External validation of the T.O.HO. score and derivation of the modified T.O.HO. score for predicting stone-free status after flexible ureteroscopy in ureteral and renal stones

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June 2, 2021

Abstract

Abstract The T.O.HO. scoring system was developed to predict stone-free status after flexible ureterenoscopy (fURS) lithotripsy applied for ureter and renal stones. This study aimed to perform the external validation of the T.O.HO. score in the Turkish population and propose a modification for this system. Material Methods Patients who underwent fURS for kidney and ureteral stones between January 2017 and January 2020 were retrospectively analyzed. The patient and stone characteristics and perioperative findings were noted. The T.O.HO. score was externally validated and compared with the STONE score. Stone-free parameters were evaluated with the multivariate analysis. Based on the results of this analysis, the T.O.HO. score was modified and internally validated. Results A total of 621 patients were included in the study. The stone-free rate was determined as 79.8% (496/621) after fURS. The regression analysis showed that stone area had better predictive power than stone diameter (p=0.025). Lower pole (reference), middle pole [odds ratio (OR)=0.492 p=0.016] and middle ureteral (OR=0.227, p=0.024) localizations, stone density (OR=1.001, p<0.001), and stone volume (OR = 1.008, p <0.001) were determined as independent predictive markers for stone-free status. Based on the effect size of the stone surface area in the nomogram, stone volume was divided into five categories, at 1-point intervals. The AUC values of the T.O.HO., STONE, and modified T.O.HO. score in predicting stone-free status were calculated as 0.758, 0.634, and 0.821, respectively. The modified T.O.HO. created by adding stone volume was statistically significantly superior to the original version (ROC curve comparison, p < 0.001). Conclusion The T.O.HO. score effectively predicted stone-free status after fURS. However, Modified T.O.HO. SS showed the best predictive performance compared with original T.O.HO. SS.

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There is no conflict of interest and relevant financial or non-financial competing interests between authors.

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Abstract

The T.O.HO. scoring system was developed to predict stone-free status after flexible ureterenoscopy (fURS) lithotripsy applied for ureter and renal stones. This study aimed to perform the external validation of the T.O.HO. score in the Turkish population and propose a modification for this system.

Material Methods

Patients who underwent fURS for kidney and ureteral stones between January 2017 and January 2020 were retrospectively analyzed. The patient and stone characteristics and perioperative findings were noted. The T.O.HO. score was externally validated and compared with the STONE score. Stone-free parameters were evaluated with the multivariate analysis. Based on the results of this analysis, the T.O.HO. score was modified and internally validated.

Results

A total of 621 patients were included in the study. The stone-free rate was determined as 79.8% (496/621) after fURS. The regression analysis showed that stone area had better predictive power than stone diameter (p=0.025). Lower pole (reference), middle pole [odds ratio (OR)=0.492 p=0.016] and middle ureteral (OR=0.227, p=0.024) localizations, stone density (OR=1.001, p<0.001), and stone volume (OR = 1.008, p <0.001) were determined as independent predictive markers for stone-free status. Based on the effect size of the stone surface area in the nomogram, stone volume was divided into five categories, at 1-point intervals. The AUC values of the T.O.HO., STONE, and modified T.O.HO. score in predicting stone-free status were calculated as 0.758, 0.634, and 0.821, respectively. The modified T.O.HO. created by adding stone volume was statistically significantly superior to the original version (ROC curve comparison, p < 0.001).

Conclusion

The T.O.HO. score effectively predicted stone-free status after fURS. However, Modified T.O.HO. SS showed the best predictive performance compared with original T.O.HO. SS.

What is already known about this topic?

Scoring systems are used to predict operation success in urinary system stones, inform patients, and standardize reporting of academic studies. T.O.HO. and STONE are scoring system developed for both ureteral and renal stones to predict stone free status after RIRS.

What does this article add?

The patient data of the STONE scoring system belong to the years 2006-2012. Today, RIRS is applied to large stones. So its current validity is not clear. In this study, we aimed to re-evaluate possible factors associated with SFS in patients after RIRS for ureteral and kidney stones and to derive a modified version of the T.O.HO score.

Introduction

Urinary system stone treatment management varies according to the characteristics of the stone and patient preference and physician experience. Treatment options include medical therapy, extracorporeal shock wave treatment (ESWL), percutaneous nephrolithotomy (PCNL), and ureterorenoscopy (URS).[1] In addition to PCNL being recommended for stones of >2 cm in size, with the recent developments in the device and laser technologies and increase in surgeon experience, flexible URS (fURS) is also reported to result in satisfactory stone-free rates (SFRs) in these stones.[2,3] Xu et al. reported that effective treatment could be applied even in stones with a cumulative burden of >4 cm.[4] The usage area and popularity of fURS is increasing day by day.[5] With the widespread use of fURS in large renal stones, the choice of treatment will become more and more difficult.

