

A cut-off value for the operation time and other risk factors in terms of the infection risk for flexible ureterorenoscopy

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Abstract

Objectives: To investigate the operation time (OT) and ureteral access sheath (UAS) usage with the infection rates and to determine a cut-off value for OT.

Methods: We retrospectively analysed the data of the patients who underwent flexible ureterorenoscopy (FURS) for renal stones larger than 20 mm between 2010 and 2019. The investigated parameters were OT, UAS using, and infection status. The data were analysed by forming two groups according to whether the OT was less than 60 minutes and more, whether the UAS was used and whether an infection occurred. In addition, independent risk factors that may affect postoperative urinary infection development were also investigated by logistic regression analysis. And, a Receiver Operating Characteristic (ROC) curve analysis was applied to determine a cut-off value in OT terms, where infection rates increase more.

Results: A total of 575 patients were enrolled in the study. The rates of the usage of UAS and infection were greater statistically in the group for longer than 60 minutes. OT was longer statistically in the infection group than in the group without infection (94.1 ± 14.2 and 68.01 ± 23.1 , for groups 1 and 2, respectively, $P < .05$, Table 2). OT was statistically longer in the UAS group than the unused one (79.3 ± 24.4 and 66.7 ± 22.4 , for groups 1 and 2, respectively, $P < .05$, Table 3). ROC analyses revealed a cut-off point of 87.5 min for OT in terms of infection rate.

Conclusion: While the infection risk increases when OT exceeds 60 minutes, FURS can be safely performed up to 87.5 minutes with 89% sensitivity and 69% specificity infection risk.

1 | INTRODUCTION

The global prevalence of urolithiasis tends to increase worldwide, leading to the need for safe, and effective treatment methods.¹ In parallel with the advances in technology, flexible ureterorenoscopes, effective lithotripters, and innovations in auxiliary equipment have enabled the treatment of most of the renal stones with flexible ureterorenoscope with no need for open surgery or percutaneous nephrolithotomy.² Although the percutaneous nephrolithotomy (PNL) is recommended as first-line treatment for renal stones larger than

20 mm in size, flexible ureterorenoscopy (FURS) or shock wave lithotripsy (SWL) may be considered as a treatment method for stones larger than 20 mm in size according to EAU-2019 guideline on urolithiasis especially in case that PNL is not an option because of other reasons³ such as the risk of anaesthesia associated with the patient and the prone position at the time of operation, risk of bleeding tendency, and patient preference.

Because of the increasing spread of FURS, it should be addressed in all aspects, including infection rates. Postoperative infections seem one of the most common complications of FURS and the

parameters that affect infective complications following FURS were analysed in some studies in the literature.^{4,5} However, the effect of operation time (OT) and the relationship of the ureteral access sheath (UAS) with the infection rates is unclear in this size of renal stones.

We aimed to investigate the relationship of the OT and the UAS usage with the infection rates and to determine a cut-off value in terms of OT, where infection rates increase more, by ROC curve analysis.

2 | MATERIALS AND METHOD

After obtaining the approval of the local ethic committee with the number of 2020-1/46 and the informed consent from all patients in the study, we retrospectively analysed the medical records of all the patients who underwent FURS for renal stones larger than 20 mm in size between 2010 and 2019 in our tertiary academic centre. All operations were performed after appropriate antibiotic prophylaxis including second-generation cephalosporine group and confirmation of no bacterial growth in preoperative urine culture. Patients who have concomitant ureter or bladder stones, presence of nephrostomy catheter during FURS, renal abnormality, and operated under antibiotic suppression were excluded from the study.

Postoperative urinary infective complications such as fever, pyelonephritis, and sepsis were investigated. The operated patients who had the body temperature lasting over 38 degrees for 48 hours or any body temperature over 39°C was considered as infective fever after the exclusion of postoperative atelectasis. When the infection source established and the presence of two or more following Systemic inflammatory response syndrome (SIRS) criteria (body temperature <36°C or >38°C; heart rate >90 beats/min; respiratory rate >12/min or PaCO₂ <32 mmHg; white blood cell count >12 000 or < 4000/ mm³) determined in that case, it was accepted as sepsis.

