Original Article

Oral rifampicin interferes with urine dipstick tests for patients with pulmonary tuberculosis

Fei Wang[1], Lihui Zhao[1], Wei Du[1], Yan Hu[2], Yi Ren[1]

[1]Department of Laboratory Medicine, Wuhan Pulmonary Hospital, Wuhan, China; [2]Central Medical Laboratory, Wuhan Pulmonary Hospital, Wuhan, China

Contributions: (I) Conception and design: F Wang; (II) Administrative support: Y Ren; (III) Provision of study materials or patients: L Zhao; (IV) Collection and assembly of data: F Wang; (V) Data analysis and interpretation: F Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yi Ren. Department of Laboratory Medicine, Wuhan Pulmonary Hospital, No. 28 Baofeng Road, Wuhan 430030, China. Email: menease@sina.com.

Background: Rifampicin (RMP) and its major metabolite, desacetyl rifampicin (dRMP), can interfere with urine dipstick tests (UDTs) in patients with tuberculosis (TB) who receive oral RMP. This study sought to examine the effects of RMP and dRMP on UDTs using 2 different urine dipsticks (i.e., Arkray's Aution Sticks 10EA and GIMA's Combi-Screen 11SYS Plus sticks).

Methods: Urine colorimetry was applied to measure RMP concentrations and determine the range of total RMP concentration in the urine within 2–6 and 12–24 h of oral administration of RMP. In vitro interference assays and confirmatory tests were performed to evaluate the effects of RMP and dRMP on the analytes.

Results: The total RMP concentration in the urine of the 40 TB patients analyzed as urine sample was 88–376 μg/mL within 2–6 h and 22–112 μg/mL within 12–24 h of oral administration of RMP. Interference was observed for different analytes at consistent or varied RMP concentrations between the *in vitro* interference assays and the confirmatory tests, including 75 patients [Aution Sticks 10EA: 250, 250 μg/mL for protein (PRO); 400, 300 μg/mL for leukocyte esterase (LEU); Combi-Screen 11SYS Plus: 125, 150 μg/mL for ketones (KET); 500, 350 μg/mL for nitrite (NIT); 200, 300 μg/mL for PRO; 125, 150 μg/mL for LEU].

Conclusions: RMP and dRMP interfered with the analytes of the UDTs using the 2 urine dipsticks in different levels. The *in vitro* interference assay is not an ideal substitute for the confirmatory test. The collection of urine samples within 12–24 h of administration of RMP can prevent the interference caused by RMP and dRMP.

Keywords: Interference; urine dipstick test (UDT); rifampicin (RMP)

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Introduction

The urine dipstick test (UDT) is a screening tool commonly used for the diagnosis of urinary tract infections (UTIs), kidney diseases, and other metabolic disorders (1). This cost-effective, easy-to-use, fast-reporting, non-invasive test is part of routine urinalysis in clinical settings. Given the long duration of therapy and potential adverse drug reactions (ADRs) associated with anti-tuberculosis (anti-TB) treatment (2,3), regular liver and kidney function tests and visual acuity assessments are required, particularly in instances of liver injury, UTIs, and diabetic nephropathy caused by anti-TB drugs, and urine chemistry analysis plays a significant role in disease screening (4,5).

Rifampicin (RMP) is a first-line anti-TB drug that has the highest bioavailability when taken on an empty stomach. Thus, individuals with TB should take RMP orally in the morning or before bedtime every day. The peak serum concentration of RMP can be measured 2–4 h after its oral

administration. The metabolites of RMP are predominantly eliminated via the biliary route, but a fraction of such excreted metabolites remains unchanged or as desacetyl rifampicin (dRMP) in the urine. The urine concentration of RMP reaches its peak at 6 h after oral administration and returns to normal at 12 h post dose (6). Urine containing RMP and its major metabolite dRMP is orange red, with a darker color indicating a higher concentration. This finding can interfere with the detection of some urine chemistry analytes in UDTs and cause erroneous results that affect clinicians' assessments of ADRs and treatment decisions.