Many scoring systems have been developed to predict the success of ESWL, URS, and PCNL in urinary system stones.[6–9] It has been proven that stone-free status (SFS) and development of complications can be effectively predicted with scoring systems, especially in PCNL.[10] In the literature, several scoring systems, including Resorlu-Unsal[11], STONE[12], S-ReSC[13], and R.I.R.S.[14] and one nomogram[15] have been defined to predict the success of fURS. Among these scoring systems, only STONE score is used for kidney and ureter stones. The STONE scoring system consists of the parameters of (S)ize, (T)opography (stone localization), (O)bstruction, (N)umber of stones, and (E)valuation of stone density (Hounsfield unit, HU). Although the developing authors reported high predictive values for this system, their patient data belong to 2006-2012.[12] Considering that the STONE scoring system would not preserve its predictive value in the face of developing technology, Hori et al. developed a practical scoring system comprising the (T)allness, (O)ccupied lesion, (HO)unsfield unit components and named it T.O.HO.[16] In the current study, we aimed to evaluate factors associated with SFS in patients treated with fURS for ureteral and kidney stones and perform the external validation of the T.O.HO. and STONE score. We also aimed to derive a modified version of the T.O.HO. score and perform the internal validation of this version.

Materials and Methods

After receiving the ethics board approval of Amasya University (decision no. 2/25/2021), patients that underwent fURS for the treatment of renal and ureteral stones between January 2017 and January 2020 were retrospectively evaluated. Patients that completed ureteral stone treatment with semi-rigid URS, those with ureteral or renal anomalies or calyceal diverticula, and those with unavailable data were excluded from the study.

All operations were started by entering the ureter through a guide wire (0.035 inch, Microvasive; Boston Scientific Corp., Natick, MA) with semi-rigid URS. Active dilatation was applied with URS. Ureterorenoscopic lithotripsy was performed using fURS (7.5F; Karl Storz Flex-X2, Tutlingen, Germany and Olympus P-5TM, Olympus, Tokyo, Japan) and 270-350 µm Holmium laser (AMS; Sureflex). Ureteral access sheath (12/14 or 14/16 F, Cook Medical, Bloomington, IN or 11/13 or 13/15 F, Boston Scientific, Natick, MA, USA) was utilized to facilitate the removal of stones and reduce intrarenal pressure in both renal and ureteral stones.

All operations were performed by experienced surgeons. In all patients, 1.5 F-2.2 F tipless nitinol baskets were used for removal of residual stones. Preoperative D-J placement was applied in cases with treatment-resistant renal colic, pyelonephritis, and a narrow ureter that could prevent access to stone. A postoperative D-J stent or ureteral catheter was placed according to the surgeon's preference and clinical necessity. if no clinically significant stones were shown by KUB, uretral catheter was removed at POD 1. D-J stent was removed 2 weeks after the procedure.

The presence of residual stones was investigated using non-contrast computed tomography at the first post-operative month (POM1). SFS was defined as no evidence of stone.

As a result of the retrospective examination, the clinical characteristics of the patients [age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, stone side, ESWL history, preoperative stent requirement, and degree of hydronephrosis], stone characteristics (localization, number, density, and size), and perioperative findings (operation time, length of hospital stay, SFS, and development of complications) were noted. Complications were graded according to the Clavien-Dindo classification. The degree of hydronephrosis was measured according to the Society For Fetal Urology Hydronephrosis Grading System Stone length was measured as the longest diameter and stone width as the shortest diameter in the reconstructed coronal section.[17] Stone area was calculated using the formula, length x width x π x 0.25, where π is a mathematical constant equal to 3.14.[18] The mean HU measurement was performed in the longest diameter of the stone with bone window and large magnification. The burden and HU value of multiple stones were calculated as described in the original T.O.HO. study.[16] The T.O.HO. scoring system does not specify how to grade multi-calyceal stones. Therefore, the stone localization with the highest score was used in the presence of multi-calyceal stones at different localizations.

Statistical analysis

Categorical data were presented with number and percentage of rows. Only ESWL, preoperative stent requirement, and complication rates were presented as percentages of column for the convenience of comparison for the reader. Continuous data were evaluated using the Kolmogorov-Smirnov test to verify the normality of distribution of variables. Normally distributed data were expressed with mean + standard deviation (SD), and non-normally distributed data with median and percentile ($25\text{-}75^{th}$) values. The independent-samples t-test was used to compare two independent normally distributed data, while the Mann-Whitney U test was conducted for the comparison of data without normal distribution. In the comparison of categorical variables, Pearson's or Yate's chi-square test was used as appropriate. The relationship of stone size and stone surface area with SFS was evaluated with the multivariate logistic regression analysis, and stone surface area was determined as an independent predictive factor [odds ratio (OR) = 1.004, $p = 0.025$] (Table 1). Therefore, the measurement of surface area, which is used in both computed tomography and kidney, ureter, bladder radiography in clinical practice, was undertaken to predict stone volume. Possible predictive variables associated with SFS were evaluated with the multivariate logistic regression analysis, and the Backward elimination (Wald) method was used to construct a model. The exclusion criterion for the model was set at $p < 0.1$. A new nomogram including stone surface area was created using the regression coefficients of independent predictive variables. The predictive ability of the nomogram was evaluated with the receiver operating characteristic (ROC) analysis. Then, the T.O.HO., STONE and modified T.O.HO. scores were calculated for each patient. The ability of the scores to predict SFS was analyzed using the ROC analysis, and sensitivity and specificity values were calculated by determining the cut-off value for each scoring. A p value of <0.05 was considered statistically significant. SPSS software (version 23.0; IBM Corporation, Armonk, NY, USA) was used for statistical analyses and the R-project statistical software and "rms" package for the construction of the nomogram.