The investigated parameters were age, body mass index (BMI), OT, size, surface area, density, and location of the stones, usage of the UAS, the presence of the infection and stone-free rates. The data were analysed by forming two groups according to whether the OT was less than 60 minutes and more, whether the UAS was used and whether an infection occurred. In addition, independent risk factors that may affect postoperative urinary infection development were also investigated by logistic regression analysis. And, ROC curve analysis was applied to determine a cut-off value in OT terms, where infection rates increase more.

The size and density of the stones for all patients in the study were evaluated with non-contrast abdominal computed tomography (CT) and the radio-opacity features of the stones were assessed with kidney-ureter-bladder (KUB) X-ray graphy, preoperatively. The total longest diameter of stones was determined as stone size. Stone surface area was calculated using the formula: length × width × (π) × 0.25. Residual stones were evaluated with non-contrast abdominal CT or KUB radiogram in postoperative first month according to the opacity of the stones. OT was defined as

What's known

- It has been suggested that increased operation time can be associated with the outcomes of the procedures by increasing complication rates.
- Nevertheless, little is known about the time limits.
- Prolonged operation times are linked to increased complication rates in ureteroscopy.
- Stone complexity, patient risk factors, surgeon experience, bilateral surgery, and instrumentation are the main factors related to the complications in ureteroscopy.

What's new

- There are a few studies that have different results about the complications in terms of operation time.
- In order to clarify this issue, further studies are needed.
- In this context, the data about this matter have been presented in this study.
- If the optimal operative time is determined correctly, the risk of infection associated with prolonged operation time can be avoided or other relevant measures can be taken.
- In this study, we aimed to establish the optimal operative time by ROC curve analyses to determine a cut-off value for the operation time, and the effect of the ureteral access sheath on this time.

the time that passed between the beginning of the procedure when the device is inserted into the ureteral orifice and the moment of removing the FURS.

2.1 | Surgical technique

A semirigid ureteroscopy was performed to cannulate the ureteric orifice with a safety guidewire (0.035 inch, Microvasive; Boston Scientific Corp., Natick, MA) and to perform active dilatation. A 9.5F 45-cm-long UAS (Cook Medical, Inc, Bloomington, IN) was placed under fluoroscopic vision in the 114 cases and while these operations were performed through the UAS, the next 461 cases were operated without using the UAS depending on the case situation by being evaluating ureteral calibration. A FURS (7.5F; Karl Storz Flex-X2, Tuttlingen, Germany) was also used in all procedures. We reached the lower pole easily after the deflection of the FURS because we used a 272-lm laser fibre (AMS; Sureflex) in all cases. Upon reaching the stone, a 272-lm laser fibre (AMS; Sureflex) was inserted, and the stone was fragmented using holmium:YAG laser (Stonelight; Cooltouch). Some fragmented stones were extracted with stone forceps in case of using UAS. At the end of the procedure, a double-J stent was inserted.

2.2 | Statistical analysis

The results are presented as the mean – standard deviation (SD). Data were analysed using SPSS 22.0 for Windows (SPSS, Inc, Chicago, IL). Statistical analyses of the means of continuous variables were performed with the Mann-Whitney *U* test. Categorical variables were compared by the Chi-Square test. Binary logistic regression analysis was performed to determine independent risk factors affecting postoperative urinary infection. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was estimated to evaluate the sensitivity and specificity of the OT in terms of predicting the infective complications. The best cutoff value was determined using the Youden index. The AUC, sensitivity, and specificity were compared using their 95% confidence intervals (CIs). The results were considered significant at $P < .05$.

3 | RESULTS

A total of 575 patients were enrolled in the study. The demographic characteristics and results of groups in terms of the OT, infection status,

and the UAS usage were summarised in Tables 1–3, respectively.

According to the analysis with regard to the OT; age, sex, BMI, stone density, and stone-free rates were similar between the groups whose operation time was less than 60 minutes and the group longer than 60 minutes. As expected, stone size and stone surface area

TABLE 2 The demographic characteristics and results according to the infection status