In this study, the colorimetric method (7), which predicts the pharmacokinetics of RMP in plasma (8,9), was applied to measure the total concentration of RMP and its essential metabolite dRMP (hereinafter collectively referred to as the "total RMP concentration") in urine. As the Combi-Screen 11SYS Plus test strips and Audio Sticks 10EA may have different test results, we evaluate the anti-interference ability of Arkray's Aution Sticks 10EA and GIMA's Combi-Screen 11SYS Plus urine dipsticks by measuring the interference caused by the total RMP in the UDTs following the oral administration of RMP. Anti interference ability is a capability of the urine test strip itself, which can counteract the influence of certain drug metabolites and other metabolites in the body, ensuring the accuracy of the results. The use of a preferable anti-interference urine test strip may improve the accuracy of the UDT results. This study sought to examine the effects of RMP and dRMP on UDTs using 2 different urine dipsticks (i.e., Arkray's Aution Sticks 10EA and GIMA's Combi-Screen 11SYS Plus sticks). We present this article in accordance with the MDAR reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-310/rc).

Highlight box

Key findings

- The collection of urine samples within 12–24 h of administration of RMP can prevent the interference caused by RMP and dRMP.

What is known and what is new?

- RMP and dRMP can interfere with the detection of some urine chemistry analytes in UDTs and produce erroneous results.
- The anti-interference ability of Aution Sticks 10EA (Arkray, Japan), Combi-Screen 11SYS Plus (GIMA, France).
- Aution Sticks 10EA (Arkray, Japan) and Combi-Screen 11SYS Plus (GIMA, France) Plus urine dipsticks were evaluated by measuring the interference caused by the total RMP in the UDTs following an oral administration of RMP.

What is the implication, and what should change now?

- In the UDTs of patients with tuberculosis who receive oral RMP, protein, leukocyte esterase, ketone, and nitrite tests interfere with the false-positive results caused by RMP and dRMP in the urine samples. The affected analytes may vary across different types of urine test strips.

Methods

Determining the range of the total RMP concentration in the urine after oral administration of RMP

Urine sample collection

This study included 40 patients with TB who underwent a 2-week treatment regimen of RMP and at least 2 other anti-TB drugs, had normal kidney function and hemo-bilirubin and blood glucose levels, and denied a history of diabetes. Oral RMP was calculated as a dose of per 10 mg/kg body weight. Urine samples were collected randomly within 2–6 and 12–24 h of administration of RMP. Each urine sample was collected in a 10-mL urine collection tube with a cap, and 1 mL of each sample was centrifuged at 13,000 rpm for 10 min to harvest the supernatant, which was stored at −70 ℃. The maximum storage time was 90 days. The patients' clinical and demographic characteristics are presented in *Table 1*.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Wuhan Pulmonary Hospital [No. (2021)8] and informed consent was taken from all the patients.

Measuring the total RMP concentration in the urine via colorimetry

A 500 mg/L mixture urine sample was prepared by adding the urine of 5 healthy individuals to RMP (SIGMA-ALDRICH, American), and 10 different concentrations were obtained by doubling the dilution. These mixtures (150 μL each) were subsequently inoculated into a 96-well plate, and the concentrations were measured by their absorbances at 475 nm. Next, an RMP absorbance-concentration standard curve was plotted, using the urine from the healthy participants as the blank control.

The frozen samples of the 40 patients were thawed in a water bath at 37 ℃ for 5 minutes, and the total RMP concentration was isolated from each urine sample using Sunahara's method (6). Next, 150 μL of each sample was added to a 96-well plate, the absorbance was read at

Table 1 Clinical and demographic characteristics of TB patients in the derivation cohort

Characteristic	Values (n=40)
Age (years), median (range)	44.5 (17 to 73)
Sex, n (%)	
Male	28 (70.0)
Female	12 (30.0)
Oral dose of rifampicin, n (%)	
300 mg	6 (15.0)
450 mg	9 (22.5)
600 mg	25 (62.5)
Serum total bilirubin, n (%)	
<21 μmol/L	40 (100.0)
Renal function	Normal
History of diabetes	None

TB, tuberculosis.

475 nm, and the total RMP concentration in the urine was then calculated in combination with the standard curve.