Results

A total of 621 patients were included in the study. The patient characteristics are presented in Table 1. The median age of the patients was 46 (36-56) years, and their median BMI was 26.0 (24.0-28.6) kg/m^2. Of the patients, 30.8% had a history of ESWL and 21.7% required preoperative stents. Stones were located in the pelvis in 35.9% of the patients, lower calyx in 17.9%, and multi-calyceal in (13.0%). In addition, 68 (11.0%) patients had proximal stones and 38 (6.1%) patients had stones in the middle ureter. According to the localization classification of the T.O.HO. scoring system, 46.2% of the stones were located in the middle pole and 31.2% in the lower pole, while 17.6% of the patients had multiple stones. The median stone size was 16 (12-22.5) mm, and the median stone area was 126 (77-204) mm^2. Total SFR was 79.9%. Complications rate was 10.6% and the majority of complications were grade I-II (n=58, 9.3%).

Table 1 presents the comparison of patient and stone characteristics according to SFS. SFR was higher in patients with higher BMI ($p = 0.018$). There was statistically significant difference in SFS according to stone localization ($p < 0.001$). In the post-hoc analysis, the multi-calyceal stones had significantly lower SFR compared to the pelvic and proximal ureteral stones, while lower the lower calyceal stones had significantly lower SFR compared to only proximal ureter stones. According to the localization classification of T.O.HO., the lower pole stones had lower SFR compared to the stones located in the middle pole and ureter. Multiple stone number, high HU value, high stone size and stone area, and prolonged operation time and length of hospital stay were determined to be associated with fURS failure. The median T.O.HO., STONE and modified T.O.HO. scores were determined as 8, 11, and 8, respectively for the failure group and 7, 10, and 6, respectively, for the patients with SFS ($p < 0.001$ for all).

Table 2 shows the multivariate logistic regression analysis results of possible predictive factors associated with SFS given in Table 1. According to the results, stone area had better predictive power than stone diameter ($p = 0.025$). Lower pole (reference), middle pole (OR = 0.492 p = 0.016) and middle ureteral (OR = 0.227, $p = 0.024$) localizations, stone density (OR = 1.001, $p < 0.001$), and stone volume (OR = 1.008, $p < 0.001$) were determined as independent predictive markers for SFS. A nomogram was constructed to predict fURS failure (Figure 1). Based on the effect size of stone surface area in the nomogram, stone volume was divided into five categories, at 1-point intervals, as <120 mm^2, 120-240 mm^2, 240-360 mm^2, 360-480 mm^2 and >480 mm^2. The newly created scoring system was defined as modified T.O.HO. (Figure 1). The nomogram was found to have high predictive power, with an area under the curve (AUC) value of 0.838 (Figure 2).

The T.O.HO., STONE and modified T.O.HO. scores were calculated for each patient included in our dataset. The external validation of the original T.O.HO. and STONE systems and the internal validation of the modified T.O.HO. system were undertaken. The AUC value was calculated as 0.758 for original T.O.HO., 0.634 for STONE, and 0.821 for modified T.O.HO. at the asymptotic significance of <0.001 for each scoring system (Figure 2). The cut-off value and sensitivity-specificity results for each scoring system are shown in Table 3. The modified T.O.HO. created by adding stone volume was statistically significantly superior to the original version (ROC curve comparison, $p < 0.001$).