Parameters	Infection status		<i>P</i>
	(+) <i>n</i> = 28 (4.8%)	(–) <i>n</i> = 547 (95.1%)	
Age ^a	52.1 ± 13.3	50 ± 15.9	0.690
Sex			
Woman: <i>n</i> (%)	16 (57.1%)	220	0.076
Man: <i>n</i> (%)	12 (42.9%)	327	
BMI	30.1 ± 7.8	27.9 ± 5.7	0.197
OT ^a	94.1 ± 14.2	67.9 ± 23.1	0.000
Stone size ^a	27.2 ± 9	27.3 ± 8.4	0.658
Stone area ^a	189.8 ± 72	199 ± 66.8	0.305
Density	851 ± 374	931.7 ± 414	0.513
Stone-free rate	26 (92.6%)	452 (82.6%)	0.159
Upper pole	4 (14.3%)	87 (15.5%)	0.858
Middle portion	9 (32.1%)	150 (27.4%)	0.586
Lower pole	10 (35.7%)	297 (54.3%)	0.055
Pelvis	12 (42.9%)	206 (37.7%)	0.580
Access sheath usage	9 (32.1%)	105 (19.2%)	0.094

Note: $P < .05$; statistical significance, written in bold

^aThe mean ± Standard deviation value.

TABLE 1 The demographic characteristics and results according to operation time

Parameters	Operation time		<i>P</i>
	≤60 min <i>n</i> = 289	>60 min <i>n</i> = 286	
Age ^a	49.9 ± 16.0	50.3 ± 15.5	0.943
Sex			
Woman: (%)	116 (40.1%)	121 (42.3%)	0.597
Man: <i>n</i> (%)	173 (59.9%)	165 (57.7%)	
BMI ^a	27.8 ± 5.6	28.3 ± 6.1	0.559
Stone size (mm) ^a	24.4 ± 6.1	30.2 ± 9.4	0.000
Stone area (mm ²) ^a	181 ± 47	217.4 ± 77	0.000
Density (HU) ^a	963 ± 399	896 ± 421	0.229
Stone-free rate, <i>n</i> (%)	242 (83.7%)	236 (82.5%)	0.696
Upper pole, <i>n</i> (%)	42 (14.5%)	47 (15.5%)	0.529
Middle portion, <i>n</i> (%)	79 (27.3%)	80 (28.0%)	0.865
Lower pole, <i>n</i> (%)	152 (52.6%)	155 (54.2%)	0.700
Pelvis, <i>n</i> (%)	97 (33.6%)	121 (42.3%)	0.031
Infection rates, (%)	1 (0.3%)	27 (9.4%)	0.000
UAS usage, <i>n</i> (%)	37 (12.8%)	77 (26.9%)	0.000

Note: $P < .05$; statistical significance, written in bold

^aThe mean ± standard deviations value.

were larger statistically, than in the group whose OT was longer than 60 minutes ($P < .05$, Table 1). The rate of the usage UAS was greater statistically in the group whose OT was longer than 60 minutes ($P < .05$, Table 1). In addition, infection rates in the group whose OT was longer than 60 minutes was higher statistically than in the group whose OT was lesser than 60 minutes ($P < .05$, Table 1).

According to the analysis with regard to the infection status; age, sex, stone size, stone surface area, localisation of the stones were not statistically different between the group with the infection and the group without the infection, but the OT was longer statistically in the group with the infection than in the group without the infection (94.1 ± 14.2 and 68.01 ± 23.1, for the groups 1 and 2, respectively, $P < .05$, Table 2).

According to the analysis with regard to the usage of the UAS; age, sex, stone size, stone surface area, stone-free rates, and infection rates were not statistically significant between the group in which the UAS was used and the group not used; however, the OT was statistically longer in the group in which the UAS was used than in the group in which the sheath was not used (79.3 ± 24.4 and 66.7 ± 22.4, for groups 1 and 2, respectively, $P < .05$, Table 3).

Logistic regression analysis revealed that OT is an independent risk factor for the infective process (Table 4). The analysis of the ROC curve to estimate the sensitivity and specificity of OT in predicting infectious events determined the cut-off point as 87.5 minutes. The

TABLE 3 The demographic characteristics and results according to the usage of the UAS