Determining the range of the total RMP concentration in the urine

The total RMP concentration range in the urine reached the maximum concentration at 2–6 h post dose and the minimum concentration at 12–24 h post dose.

In vitro assays: *simulating interference with UDT caused by RMP*

Interference assays with false-positive results

The reference standard RMP (SIGMA-ALDRICH, America) was initially added to the mixture of the urine of the healthy individuals and then diluted to concentrations of 0, 100, 125, 200, 250, 300, 350, 400, 500, and 1,000 mg/L. Urine chemistry analyzers and urine test strips (i.e., Aution Sticks 10EA, Arkray, Japan; Combi-Screen 11SYS Plus, GIMA, France) were used for the urinalysis. Positive degrees and corresponding RMP concentrations were documented if any positive results were derived from the assays.

Interference assays with false-negative results

The positive control (BIO-RAD, California, American) was diluted until it reached a positive degree of "1+" provided in the different urine chemistry parameters, and the specific RMP concentrations of the diluted samples were 125, 250, 500, and 1,000 mg/L. Next, these samples were tested using Combi-Screen 11SYS Plus and Aution Sticks 10EA, and given urine test strips.

Definition of the *in vitro i*nterference threshold

The *in vitro* interference threshold was defined as the known RMP concentration that caused (false-positive or false-negative) interference with any urine chemistry analyte in a UDT.

Confirmatory test: *revealing the interference with the UDT caused by RMP and dRMP in the urine of patients with TB*

Patients and sampling

In total, 75 other patients who were diagnosed with pulmonary TB, had normal kidney function and serum total bilirubin (BIL) and glucose levels, denied a history of diabetes, and received oral RMP and at least 2 other anti-TB drugs for 2 weeks were enrolled in this study. Urine samples were obtained from these patients at any time within 2–12 h post dose and placed in a 10-mL urine collection tube with a cap. Next, 1 mL of the sample was centrifuged at 13,000 rpm for 10 min to harvest the supernatant, which was stored at −70 ℃ awaiting the subsequent determination of the total RMP concentration in the urine. The remaining samples were subjected to UDTs, urine microalbumin testing, and urine sediment microscopy using Combi-Screen 11SYS Plus and Aution Sticks 10EA. The patients' clinical and demographic characteristics are presented in *Table 2*.

UDT, urine sediment microscopy, and urine microalbumin tests

All the 75 urine collection tubes with urine samples were loaded into Arkray's and Gima's urine chemistry analyzers for the UDTs. The supernatants obtained from these samples via low-speed centrifugation were tested for microalbumin, and the sediments were examined by microscopy. All the procedures were completed within 2 h of the sampling.

Determination of the total RMP concentration in the urine

The total RMP concentration in the urine was determined as described in Section "Measuring the total RMP concentration in the urine via colorimetry".

Interpretation criteria for the true-negative results for the urine chemistry analytes

In the urine sediment microscopy, "white blood cell count <1/high-power field" and "bacterial negative" were interpreted as true negatives for leukocyte esterase (LEU) and nitrite (NIT), respectively. "Urine microalbumin <150 mg/L" was classified as a true negative for protein (PRO), and "serum total BIL <21 mmol/L" was classified as a true negative for BIL. A normal blood glucose level was considered a true negative for ketone (KET).

Table 2 Clinical and demographic characteristics of TB patients who received the confirmatory test

Characteristic	Values (n=75)
Age (years), median (range)	42 (17 to 82)
Sex, n (%)	
Male	52 (69.3)
Female	23 (30.7)
Urine microalbumin <150 mg/L, median (range)	70 (0.6 to 88.2)
Urine sediment, n (%)	
RBC (<1/HPF)	54 (72.0)
WBC (<1/HPF)	33 (44.0)
Bacterial (negative)	75 (100.0)
Serum total bilirubin, n (%)	
<21 μmol/L	75 (100.0)
Renal function	Normal
History of diabetes	None

TB, tuberculosis; RBC, red blood cell; WBC, white blood cell; HPF, high-power field.

Urine dipstick grading systems given by Arkray and Gima

Grading systems used for the Aution Sticks 10EA and the Combi-Screen 11SYS Plus dipsticks. And Grading systems included negative, weakly positive and positive (*Table 3*).