Discussion

The current European Association of Urology (EAU) and American Association of Urology (AUA) guidelines recommend PCNL for the treatment of renal stones sized >2 cm.[19,20]However, due to the potential advantages of fURS (e.g., not causing renal parenchymal damage and severe bleeding, applicability in patients with bleeding diathesis or those receiving anticoagulant therapy, short length of hospitalization, and daily work routine not being restricted) and its ability to access almost all calyceal stones as a result of improvements in deflection, fURS has become a preferred method for the treatment of both proximal ureteral and renal stones.[2,21] In a recent meta-analysis, the final SFR was reported to be 89.4% in an average of 1.4 procedures performed in 2-3 cm stones, and this rate was stated to be comparable to PCNL.[22] Although complication rates of up to 16% have been reported in previous studies, most were classified as minor. In addition to the development in fURS technology, increasing surgical experience has reduced the rate of major complication from 5.01% between 1990 and 2011 to 1.48% between 2011 and 2016 and increased the success of treatment.[23] While semi-rigid URS is sufficient in most cases in the treatment of ureteral stones, performing a procedure without fURS in the treatment of middle and upper ureteral stones creates problems in terms of medicolegal aspects. In a study published by the Clinical Research Office of the Endourological Society ureteroscopy study group in 2014, it was reported that middle and proximal stones were both larger and difficult to reach compared to distal stones. In the same study, it was emphasized that the risk of perforation due to impaction was high in middle ureteral stones and low-caliber URS should be used.[24] fURS, which has a wide range of treatment options in terms of both localization and stone burden and is even preferred in much larger stones to avoid PCNL-related complications, requires further investigation in terms of how to predict its outcomes. Almost all the scoring systems used in fURS have been developed for renal stones, and STONE, which is an option for ureteral stones in which fURS will be performed[11,12,14,15], is based on low stone burden and use of old devices. Hori et al. identified this gap in the literature and defined a scoring system, which they named T.O.HO., including the stone diameter, localization and density parameters and covering patients with larger stones that are planned to undergo fURS.[16] The authors reported that T.O.HO. had better predictive value than STONE (AUC = 0.833 and 0.633, respectively).

In this study, the external validation of the T.O.HO. and STONE scores was performed, and SFS-related parameters after fURS were evaluated. The overall SFR was found to be 79.9%, and SFR in renal and ureteral stones was 77.6% and 90.5%, respectively. Our SFR was similar to the rate reported in the original study. In addition, in our study, the SFS prediction accuracy (AUC value) was calculated as 0.758 for T.O.HO. and 0.634 for STONE. T.O.HO. The cut-off value of T.O.HO. was determined as 8, at which it had 71.4% sensitivity and 68.8% specificity in predicting SFS. STONE was able to predict SFS with 57.5% sensitivity and 63.2% specificity at a cut-off value of 11. When compared to the original T.O.HO. study, the modified T.O.HO. score had lower specificity but similar sensitivity (AUC = 0.758). This difference may be due to the large stone sizes in our study and the lower number of patients with ureteral stones compared to the original TOHO study. The modified T.O.HO. scoring system was observed to have better predictive value than the original version (AUC = 0.821 and 0.758, respectively). At a cut-off value of 7, the modified T.O.HO. scoring system was able to predict SFS with 71.2% sensitivity and 80.8% specificity.

Many studies in the literature have shown that stone burden is the most important parameter affecting SFS after fURS.[11,12,14,15] In the T.O.HO. scoring system, stone burden was reported to be the most important predictive value.[16] We also determined that stone burden was associated with SFS ($p < 0.001$). The effect size of stone burden was clearly demonstrated by the constructed nomogram (Figure 1). Stone diameter is widely used in clinical practice since it is simple and easy to obtain in the assessment of stone burden.[25] The EAU and AUA guidelines also include stone diameter in their recommendations concerning decision-making with regard to the treatment of urinary system stones.[19,20]Hori et al. used stone diameter while evaluating stone burden and categorized it over 5 points based on the effect size obtained from the nomogram. They reported that treatment success decreased by <30% in patients with 5 points.[16] However, since stone diameter does not reflect the width and depth of the stone, it will naturally have certain limitations in predicting the results of the operation compared to stone volume. Ito et al., evaluating patients who underwent fURS, emphasized that stone diameter was able to accurately predict stone volume in <2 cm stones but it was necessary to directly calculate stone volume in stones larger than 2 cm.[25] Considering that stone volume increases exponentially as stone diameter increases, this result is expected. Today, with the developments in technology and increase in experience, it is possible to apply fURS treatment to larger stones; therefore, it would not be realistic to expect stone diameter alone to predict success. Supporting this, in our study, the rate of treatment success was 42% in the patients with 5 points in stone diameter ([?]30 mm) according to the original T.O.HO. score while it was only 21% for those with 5 points (>480 mm^2) according to the modified T.O.HO. score, in which stone area rather than diameter was evaluated. Hori et al. also stated that the STONE scoring system, which has different cut-off values, does not have predictive value for stone size classification.[16] Consistently, we found that the patients scoring 3 points (>10 mm) in the stone diameter of the STONE scoring system had a treatment success rate of 79%. This indicated that the stone size classification of the STONE scoring system was far from differentiating SFS.

