytology tests for rapid screening of inflammatory infection in the gastrointestinal and urological systems in patients with Coronavirus disease 2019

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Abstract

Background: Gastrointestinal infections (GI) and urological infections (UI) have not been fully addressed in COVID-19 patients. We aimed to evaluate the values of routine fecal occult blood (FOB) test and urinary cytology test (UCT) for screening of GI and UI in COVID-19 patients.

Methods: In this retrospective study, COVID-19 patients without associated comorbidities were divided into FOB- or UCT-positive or FOB- or UCT-negative groups. Their clinical characteristics and laboratory findings were then compared.

Results: A total of 13.6% of patients (47 of 345) tested positive for FOB, and 57.4% (27 of 47) of these patients lacked gastrointestinal symptoms. A total of 30.1% of patients (104 of 345) exhibited gastrointestinal symptoms, and 38.0% (131 of 345) were positive for either FOB or gastrointestinal symptoms. FOB-positive patients possessed significantly higher levels of C-reactive protein and fewer lymphocytes than FOB-negative patients. A total of 36.9% of patients (80 of 217) exhibited positive UCT, and 97.5% (78 of 80) of these patients possessed normal levels of serum markers for renal injuries. Significant differences in age and sex ratios were observed between the UCT-positive and UCT-negative groups, and 72.4% (42 of 58) of female patients over 60 years old were UCT-positive.

Conclusions: Fecal occult blood test in combination with gastrointestinal symptoms could serve as a simple and useful screening approach for GI diagnoses for COVID-19. Age and sex are risk factors for UI in COVID-19 patients. UCT could be a sensitive tool for assessing early UI at a stage in which serum markers for renal injuries appear normal.

Abbreviations: ACE2, angiotensin-converting enzyme 2; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; FOB, fecal occult blood; GI, gastrointestinal infection; IQR, interquartile range; IRB, Institutional Review Board; LV, lymphocytes; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UCT, urinary cytology test; UI, urological infection; WBC, white blood cell.

Du, Cao, Tan and Wang equally contributed to this study.

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1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has become a global threat to public health, where it has spread to 188 countries to cause infections in more than 26,522,000 people and has claimed 873,270 global victims to date (https://coronavirus.jhu.edu/map.html). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative organism of COVID-19. The spike protein of SARS-CoV-2 is believed to mediate the entry of the virus into host cells via angiotensin-converting enzyme 2 (ACE2).1 ACE2 has been found to be highly expressed in multiple tissues, including the lungs, heart, kidneys, testes, and intestines,2,3 suggesting that these organs are vulnerable to attack by SARS-CoV-2. Indeed, many patients with COVID-19 develop digestive symptoms,4,5 and viral nucleic acids have been identified in patient stool and urine specimens.6,7 Detection of SARS-CoV-2 is typically performed using nasopharyngeal swabs to determine viral load in the upper respiratory tract. Diagnoses of gastrointestinal infection (GI) and urological infection (UI) have been generally underestimated. Reports have shown that approximately 3%-26.0% of COVID-19 patients exhibit associated gastrointestinal symptoms.4,5,8,9

In this study, we speculated that simple and feasible tests could aid clinicians in quickly assessing the presence of GI and UI in COVID-19 patients. We found that 57.4% of patients (27 of 47) that tested positive for fecal occult blood (FOB), a test revealing the presence of GI, did not exhibit noticeable gastrointestinal symptoms. Furthermore, we found that 36.9% of patients (80/217) were positive for urinary cytology test (UCT); however, only 2.8% of patients (6/217) showed symptoms of UI (such as lumbago or urgent or frequent urination). Our results suggest that both FOB and UCT, which are convenient, cheap, and rapid, can serve as valuable screening tools for the assessment of potential virus-induced GI and UI, particularly for patients in rural areas and underdeveloped countries where detection of viral nucleic acids or antibodies is not yet feasible.

2 | MATERIALS AND METHODS

2.1 | Study design

This retrospective study was performed at the Cancer Center of Union Hospital, Tongji Medical College (Wuhan, P. R. China), which is a designated hospital for the management of patients with COVID-19. This study was approved by the Institutional Review Board (IRB) at the Union Hospital, and the requirement for a written consent form was waived by the IRB committee. A total of 347 COVID-19 patients (confirmed by laboratory real-time reverse transcriptase-polymerase chain reaction [RT-PCR] assay) who were admitted to our hospital between February 14 and March 3, 2020, were included in this study. The patients were classified into one of three severity categories that included mild, severe, or critical according to guidance on COVID-19 (6th edition) released by the National Health Commission of China.10 Patients with gastrointestinal medical histories were excluded from the use of FOB for the assessment of GI. Similarly, patients with urological preconditions were excluded.
from the use of UCT for the assessment of UI. UCT included red blood cell (RBC) and white blood cell (WBC) analyses and routine urine analysis using a urine sample. We excluded patients with diabetes or hypertension to prevent the potential influence of secondary nephropathy. Figure 1 presents the application of the inclusion and exclusion criteria for patient enrollment. Based on FOB and UCT results, patients were divided into FOB- or UCT-positive or FOB- or UCT-negative groups, respectively. Clinical characteristics, specific symptoms, laboratory findings, and disease severity were compared between the groups.