Definition of interference threshold in the confirmatory test

The interference threshold was defined as the minimum level of increasing RMP concentration when the interference (the false-positive or false-negative results) reached 95% for a specific urine chemistry analyte.

Statistical analysis

SPSS 19.0 statistical software was used. P<0.05 was defined as a statistically significant difference. This study mainly applied descriptive statistics, with counting data represented by n (%), and measurement data represented by mean ± standard deviation (SD) or scatter diagram.

Results

Total RMP concentration range in the urine

As the RMP concentration-absorbance calibration curve in *Figure 1* shows, a good linear correlation (r^2=0.9982) was observed when the absorbance wavelength was 475 nm and the RMP concentration was between 1.95 and 500 μg/mL. Based on the test results of the 40 urine samples and the standard curve, the concentration of total RMP

Table 3 Grading systems used for the Aution Sticks 10EA and the Combi-Screen 11SYS Plus dipsticks

Projects	Aution Sticks 10EA					Combi-Screen 11SYS Plus				
	Negative (–)	Positive				Negative (–)	Positive			
		±	1+	2+	3+		±	1+	2+	3+
Protein, g/L	–	0.15	0.3	1	3	–	0.15	0.3	1	5
Leukocyte, μL	–	<25	25	75	250	–	<25	25	75	500
Ketones, mmol/L	–	0.5	1.5	4	8	–	1.0	2.5	10	30
Nitrite	–	+				–	+			

"–": negative; "±": weakly positive; "+": positive.

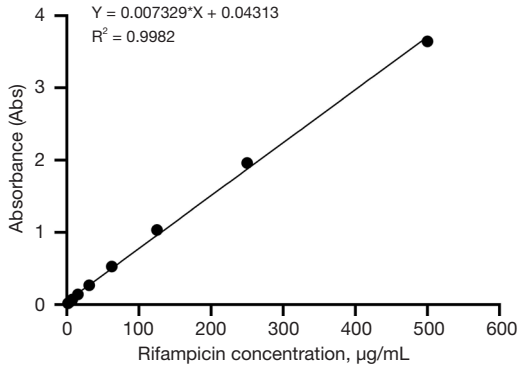

Figure 1 Calibration curve for the urine colorimetric assays.

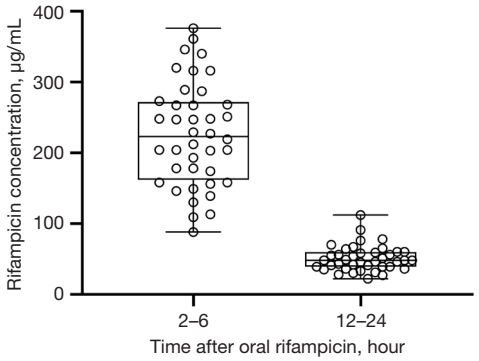

Figure 2 Urinary total rifampicin concentration in the 2 periods.

ranged from 88 to 376 μg/mL (median: 223 μg/mL) within 2–6 h of the oral administration of RMP, and between 22 and 112 μg/mL (median: 48 μg/mL) within 12–24 h of the oral administration of RMP (*Figure 2*).

In vitro interference assays

Aution Sticks 10EA

When the RMP had a concentration range of 0–500 μg/mL, false-positive interferences were observed at above 250 and 400 μg/mL for PRO (±) and LEU (1+), respectively. No false-negative interference was detected in the measurement of the given 10 parameters.

Combi-Screen 11SYS Plus

For the 0–500 μg/mL range, RMP was associated with false-positive interferences that appeared in the measurements of LEU (1+) and KET (±) when the RMP concentration was ≥125 μg/mL, in the measurements of PRO (3+) when the RMP concentration was ≥200 μg/mL, and in the measurements of NIT (+) when the RMP concentration was ≥500 μg/mL. No false-negative interferences were observed in the measurements of the given substances.

Confirmatory tests

Aution Sticks 10EA

When the total RMP concentration in the urine reached 219 μg/mL, interferences emerged in the measurement of PRO, and the false-positive rate increased from 88.9% to 100% at a concentration of 250 μg/mL. When the total RMP concentration in the urine reached 267 μg/mL, interference emerged in the measurement of LEU, and the false-positive rate increased from 77.8% to 100% at a concentration of 300 μg/mL and above (*Table 4*).