Another component of the T.O.HO. scoring system is stone localization. Studies have shown that stone localization is an independent marker in the treatment of ureteral and renal stones, and especially lower pole stones are associated with fURS treatment failure.[11,12,14,15,19,26] For practical use, T.O.HO. classified renal stone localizations as upper, middle and lower pole and ureteral stones as proximal, middle, and distal. In our study, it was observed that the rate of SFS was 71.2% in lower pole stones and 66.7% in multi-calyceal stones, while it was 89.5%, 91.2% and 87.9% for middle ureteral, proximal ureteral and pelvic stones, respectively. However, the authors that developed T.O.HO. did not specify how multi-calyceal were graded in this scoring system. In order to continue the validation process, we scored multi-calyceal stones containing those with middle and upper pole localizations and similar SFR as the upper and middle pole group, and multi-calyceal stones with low SFR located in the lower calyx as the lower pole group. According to the T.O.HO. score based on stone localization, the worst SFR was in the lower pole, and this was at a statistically significant level ($p < 0.001$). In the multivariate analysis, it was determined that the middle ureter and middle pole stones provided an increase of 76.2% and 50.4% in the operation success, respectively, compared to the lower pole stones. In the original T.O.HO. study, lower SFR (51.6%) was reported in the upper pole stones than in the lower calyceal group, whereas in our study, higher SFR (82.4%) was found in the upper pole stones similar to the middle pole stones. This difference was attributed to the small number of patients with upper pole stones in both studies and presumably different stone sizes.

As an important parameter in the treatment of urinary system stones, stone density is also a component of the T.O.HO. scoring system. The relationship of stone density with SFS has been shown in many studies.[12,27] Hussain et al.[28] used the cut-off value of T.O.HO. stone density as 1100 HU and graded the cases over 3 points. In our study, it was observed that stone density was an independent marker for SFS in the multivariate analysis, and the cut-off value was calculated as 1125 HU. A 100 HU increase in stone density increased treatment failure by 1.1 times. The STONE scoring system, which has a different cut-off value for stone density, was also found to have similar predictive value for SFR (AUC = 0.570 for STONE and T.O.HO for and 0.581). In our study, according to the stone density score, SFR was determined as 83.7%, 84.0%, and 72.2% for 1, 2 and 3 points, respectively. There was no difference between 1 and 2 points in terms of SFS ($p > 0.05$). We consider that the HU value can be reduced to 2 points for a practical scoring system. However, in the current study, we left the HU prediction values as in the original system since it would not further increase the predictive value of the modified system.

In addition to the three main parameters explained above, many other parameters have been defined in the literature to be associated with SFS after fURS, such as the number of stones, preoperative stenting, presence of hydronephrosis, and operator experience.[11,12,14,15] The STONE scoring system uses preoperative stent application, number of stones, and presence of hydronephrosis as predictive factors.[12] In the original T.O.HO. study, Hori et al. reported both parameters to be associated with SFS but found no independent marker in the multivariate analysis.[16] Similarly, in our study, the presence of multiple stones was statistically significantly associated with SFS, but it was observed that there was no independent marker in the multivariate analysis. Since stone burden is directly related to the number of stones, the latter loses its importance. We did not determine preoperative stenting to be associated with SFS. There are publications in the literature stating that preoperative stenting increases the success of ureteral access sheath and is not associated with SFS.[29,30] Another parameter included in the STONE scoring system is the presence of hydronephrosis. Hori et al. did not evaluate the presence of hydronephrosis. In our study, although the presence of hydronephrosis was high in patients with residual stones, it was not found to be a statistically significant parameter. In the nomogram developed by Ito et al., the presence of hydronephrosis had very low power but it was not used as a marker in other scoring systems.[15] The same authors also used operator experience as a marker in their nomogram. Since all surgical procedures in our study were performed by experienced endourologists, similar to the original T.O.HO. study, this marker is not discussed further.

Our study has certain limitations. The main limitations are retrospective design, relatively small number of patients, and lack of data on second-session attempts in patients with residual stones and final success rates. Another important limitation is the lack of stone composition that may affect SFS.

Conclusion

In predicting SFS after fURS, the T.O.HO. score has better predictive ability than the STONE score. The modified T.O.HO. score, which was created by adding the stone area parameter, was able to better predict SFS after fURS. Based on these results, we consider that the modified T.O.HO. score can be used effectively in ureteral and renal stones without losing its practicality. Our study proved the efficacy of the modified

T.O.HO. score in predicting SFS but there is a need for large-series studies with a prospective design to validate it.

References

1. Türk C, Neisius A, Petřík A, Seitz C, Thomas K, Skolarikos A. EAU Guidelines on Urolithiasis 2020. In: *European Association of Urology Guidelines. 2020 Edition.* Vol presented. The European Association of Urology Guidelines Office; 2020. http://uroweb.org/guideline/urolithiasis/ LK - Urolithiasis Uroweb%7Chttp://uroweb.org/guideline/urolithiasis/%7C FG - 0

2. Huang JS, Xie J, Huang XJ, Yuan Q, Jiang HT, Xiao KF. Flexible ureteroscopy and laser lithotripsy for renal stones 2 cm or greater: A single institutional experience. *Medicine (Baltimore)* . 2020;99(43):e22704. doi:10.1097/MD.0000000000022704

3. Li Z, Lai C, Shah AK, et al. Comparative analysis of retrograde intrarenal surgery and modified ultra-mini percutaneous nephrolithotomy in management of lower pole renal stones (1.5-3.5 cm). *BMC Urol* . 2020;20(1). doi:10.1186/s12894-020-00586-6