2.2 | Data collection

Epidemiological data, clinical symptoms, comorbidities, and laboratory findings were obtained from electronic medical records. All data were reviewed by three experienced doctors.

2.3 | Statistical analysis

Categorical variables were described according to frequency and percentage, and continuous variables were described as median values (interquartile range [IQR]). All statistical analyses were performed using the statistical software SPSS (version 23.0; IBM, Armonk, New York), and P ≤ .05 was considered statistically significant. An independent-samples nonparametric test was used to analyze differences between the two groups. Binary logistic regression analysis was used to calculate odds ratios to assess risk factors associated with positive UCT according to gender. The data are presented as mean ± 95% confidence interval (CI).

3 | RESULTS

3.1 | FOB test for assessment of GI in COVID-19 patients

This study included 345 confirmed COVID-19 patients (165 men and 180 women) with a median age of 63.0 years (50.0-68.0). A total of 13.6% patients (47 of 345) were FOB-positive, and 86.4% (298 of 345) were FOB-negative. Among all patients, 30.1% (104 of 345) exhibited gastrointestinal symptoms that included abdominal pain (3.8%, 13 of 345), vomiting (5.2%, 18 of 345), diarrhea (21.2%, 73 of 345), nausea (7.0%, 24 of 345) and abdominal distension (4.6%, 16 of 345). A total of 42.6% of the FOB-positive patients exhibited gastrointestinal symptoms, and this was significantly higher than the proportion of FOB-negative patients who exhibited gastrointestinal symptoms (28.2%) (P = .046). The presence of gastrointestinal symptoms and testing positive for FOB were both recognized signs of GI in COVID-19 patients. Interestingly, 57.4% (27 47) of patients that tested positive for FOB did not exhibit gastrointestinal symptoms. In total, 38.0% of patients (131 of 345) had either a positive FOB test or gastrointestinal symptoms, and this was a much higher proportion than that of individuals with only a positive FOB test (13.6%, 47 of 345) or gastrointestinal symptoms (30.1%, 104 of 345). These data suggest that the combination of a positive FOB test and gastrointestinal symptoms provides comprehensive diagnostic value for the assessment of GI.

It has been reported that a decrease in lymphocytes (LY) and an elevation in the inflammatory marker C-reactive protein (CRP) are both more common in severe COVID-19 cases than they are in moderate cases or in healthy subjects.11,12 COVID-19 patients also exhibited higher WBC levels.13 Similarly, we found that there were significantly higher levels of CRP and significantly lower number of LY in FOB-positive patients compared to those in FOB-negative patients (CRP, 6.5 mg/L [1.2-27.2] vs. 1.6 mg/L [1.2-13.0], P = .022; LY, 1.3 × 10^9/L [0.6-1.6] vs. 1.4 × 10^9/L [1.0-1.8], P = .030, Table 1). There was a significant increase in the proportion of FOB-positive cases as disease severity increased (mild, 11.7%; severe, 13.7%; and critical, 66.7%, P < .001, Table 1). Finally, the FOB-positive patients were significantly older than those who were FOB-negative (66 [50.0-75.0] vs 62 [50.0-67.0], P = .038); however, the FOB-positive patients exhibited similar gender and complication rates compared to those of FOB-negative patients (Table 1). Additionally, we found that only 1.2% of patients (4 of 345) were positive according to the fecal white blood cell test (data not shown).