Combi-Screen 11SYS Plus

The false-positive results were found to interfere with KET when the total RMP concentration in the urine reached ≥123 μg/mL (with a false-positive rate of 85%), with LEU at 131 μg/mL (with a false-positive rate of 90.9%), with KET and LEU at 150 μg/mL (with false-positive rates of 100% and 94.4%, respectively), with PRO at 289 μg/mL (with a false-positive rate of 87.5% and a false-positive rate of 100% if the concentration ≥300 μg/mL), and with NIT at 346 μg/mL (with a false-positive rate of 100%) (*Table 5*).

Comparison of the degrees of interference between the 2 urine dipsticks

In relation to the Aution Sticks 10EA, false-positive interferences were only observed for PRO and LEU. Moreover, the false-positive results were not detectable until after the total RMP concentration reached 250 μg/mL in the confirmatory test. In relation to the Combi-Screen 11SYS Plus urine strips, false-positive interferences were observed in some analytes, including NIT, PRO, LEU, and KET. However, the phenomenon was not observed until the total RMP concentration reached ≥150 μg/mL in the confirmatory test (*Table 6*). Thus, the Aution Sticks 10EA were more resistant to the interference caused by RMP than the Combi-Screen 11SYS Plus urine dipsticks.

Discussion

In this study, the total RMP concentration in the urine fell within the range of 88–376 μg/mL at 2–6 h post dose, which

Table 4 Confirmatory test results for the Aution Stick 10EA dipstick

Analyte	Urinary total rifampicin concentration range (μg/mL)	Negative No.	Interference results			
			±	1+	2+	Subtotal, n (%)
Protein	219–400	18	9	7	–	16 (88.9)
	250–400	13	8	5	–	13 (100.0)
Leukocyte esterase	267–400	9	–	6	1	7 (77.8)
	300–400	4	–	3	1	4 (100.0)

Table 5 Confirmatory test results for the Combi-Screen 11SYS Plus dipstick

Analyte	Urinary total rifampicin concentration range (μg/mL)	Negative No.	Interference results			
			1+	2+	3+	Subtotal, n (%)
Ketones	123–400	27	23	–	–	23 (85.2)
	150–400	19	19	–	–	19 (100.0)
Leukocyte esterase	131–400	22	7	11	2	20 (90.9)
	150–400	18	5	10	2	17 (94.4)
Protein	289–400	8	–	–	7	7 (87.5)
	300–400	6	–	–	6	6 (100.0)
Nitrite	346–400	3	3	–	–	3 (100.0)
	350–400	2	2	–	–	2 (100.0)

Table 6 Comparison of degrees of interference between the 2 urine dipsticks

Tests	*In vitro* interference assays (μg/mL)				Confirmatory tests (μg/mL)			
	NIT	PRO	LEU	KET	NIT	PRO	LEU	KET
Aution Sticks 10EA	–	250	400	–	–	250	300	–
Combi-Screen 11SYS Plus	500	200	125	125	350	300	150	150

NIT, nitrite; PRO, protein; LEU, leukocyte esterase; KET, ketones.

is similar to the results reported by Acocella (6). At 475 nm, the RMP concentration was less affected by other anti-TB drugs and their metabolites, while the maximum urine BIL absorption peak at 460 nm can affect the determination of RMP concentrations by colorimetry. The true negativity of urine BIL was defined on the basis of the serum total BIL within the normal range to eliminate the effect of BIL, and all the TB patients included in the study had a normal serum BIL level.

The study results suggested that RMP and dRMP caused false-positive interference in the urine dipstick tests, including in relation to PRO, LEU, KET, and NIT, but they were independent of pH, specific gravity, glucose, occult blood, urobilinogen, and BIL. In this study, patients with normal blood glucose levels and without diabetes were considered a true negative for urine ketone. This result might have affected the accuracy of the study results, as an individual can test positive for urine KET after fasting or drinking (10,11). Thus, positivity should not be ruled out simply based on urine and blood glucose results that fall within the normal ranges before a blood KET test. There were 19 urine samples with a total RMP concentration >150 μg/mL. All these samples tested positive for KET with the Combi-Screen 11SYS Plus test strips and negative with the Aution Sticks 10EA, which indicates that there is a high probability of false-positive results in the KET test when

the Combi-Screen 11SYS Plus urine strips are used.