4. Xu C, Song RJ, Jiang MJ, Qin C, Wang XL, Zhang W. Flexible ureteroscopy with holmium laser lithotripsy: A new choice for intrarenal stone patients. *Urol Int* . 2015;94(1):93-98. doi:10.1159/000365578

5. Heers H, Turney BW. Trends in urological stone disease: a 5-year update of hospital episode statistics. *BJU Int* . 2016;118(5):785-789. doi:10.1111/bju.13520

6. Wang M, Shi Q, Wang X, Yang K, Yang R. Prediction of outcome of extracorporeal shock wave lithotripsy in the management of ureteric calculi. *Urol Res* . 2011;39(1):51-57. doi:10.1007/s00240-010-0274-5

7. Imamura Y, Kawamura K, Sazuka T, et al. Development of a nomogram for predicting the stone-free rate after transurethral ureterolithotripsy using semi-rigid ureteroscope. *Int J Urol* . 2013;20(6):616-621. doi:10.1111/j.1442-2042.2012.03229.x

8. Thomas K, Smith NC, Hegarty N, Glass JM. The guy's stone scoregrading the complexity of percutaneous nephrolithotomy procedures. *Urology* . 2011;78(2):277-281. doi:10.1016/j.urology.2010.12.026

9. Smith A, Averch TD, Shahrour K, et al. A nephrolithometric nomogram to predict treatment success of percutaneous nephrolithotomy. *J Urol* . 2013;190(1):149-156. doi:10.1016/j.juro.2013.01.047

10. Jiang K, Sun F, Zhu J, et al. Evaluation of three stone-scoring systems for predicting SFR and complications after percutaneous nephrolithotomy: A systematic review and meta-analysis. *BMC Urol* . 2019;19(1):57. doi:10.1186/s12894-019-0488-y

11. Resorlu B, Unsal A, Gulec H, Oztuna D. A new scoring system for predicting stone-free rate after retrograde intrarenal surgery: The "resorlu-Unsal Stone Score." *Urology* . 2012;80(3):512-518. doi:10.1016/j.urology.2012.02.072

12. Molina WR, Kim FJ, Spendlove J, Pompeo AS, Sillau S, Sehrt DE. The S.T.O.N.E. Score: A new assessment tool to predict stone free rates in ureteroscopy from pre-operative radiological features. *Int Braz J Urol* . 2014;40(1):23-29. doi:10.1590/S1677-5538.IBJU.2014.01.04

13. Jung JW, Lee BK, Park YH, et al. Modified seoul national university renal stone complexity score for retrograde intrarenal surgery. *Urolithiasis* . 2014;42(4):335-340. doi:10.1007/s00240-014-0650-7

14. Xiao Y, Li D, Chen L, et al. The R.I.R.S. scoring system: An innovative scoring system for predicting stone-free rate following retrograde intrarenal surgery. *BMC Urol* . 2017;17(1):1-8. doi:10.1186/s12894-017-0297-0

15. Ito H, Sakamaki K, Kawahara T, et al. Development and internal validation of a nomogram for predicting stone-free status after flexible ureteroscopy for renal stones. *BJU Int* . 2015;115(3):446-451. doi:10.1111/bju.12775

16. Hori S, Otsuki H, Fujio K, et al. Novel prediction scoring system for simple assessment of stone-free status after flexible ureteroscopy lithotripsy: T.O.HO. score. *Int J Urol* . 2020;27(9):742-747. doi:10.1111/iju.14289

17. Fernbach SK, Maizels M, Conway JJ. Ultrasound grading of hydronephrosis: Introduction to the system used by the society for fetal urology. *Pediatr Radiol* . 1993;23(6):478-480. doi:10.1007/BF02012459

18. Tiselius HG, Andersson A. Stone burden in an average Swedish population of stone formers requiring active stone removal: How can the stone size be estimated in the clinical routine? In: *European Urology* . Vol 43. Elsevier; 2003:275-281. doi:10.1016/S0302-2838(03)00006-X

19. C. Türk, Neisius A, Petrik A, Seitz C, Skolarikos A, Thomas K. EAU Guidelines on Urolithiasis. Edn. presented at the EAU Annual Congress Amsterdam 2020. European Association of Urology. doi:10.1159/000049803

20. Assimos D, Krambeck A, Miller NL, et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART II. *J Urol* . 2016;196(4):1161-1169. doi:10.1016/j.juro.2016.05.091

21. Scotland KB, Rudnick B, Healy KA, Hubosky SG, Bagley DH. Retrograde ureteroscopic management of large renal calculi: A single institutional experience and concise literature review. *J Endourol* . 2018;32(7):603-607. doi:10.1089/end.2018.0069

22. Zewu Z, Cui Y, Feng Z, Yang L, Chen H. Comparison of retrograde flexible ureteroscopy and percutaneous nephrolithotomy in treating intermediatesize renal stones (2-3cm): A meta-analysis and systematic review. *Int Braz J Urol* . 2019;45(1):10-22. doi:10.1590/S1677-5538.IBJU.2018.0510