3.2 | UCT for assessment of UI in COVID-19 patients

The study design is outlined in Table 2. A total of 217 patients were included (97 men [44.7%] and 120 women [55.3%]) with a median age of 58.0 years (43.0-66.0). A total of 2.8% of patients (6 of 217) exhibited urinary symptoms that included lumbago (2.3%, 5 of 217) and urgent or frequent urination (0.5%, 1 of 217). In this study, a UCT-positive sample was defined as meeting one of the following criteria that included (1) more than 17 RBCs or 18 WBCs per micro-liter in sample, (2) urine occult blood test positive, or (3) urine WBC dry chemistry test positive. A total of 36.9% of patients (80 of 217) exhibited positive UCT, and 63.1% (137 of 217) were UCT-negative. The patients who exhibited positive UCT were significantly older than those who were UCT-negative (63.0 years [50.3-67.0] vs 55.0 years [41.5-65.0], P = .001). More female patients than male patients were UCT-positive (female: 55.0%; male: 14.4%, P < .001). Logistic regression analysis showed significantly increased odds of females being associated with positive UCT (chi-square = 40.5, P < .001; odds ratio: 7.2: 95% CI: 3.7-14.2, P = .014). More importantly, 72.4% (42 of 58) of female patients aged > 60 years were UCT-positive, and this rate was significantly higher than that of male patients in the same age range (20.8%, 10 of 48, P < 0.001) and for that of the entire patient group (36.9%, 80 of 217, P < .001) (Figure 2). Approximately 6.3% of UCT-positive patients exhibited urological symptoms, and this was significantly higher than the ratio of UCT-negative patients with urological symptoms (0.7%) (P = .033).
The inflammatory marker CRP and the WBC were both higher (but not significantly higher) in UCT-positive patients than they were in UCT-negative patients (Table 2). Among the UCT-positive patients, 97.5% (78 of 80) still possessed serum renal function markers (such as creatinine and blood urea nitrogen) that were within the reference ranges (data not shown). These data indicate that UCT could provide a sensitive tool for the assessment of early UI at a stage in which serum renal function markers appear normal due to compensation from undamaged kidney tissues. Patients with positive UCT showed similar rates of complications and disease severity compared to those of UCT-negative patients. Additionally, hematuria or leukocyturia alone provided a similar value for the assessment of UI in COVID-19 patients (Table S1).

4 | DISCUSSION

In this study, we evaluated the benefits of using routine FOB and UCT to achieve a rapid assessment of GI and UI in COVID-19 patients. We found that FOB acts as a valuable indicator for unnoticeable GI in COVID-19 patients. A combination of a FOB test and gastrointestinal symptoms can serve as a comprehensive diagnostic tool for GI. Age
and sex are risk factors for UI in COVID-19 patients. Routine UCT is a sensitive tool to assess early urinary infection, particularly for elderly female COVID-19 patients, prior to the occurrence of renal dysfunction. Considering that both FOB and urinary cytology tests are extremely convenient, inexpensive, and fast, they can serve as cost-effective screening tools for GI and UI in patients. In particular, the impacts of such tools in the fight against this pandemic cannot be underestimated for rural areas and for underdeveloped countries where molecular diagnoses are not currently feasible.

Early diagnosis of digestive and urological infections in COVID-19 has drawn a great deal of recent attention. Current data have indicated that gastrointestinal symptoms such as vomiting and diarrhea are evidence of digestive system infection. Among mild COVID-19 cases with diarrhea, 19.4% of these patients have experienced diarrhea as the onset symptom during their illness courses. One recent study reported that diarrhea exhibited the smallest P-value (P = .016) among the different symptoms experienced by COVID-19 patients. However, the gastrointestinal symptom rate in this study is slightly higher than the range of gastrointestinal symptoms (3%-26%) reported by other studies. This variation may result from different criteria for diagnosing diarrhea among different hospitals or from different physicians and/or sample sizes. This suggests that a more objective tool is needed to improve the diagnostic accuracy for GI. A FOB is a relatively objective laboratory test for the assessment of GI, although false-negative results have been a concern for physicians. In this study, 57.4% of FOB-positive patients did not...
exhibit gastrointestinal symptoms, suggesting that FOB can assess previously undetectable GI in COVID-19 patients. Furthermore, our study revealed that 38.0% of patients either exhibited gastrointestinal symptoms or tested positive for FOB. Therefore, a combination of FOB and gastrointestinal symptoms offers a more comprehensive diagnostic value for GI in COVID-19 patients than does an FOB test or gastrointestinal symptoms alone. Unlike other systems, such as those involving the heart, liver, and lungs that possess established laboratory indices to indicate their malfunctions, there are no specific laboratory markers for GI. Endoscopy is an option for directly examining gastrointestinal lesions; however, COVID-19 patients generally do not meet the indications for emergency endoscopy. Furthermore, endoscopic procedures increase the risk of disease transmission in COVID-19 patients.19 Based on these factors, a FOB test that provides a cheap and convenient assessment that can be performed routinely in most hospitals can provide an appropriate tool for the assessment of GI in COVID-19 patients.

A recent report indicated that 7 out of 57 male COVID-19 patients experienced a urinary frequency as the leading symptom.20 However, in our cohort we found that only 2.8% of patients exhibited urinary system symptoms. Our study suggests that positive UCT is a sign of UI in COVID-19 patients. Age and sex are risk factors for UI in COVID-19 patients, and a positive UCT is more prevalent in female patients aged 60 years or older. It has been reported that in adult rats, females possess higher mRNA levels of ACE2 in their kidneys than do age-matched males.21 and this may explain why older females are more vulnerable to SARS-CoV-2-induced UI. In our study, 97.5% of those (78 of 80) with positive UCT still possessed values within the normal ranges for a series of serum renal function indices, indicating that UCT is a more sensitive indicator of early UI than are serum biomarkers.