Despite its advantages, the easy-to-operate *in vitro* interference assay does not accurately describe the degree of interference with UDT. Differences existed in the corresponding interference thresholds, but the affected analytes were consistent between the *in vitro* interference assays and confirmatory tests. This might be due to the presence of dRMP in the urine samples obtained from the patients with TB in the confirmatory tests. Apart from RMP and dRMP, the urine samples of the participants treated with combination therapies contained metabolites, such as isoniazid, pyrazinamide, ethambutol, and/or other anti-TB agents. These substances might have contributed to the differences in the interference thresholds between the confirmatory tests and *in vitro* interference assays. Thus, the *in vitro* interference assay cannot be used as a substitute for the confirmatory test.

The test principles of the urine test strips are another significant factor contributing to the difference in the interference threshold for LEU. In relation to the Aution Sticks 10EA, LEU catalyzes the hydrolysis of 3-(N toluene sulfonyl-L-alanyloxy) indole to form indoxyl, which further reacts with 2-methoxy-4-(N-morpholino) benzene diazonium to generate a purple product. When tested by the Combi-Screen 11SYS Plus urine strips, LEU splits heterocyclic carboxylates, and the product ethanol reacts with diazonium salt, producing a violet color. The interference caused by RMP and dRMP likely occurs in tests using the Combi-Screen 11SYS Plus urine strips.

The anti-interference performance of the urine test strips vary in the presence of RMP. When the total RMP concentration in the urine was 150 μg/mL, interference occurred simultaneously in the LEU and KET tests using the Combi-Screen 11SYS Plus urine strips. When the Aution 10EA Sticks were used, interference with PRO was not detectable until the total RMP concentration in the urine increased to 250 μg/mL. Notably, fewer analytes interfered with RMP when the AUTION Sticks 10EA were used for the urinalysis. The highest degree of interference with PRO was limited to "1+" for the Aution Sticks 10EA, which was significantly lower than that ("3+") for the Combi-Screen 11SYS Plus urine strips. Moreover, a lower degree of interference was observed in the LEU test with the Aution Sticks 10EA than the Combi-Screen 11SYS Plus urine strips ("2+" *vs.* "3+"). Thus, the Aution Sticks 10EA outperformed the Combi-Screen 11SYS Plus urine strips in terms of resisting RMP-induced interference. In clinical settings, highly resistant urine test strips are needed to obtain the most accurate test results.

The resistance of urine test strips to the interference caused by RMP should be evaluated, particularly in medical institutions for TB prevention and control. As reported by numerous clinical studies, high doses of RMP are widely used to shorten the course of anti-TB treatments and may be included in clinical treatments for TB (12,13). Our findings highlight the importance of evaluating the anti-interference performance of test strips, as patients with TB are likely to have higher concentrations of RMP in their urine. In this study, the oral RMP recipients had a total RMP concentration in their urine ranging from 22 to 112 μg/mL within 12–24 h post dose, but no interference was observed with any of the UDTs. Thus, the suspension of therapy is not necessary for every patient with TB. However, UDTs can be conducted within 12–24 h following the administration of oral RMP.

Conclusions

In the UDTs of TB patients who are receiving oral RMP, tests of PRO, LEU, KET, and NIT interfere with the false-positive results caused by RMP and dRMP in the urine samples, and the affected analytes may vary across different types of urine test strips. Given that *in vitro* interference assays cannot comprehensively reveal the interference in UDTs based on the urine samples of oral RMP recipients, laboratory testing is required to evaluate the resistance of urine dipsticks to the interference caused by RMP and dRMP. False-positive interference can be avoided by conducting UDTs within 12–24 h of the oral administration of RMP.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-310/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-310/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-310/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Wuhan Pulmonary Hospital [No. (2021)8] and informed consent was taken from all the patients.

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