23. Cindolo L, Castellan P, Scoffone CM, et al. Mortality and flexible ureteroscopy: analysis of six cases. *World J Urol* . 2016;34(3):305-310. doi:10.1007/s00345-015-1642-0

24. Perez Castro E, Osther PJS, Jinga V, et al. Differences in ureteroscopic stone treatment and outcomes for distal, mid-, proximal, or multiple ureteral locations: The clinical research office of the endourological society ureteroscopy global study. *Eur Urol* . 2014;66(1):102-109. doi:10.1016/j.eururo.2014.01.011

25. Ito H, Kawahara T, Terao H, et al. Utility and Limitation of Cumulative Stone Diameter in Predicting Urinary Stone Burden at Flexible Ureteroscopy with Holmium Laser Lithotripsy: A Single-Center Experience.*PLoS One* . 2013;8(6). doi:10.1371/journal.pone.0065060

26. Zhao Z, Sun H, Zeng T, Deng T, Liu Y, Zeng G. An easy risk stratification to recommend the optimal patients with 2–3 cm kidney stones to receive retrograde intrarenal surgery or mini-percutaneous nephrolithotomy. *Urolithiasis* . 2020;48(2):167-173. doi:10.1007/s00240-019-01134-0

27. Gücük A, Yilmaz B, Gücük S, Üyetürk U. Are stone density and location useful parameters that can determine the endourological surgical technique for kidney stones that are smaller than 2 cm? A prospective randomized controlled trial. *Urol J* . 2019;16(3):242-245. doi:10.22037/uj.v0i0.4280

28. Hussain M, Acher P, Penev B, Cynk M. Redefining the limits of flexible ureterorenoscopy. *J Endourol* . 2011;25(1):45-49. doi:10.1089/end.2010.0236

29. Yuk HD, Park J, Cho SY, Sung LH, Jeong CW. The effect of preoperative ureteral stenting in retrograde Intrarenal surgery: A multicenter, propensity score-matched study. *BMC Urol* . 2020;20(1). doi:10.1186/s12894-020-00715-1

30. Sung LH, Cho DY. The role of preoperative ureteral stenting in retrograde intrarenal surgery in renal stone patients: a propensity score-matched study. *Transl Androl Urol* . 2020;9(2):276-283. doi:10.21037/tau.2020.03.09

Table 1. Comparison of patient characteristics according to post- operative stone-free status

Variables	Total (n = 621)	Not stone-free (n = 125)	Stone-free (n = 496)	*P value*
Age, years	46 (36-56)	44 (32.5-56)	46 (36-56)	0.174
Gender, n (%) Female Male	215 (34.6) 406 (65.4)	49(22.8) 76 (18.7)	166 (77.2) 330 (81.3)	0.229*
BMI, kg/m^2	26.0 (24.0-28.6)	25.5 (23.5-27.5)	26.3 (24.2-29)	**0.018**
Side Left Right	334 (53.8) 287 (46.2)	64 (19.2) 61 (21.3)	270 (80.8) 226 (78.7)	0.517*
ASA category, n (%) ASA I ASA II ASA [?] III	266 (42.8) 318 (51.2) 37 (6.0)	46 (17.3) 71 (22.3) 8 (21.6)	220 (82.7) 247 (77.7) 29 (78.4)	0.311*
Previous history of ESWL, n (%)	191 (30.8)	34 (27.2)	157 (31.7)	0.335*
Preoperative stent, n (%)	135 (21.7)	33 (26.4)	102 (20.6)	0.102*
Preoperative hydronephrosis, n(%) Grade 0 Grade 1-2 Grade 3-4	126 (20.3) 362 (58.3) 133 (21.4)	27 (21.4) 65 (18.0) 33 (24.8)	199 (78.6) 297 (82.0) 100 (75.2)	0.222*
Stone location, n (%)+				**0.001***
Lower pole Middle pole Upper pole Pelvis Middle ureter Proximal ureter Multi-calyceal Ureter + Kidney	111 (17.9) 58 (9.3) 20 (3.2) 223 (35.9) 38 (6.1) 68 (11.0) 81 (13.0) 22 (3.5)	32 (28.8) [a,b] 11 (19.0) [a,b,c,d] 4 (20.0) [a,b,c,d] 27 (12.1) [b,d] 4 (10.5) [a,b,c,d] 6 (8.8) [c,d] 27 (33.3) [a] 6 (27.3) [a,b,c,d]	79 (71.2) [a,b] 47 (81.0) [a,b,c,d] 16 (80.0) [a,b,c,d] 196 (87.9) [b,d] 34 (89.5) [a,b,c,d] 62 (91.2) [c,d] 54 (66.7) [a] 16 (72.7) [a,b,c,d]	
Stone location by T.O.HO., n (%)+ Lower pole Middle pole Upper pole Proximal ureter (U1) Middle ureter (U2)	194 (31.2) 287 (46.2) 34 (5.5) 68 (11.0) 38 (6.1)	58 (29.9) [a] 51 (17.8) [b] 6 (17.6) [a,b] 6 (8.8) [b] 4 (10.5) [b]	136 (70.1) [a] 236 (82.2) [b] 28 (82.4) [a,b] 62 (91.2) [b] 34 (89.5) [b]	**<0.001***
Stone number Single Multiple	512 (82.4) 109 (17.6)	88 (17.2) 37 (33.9)	424 (82.8) 72 (66.1)	**<0.001[&]**
Stone density, HU	897 (592-1230)	1050 (665-1313)	851 (572.5-1200)	**0.006**
Stone length, mm	16 (12-22.5)	25 (15.5-32)	15 (12-20)	**<0.001**
Stone area, mm^2	126 (77-204)	342 (141-573)	110 (66-175)	**<0.001**
Operation time, min	75 (60-99)	100 (80.5-120)	70 (60-90)	**<0.001**
Length of hospital stay, days	1 (1-2)	2 (1-3)	1 (1-2)	**<0.001**
Complication rates, n(%)	66 (10.6)	21 (16.8)	45 (9.1)	**<0.019****
Complication grades, n(%)				**0.038***
Grade 1-2	58 (9.3)	19 (15.2)	39 (7.9)	