Parameters	UAS usage		P
	UAS (+) n = 114 (19.7%)	UAS (-) n = 461 (80.3%)	
Age ^a	52.6 ± 13.7	49.5 ± 16.2	0.290
Sex			
Woman: n (%)	49 (43%)	188 (40.8%)	0.669
Man n: (%)	65 (57%)	273 (59.2%)	
BMI	29 ± 5.7	27.8 ± 5.8	0.046
OT ^a	79.4 ± 24.5	66.7 ± 22.5	0.000
Stone size ^a	27.5 ± 7.9	27.3 ± 8.5	0.342
Stone area ^a	198.3 ± 70	199.3 ± 66	0.603
Density	797.6 ± 405	977.8 ± 404	0.004
Stone-free rate	382 (82.9%)	96 (84.2%)	0.731
Upper pole	20 (17.5%)	69 (15%)	0.496
Middle portion	36 (31.0.6%)	123 (26.7%)	0.295
Lower pole	68 (59.6%)	239 (51.8%)	0.135
Pelvis	34 (29.8%)	184 (39.9%)	0.047
Infection rates	9 (7.9%)	19 (4.1%)	0.094

^aThe mean ± standard deviations, $P < .05$; statistical significance, written in bold.

area under curve (AUC) for OT time in terms of the infection risk was 0.82 (sensitivity 89.3%, specificity 69.5%, 95% CI 0.77-0.88; $P = .000$) (Figure 1) (Table 5).

4 | DISCUSSION

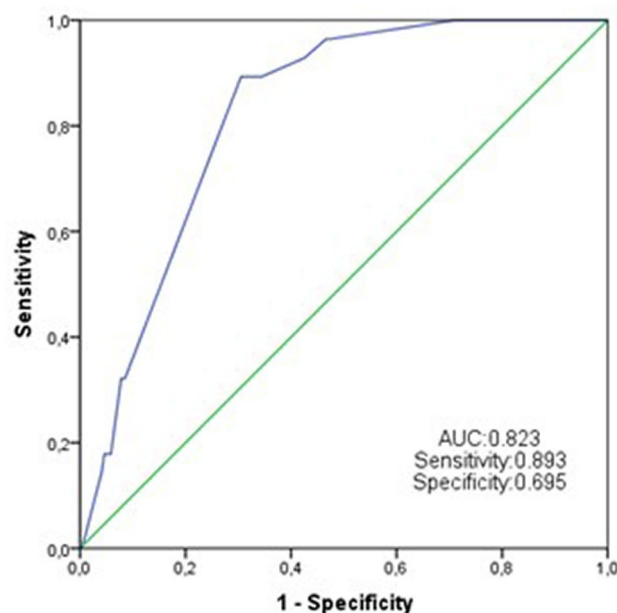
The indications of FURS in the management of urolithiasis have expanded considerably in recent years thanks to the development related to technology in terms of miniaturisation and durability of flexible ureterorenoscope. Therefore, publications on the use of FURS for kidney stones larger than 20 mm have began to be published in the literature.⁶⁻⁸ Because of being a minimally invasive method, the choice of the FURS has been increased in the treatment of large renal stones.⁶⁻⁸ Despite reports on the safety of this operation, severe infective complications, such as sepsis, may occur in FURS.⁹ For that reason, we believe that the factors affecting infection should be analysed in all aspects.

In the literature, infective complication rates following FURS change between 1.7% and 18.8%⁴ and it was found as 4.7% in consistence with the literature in the present study. Factors that affect infective complications following FURS were investigated by various studies.⁵⁻¹⁰ OT is one of the important factors associated with infective events.⁴ However, in the treatment of kidney stones larger than 20 mm with FURS, studies that reported the most appropriate operation time to avoid infective complications and evaluated the effect of UAS use on these complications are limited.

TABLE 4 Independent risk factors effecting postoperative urinary infective process by binary logistic regression (n:575; none infection [-] = 547, infection [+] = 28)

Factor	B	OR (95%CI)	P
Age	0.036	1.03 (0.98:1.08)	0.149
Sex (ref,cat:woman)	-0.254	0.77 (0.16:3.56)	0.744
BMI	0.042	1.04 (0.91:1.18)	0.515
Operation time	0.069	1.07 (1.02:1.12)	0.002
Stone size	0.077	1.08 (0.92:1.26)	0.333
Stone area	-0.007	0.99 (0.97:1.01)	0.413
Density	0.000	1.00 (0.99:1.00)	0.784
Stone-free rate (ref,cat:none)	-1.239	0.29 (0.02:3.52)	0.331
Upper pole (ref,cat:none)	-0.704	0.49 (0.06:3.0.91)	0.505
Middle pole (ref,cat:none)	0.196	1.21 (0.21:6.98)	0.826
Lower pole (ref,cat:none)	-1.381	0.25 (0.03:1.67)	0.153
Pelvis (ref,cat:none)	-1.060	0.34 (0.39:3.06)	0.341
Access sheath (ref,cat:none)	1.054	2.86 (0.61:13.35)	0.179

$P < .05$, statistical significance, written in bold.