Our study does have several limitations. First, we did not have available data for viral nucleic acids from patient stool or urine specimens. Therefore, we were unable to link the virus load to the results of FOB and UCT. Second, many patients who exhibited gastrointestinal symptoms but were FOB-negative may have received treatments prior to being admitted, and any original FOB information was unavailable. Third, patients with existing diabetes or hypertension were excluded in an attempt to remove those UCT-positive cases that were caused by potential secondary nephropathy and not by SARS-CoV-2; however, this may have resulted in a shielding of the correlation between UI status and diabetes or hypertension. Fourth, in rare instances, other factors may have contributed to UI in patients. Finally, repeated FOB tests17 would be helpful for increasing the chances of detecting GI in COVID-19 patients.

In conclusion, our data provide insight into the benefits of FOB and UCT in regard to assessing GI and UI in COVID-19 patients. These simple and cost-effective measures are of value for all COVID-19 patients, and they are particularly valuable for individuals in underdeveloped regions and countries where molecular diagnosis resources are lacking.

CONSENT FOR PUBLICATION

The manuscript has been approved by all of the authors for publication.

AUTHOR CONTRIBUTIONS

LD, XC, HW, and WT supervised and designed the study. LD, JC, XW, YZ, CC, YL, and HW performed the tests and collected the data. XC, LD, and YZ performed the statistical analysis. LD, XC, JC, HW, and WT contributed to data interpretation. LD, HW, and WT prepared and revised the manuscript.

ETHICAL APPROVAL

This study was approved by the Institutional Review Board (IRB) at the Union Hospital, and the requirement for a written consent form was waived by the IRB committee.

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REFERENCES

1. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280 e278.
2. Yan R, Zhang Y, Li Y, et al. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020;367(6485):1444-1448.
3. Verma S, Saksena S, Sadri-Ardekani H. ACE2 receptor expression in testes: Implications in COVID-19 pathogenesis. Biol Reprod. 2020;103(3):449-451.
4. Zhou Z, Zhao N, Shu Y, et al. Effect of gastrointestinal symptoms in patients with COVID-19. Gastroenterology. 2020;158(8):2294-2297.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
6. Wang L, Li X, Chen H, et al. Coronavirus disease 19 infection does not result in acute kidney injury: An analysis of 116 hospitalized patients from Wuhan, China. Am J Nephrol. 2020;51(5):343-348.
7. Zhang J, Wang S, Xue Y. Fecal specimen diagnosis 2019 novel coronavirus-infected pneumonia. J Med Virol. 2020;92(6):680-682.
8. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.
9. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720.
10. New coronavirus pneumonia prevention and control program (6th ed) (in Chinese). 2020. http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2/files/b218cfeb1bc54639af227f922bf6b817.pdf
11. Peng J, Qi D, Yuan G, et al. Diagnostic value of peripheral hematologic markers for coronavirus disease 2019 (COVID-19): A multicenter, cross-sectional study. J Clin Lab Anal. 2020;e23475.
12. Zhao G, Su Y, Sun X, et al. A comparative study of the laboratory features of COVID-19 and other viral pneumonias in the recovery stage. J Clin Lab Anal. 2020;e23483.
13. Gu J, Han B, Wang J. COVID-19: Gastrointestinal manifestations and potential fecal-Oral transmission. Gastroenterology. 2020;158(6):1518-1519.
14. Han C, Duan C, Zhang S, et al. Digestive symptoms in COVID-19 patients with mild disease severity: Clinical presentation, stool viral RNA testing, and outcomes. Am J Gastroenterol. 2020;115(6):916-923.
15. Liang W, Feng Z, Rao S, et al. Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus. Gut. 2020;69(6):1141-1143.
16. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-1069.
17. Murphy CC, Sen A, Watson B, et al. A systematic review of repeat fecal occult blood tests for colorectal cancer screening. Cancer Epidemiol Biomarkers Prev. 2020;29(2):278-287.
18. Sokoro A, Singh H. Fecal occult blood test for evaluation of symptoms or for diagnostic testing. Am J Gastroenterol. 2020;115(5):679-680.
19. Ungaro RC, Sullivan T, Colombel JF, et al. What should gastroenterologists and patients know about COVID-19? Clin Gastroenterol Hepatol. 2020;18(7):1409-1411.
20. Mumm JN, Osterman A, Ruzicka M, et al. Urinary frequency as a possibly overlooked symptom in COVID-19 patients: Does SARS-CoV-2 cause viral cystitis? Eur Urol. 2020;78(4):624-628.
21. Sampson AK, Moritz KM, Denton KM. Postnatal ontogeny of angiotensin receptors and ACE2 in male and female rats. Gend Med. 2012;9(1):21-32.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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