Variables	Total (n = 621)	Not stone-free (n = 125)	Stone-free (n = 496)	*P value*
Grade 3-4	8 (1.3)	2 (1.6)	6 (1.2)	
T.O.HO. score	7 (6-8)	8 (7-9.5)	7 (6-8)	**<0.001**
STONE score Modified T.O.HO. score	10 (9-11) 6 (5-7)	11 (10-12) 8 (7-9)	10 (9-11) 6 (5-7)	**<0.001 <0.001**

BMI, body mass index; ESWL, extracorporeal shock wave lithotripsy

* Pearson's chi-square test

**Yate's chi-square test

+No significant difference between the same superscripts

Table 2. Multivariate logistic regression analysis of independent predictors of post-operative stone-free status

	Multivariate
Variables	OR (95% CI)
Stone-free status Stone length Stone area	1.046 (0.979-1.117) 1.004 (1.0
Stone-free status	
BMI	0.965 (0.905-1.029)
Stone location Lower pole Middle pole Upper pole Proximal ureter (U1) Middle ureter (U2)	Ref. 0.492 (0.276-0.878) 0.51
Stone density	1.001 (1.001-1.002)
Stone area	1.008 (1.006-1.009)
Number of stones	
Single stone	Ref.
Multiple stones	1.026 (0.543-1.937)

CI, confidence interval

Table 3. Cut-off, sensitivity, specificity and AUC values of the T.O.HO., STONE and modified T.O.HO. scoring systems in predicting treatment failure

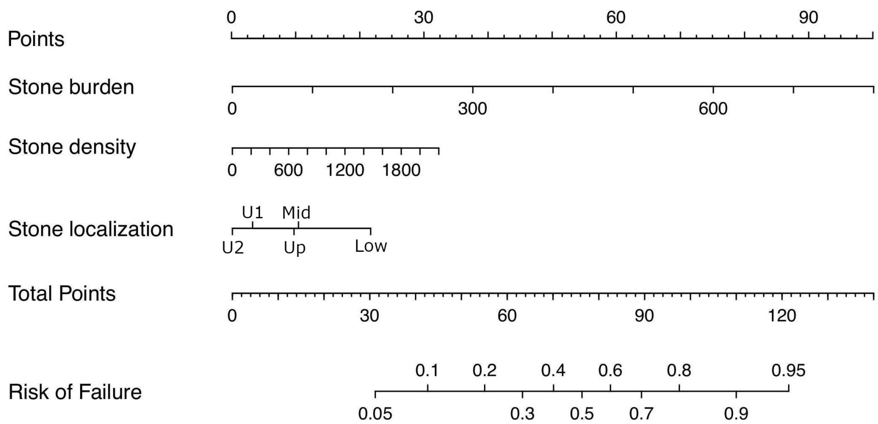
	Cut-off	Sensitivity (%)	Specificity (%)	AUC (95% CI)
T.O.HO.	8	71.4	68.8	0.758 (0.708-0.809)
STONE	11	57.5	63.2	0.634 (0.580-0.689)
Modified T.O.HO.	7	71.2	80.8	0.821 (0.773-0.868)

AUC, area under the curve

Figures Legends

Figure 1: New nomogram created by adding stone burden and the modified T.O.HO. scoring system based on the effect size of stone volume on stone-free status

Figure 2: (a) ROC curve based on the created nomogram (AUC=0.838, 95% CI: 0.810-0.867), (b) results of the ROC analysis of the T.O.HO., STONE and modified T.O.HO. scores in predicting treatment failure



	1 pt	2 pts	3 pts	4 pts	5 pts
S(T)one burden, mm^2	<120	120-240	240-360	360-480	>480
(O)ccupied lesion	Ureter	Middle and Upper pole	Lower pole		
(HO)unsfied Units evaluation	<620	620-1100	>1100