**FIGURE 1** ROC curve analysis to estimate the infective process using operation time

According to our results in terms of the OT, it could not establish the statistical difference concerning age, BMI, density, localisation of the stones and stone-free rates between the group lasting less than 60 minutes and the group lasting longer than 60 minutes. In this way, two homogeneous groups were consisted and therefore we could more accurately analysed the effect of

TABLE 5 The sensitivity and specificity rates of the cut-off value for the operation time in terms of the infection risk

Operation time	Sensitivity	Specificity
29.000	1.00	0.00
37.500	1.00	0.009
48.500	1.00	0.24
57.500	1.00	0.29
67.500	0.96	0.53
77.500	0.89	0.66
87.500	0.89	0.70
97.500	0.32	0.92
107.500	0.18	0.95
115.000	0.14	0.96
127.500	0.00	1.00
142.500	0.00	1.00
151.000	0.00	1.00

$P < .05$, statistical significance, written in bold.

operation time on infective events following FURS (Table 1). As expected, the stone size and area were larger statistically in the group lasting longer 60 minutes than in the group lasting less than 60 min ($P < .05$, Table 1). Increased stone size has the strongest impact on OT.¹¹ The OT was prolonged proportionally with the burden of stone in the present study. According to Sorokin's et al, localisation of stone is another related factor with OT and it was reported that lower pole stones increase the OT.¹¹ However, in contrast to that study, Jacquemet et al stated the OT did not differ between lower pole stones and stones in locations other than lower pole.¹² Whereas, according to our results, the stones localised in the renal pelvis caused longer operation time. The main reason for this situation may be because of the migration of some fragments to different calyx during stone fragmentation and the time lost during the search for these fragments in calyces of kidney. When the groups formed according to the OT we determined, inspired by our previously published work on the survival of the flexible ureterorenoscope,¹³ were compared in terms of infection rates, the infection rates were found to be significantly lower in the group lasting less than 60 minutes [1(0.3%) and 27 (9.2%) for the groups lasting lesser than 60 minutes and longer than 60 minutes, respectively, $P < .05$, Table 1]. According to the Jung's et al study, with the use of forced irrigation during ureteroscopy, intrarenal pressure increases above 300 mmHg.¹⁴ And it was established that according to the results obtained from some animal and human studies, when intrarenal pressure rises above 30 mmHg, some defence mechanisms which depend on the intrarenal pressure including pyelo-tubular, pyelo-venous, pyelo-sineous and pyelo-lymphatic backflow come into play.¹⁵⁻¹⁸ These mechanisms have the potential to decrease kidney function as well as they may be related to infectious and hemorrhagic process.¹⁴ According to our results, the OT is related to the infectious process. These defence mechanisms, which initially tried

to balance intrarenal pressure with the compensatory mechanism, create an effect that worsens the situation in terms of infectious, inflammatory, and hemorrhagic processes as the operation time is prolonged.

When we analysed our data according to the presence of infection, while there was no statistical difference in terms of age, sex, stone size, surface area, and location parameters. We also evaluated the probable factors that affecting infective complications following FURS in this current study. The infection rates were primarily affected by the OT (Table 2). In the same group, the OT was longer statistically in the infection group (94.1 ± 14.2 and 67.9 ± 23.1 for the groups with and without infection, respectively, $P < .05$, Table 2). In fact, this result has been confirmed in our precede analysis according to the OT by determining the rate of infection statistically significantly higher in the group whose operation time lasts longer than 60 minutes (Table 1). This result shows us that the OT is also an important factor in the formation of infection besides the effect of the UAS. In addition, it may be related to not only the OT but also other factors that facilitate urinary tract infection, such as age, gender, constipation.

A logistic regression analysis was performed in order to determine independent risk factors affecting postoperative urinary infective process. In our analysis, the only independent factor affecting the occurrence of infection in the FURS was the OT (Table 4). In addition to this analysis, in terms of the operation time, we applied the ROC analysis to determine a cut-off value that facilitates the postoperative risk of infection and, the cut-off value of OT for the infective process was found as 87.5 minutes with 89.3% sensitivity and 70% specificity (Table 5). The area under curve (AUC) for OT time was 0.82 (95% CI 0.77-0.88; $P = .000$) (Figure 1). According to this result, in cases the operation time exceeds 87.5 minutes, a closer follow-up of patients may be recommended in order not to get worse in terms of infection risk. The earlier diagnosis means the more effective treatment in case of infection. This approach may be more important for patients who are at risk in terms of undergoing anaesthesia for the other session. However, if there is no problem for the patient to receive anaesthesia for the second time, the operation can be terminated by postponing the operation to a second session when the operation time is close to 87.5 minutes by making a decision with the patient before the operation. In the study conducted by Ozgor et al, The operation times in the non-infection and infection groups were 47 and 65, respectively.⁵ When we compare our own study and this study in terms of operation time and infection formation results, it is seen that the operation time in the infected group is longer than in the group without infection, as in our study. Our differences in operation times may have resulted from methodological differences in terms of size, placement, and number of stones in two studies. In addition to this, it is obvious that operation times are related to surgical experience. This issue is especially important in such operations where high technology vulnerable devices are used. In this article, being a little more descriptive about the effect of surgical experience on the operation time and therefore

the risk of infection formation will provide a more accurate guide for surgeons who will intervene with this type of stone by this method.

According to our results, the only difference between the groups that formed in terms of UAS usage was the longer OT in the UAS using group. (79.3 ± 24.4 and 66.7 ± 22.4 , for the groups which used and unused the UAS, respectively, $P < .05$, Table 3). This time difference depends on the wasted time because of the extraction of the fragmented parts of the stone and refocusing on the stone in the kidney. In addition, it was a striking finding that the infection rate in the group which the UAS used is not statistically different than the unused group. According to the analysis of this kind of group, although the infection rate in the group which used the UAS was a bit higher than in the group which unused, this difference is not significant statistically (Table 3). But, we associated this difference with the length of the OT in the group which used the UAS. While some studies in the literature focused on some of the benefits of the sheath, they indicated its importance in terms of infection formation, indirectly interpreting the results they obtained from these studies.^{4,9,10,15-17,19}

According to the literature, entrance of the bacteria or bacterial endotoxins into the bloodstream because of the intrarenal backflow because of elevated intrarenal pressure could be the reason for infective events following FURS.⁴ Based on this knowledge, the reduction of the intrarenal pressure constitutes protection from risk for bacterial dissemination during stone fragmentation.²⁰ Although it has been reported that the usage of the UAS reduced the intrarenal pressure in some literature,¹⁹ Berardinelli has shown that the absence of UAS does not increase the risk of postoperative infection rate in accordance with our results.¹⁰ In fact, the reduction of intrarenal pressure because of UAS usage may constitute protection for infective events. According to this theory, we were expecting lower infection rates in UAS using group. However, increased risk of infection because of long-term operation seems to have got ahead of the protective effect of UAS, as shown in Table 3. The fact that OT was independent risk factor in our regression analysis also supports this finding.

In addition, the usage of UAS seems as a two-edged sword; on the one hand, it reduces the intrarenal pressure which might be related to infective complications, on the other hand, it might increase tension-related lesions on the ureter wall.⁹ Thus, Osther et al had recommended using UAS in case of the indication rather than routinely.⁹ Since the long-term effects of UAS usage on the ureter wall are uncertain, we do not prefer to use UAS during FURS routinely, especially for long-term operations. The protective effect of using the UAS in terms of infection risk appears to decrease as the operation time increases. In the light of these findings, we believe that FURS without using UAS could be performed without an increased risk in terms of infective complications.

4.1 | Limitations of the study

Lack of stone analysis is one of the limitations of the study in addition to its being a retrospective non-randomised study.

5 | CONCLUSION

In kidney stones larger than 2 cm, the most important parameter determining the benefit of the UAS and general infective complications in terms of infective process is the operation time. While the risk of infection increases when the operation time exceeds 60 minutes, FURS can be safely performed up to 87.5 minutes in terms of infection risk, with 89% sensitivity and 69% specificity.

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DISCLOSURE

The authors have declared that they have no conflicts of interest.

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