INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2020) doi: 10.1111/iju.14203

Original Article

STone Episode Prediction: Development and validation of the prediction nomogram for urolithiasis

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Abbreviations & Acronyms
Alb = serum albumin
AUC = area under the curve
BMI = body mass index
CI = confidence interval
Ctrl = control
CVD = cardiovascular disease
DM = diabetes mellitus
eGFR = estimated glomerular filtration rate
HR = hazard ratio
HTN = history of hypertension
IQR = interquartile range
OR = odds ratio
ROC = receiver operating characteristics
STEP = STone Episode Prediction
UA = serum uric acid
VIF = variance inflation factor

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Received 28 August 2019; accepted 26 January 2020.

Objectives: To develop and validate a nomogram predicting the occurrence of a stone episode, given the lack of such predicting risk tools for urolithiasis.
Methods: We retrospectively analyzed 1305 patients with urolithiasis and 2800 community-dwelling individuals who underwent a comprehensive health survey. The STone Episode Prediction nomogram was created based on data from the medical records of 600 patients with urolithiasis and 1300 controls, and was validated using a different population of 705 patients with urolithiasis and 1500 controls. Logistic regression analysis was used to construct a model to predict the potential candidate for a stone episode. The predictive ability of the model was evaluated using the results of the area under the receiver operating characteristics curve (area under the curve).
Results: Age, sex, diabetes mellitus, renal function, serum albumin, and serum uric acid were found to be significantly associated with urolithiasis in the training set and were included in the STone Episode Prediction nomogram. The optimal cut-off value for the probability of a stone episode using the nomogram was >28% with a sensitivity of 79%, a specificity of 76%, and area under the curve of 0.860. In the validation test, area under the curve for the detection of urolithiasis was 0.815 with a sensitivity of 81% and specificity of 63%.
Conclusions: Herein, we developed and validated the STone Episode Prediction nomogram that can predict a potential candidate for an episode of urolithiasis. This nomogram might be beneficial for the first step in stone screening in individuals with lifestyle-related diseases.

Key words: kidney, nomogram, prediction, urinary stone, urolithiasis.

Introduction

The incidence of urolithiasis (urinary tract stones) has increased steadily in Japan since 1955, owing to an aging population and a shift toward a Westernized lifestyle, including dietary habits.[1,2] In 2015, the estimated annual incidence of a first-episode upper urinary tract stone was 137.9 (191.9 in men and 86.9 in women) per 100 000.[1] With the increase in the prevalence of urolithiasis, there is a need for an accurate tool by which the risk of a first episode can be predicted to optimize patient screening and treatment strategies.[3,4] Several studies have identified predictors for the recurrence of a stone after the first episode,[5,6] the ureteral calculi-related urosepsis[7] and the stone-free rate after intervention.[8,9] However, the clinical diagnosis of the disease must rely mainly on a painful stone episode, and no tool has been developed in routine clinical practice for predicting a potential candidate for any stone episodes. Therefore, we aimed to develop and validate a nomogram that would predict the potential candidate for a stone episode using commonly available characteristics.

Methods

Ethics statement

This study was carried out in accordance with the ethical standards of the Declaration of Helsinki, and was approved by the ethics review board of Hirosaki University School of Medicine (authorization no. 2018-062). All participants provided written informed consent.

Study design and patient selection

We retrospectively analyzed the clinical data of 1305 patients (Stone group) with the first episode of symptomatic urolithiasis who visited our hospitals from May 2010 to March 2018. The Ctrl group were selected from 2800 community-dwelling individuals who underwent a comprehensive health survey between May 2006 and May 2016 in connection with the Iwaki Health Promotion Project, Hirosaki, Japan.[10–16] The inclusion criteria for the Stone group were as follows: (i) imaging results, such as ultrasound, excretory urography or computed tomography, that led to a diagnosis of urolithiasis; (ii) availability of clinical and laboratory data at the time of stone diagnosis, comprising age, sex, BMI (kg/m^2), eGFR (mL/min/1.73 m^2), Alb (g/dL), UA (mg/dL), HTN, CVD and DM. The exclusion criterion for the study was insufficient information against the criteria.

Evaluation variables

Measurement methods were the same in serum creatinine, Alb, and uric acid between the training and validation tests. Renal function was evaluated using the eGFR at the time of diagnosis with a modified version of the abbreviated formula from the Modification of Diet in Renal Disease Study for Japanese patients.[17–19] Diabetes patients were defined as those with a history of type 2 diabetes or those who met the relevant diagnostic criteria and requirements. Hypertension was defined as two consecutive blood pressure readings >140/90 mmHg (when not painful) or the use of antihypertensive medications. CVD was defined as a positive history of cardiac surgery, heart failure, heart arrhythmia, atrial fibrillation/flutter, valvular heart disease, stroke, angina pectoris, myocardial infarction or use of any cardiotonic agents or coronary vasodilators.

Training and validation tests

Eligible patients with urinary stones and Ctrl participants were randomly selected from the database. A training test was carried out to determine the appropriate cut-off values to discriminate between the Ctrl (n = 1300) and Stone (n = 600) groups, and was used to create the STEP nomogram. A validation test was carried out using 705 patients with stone episodes and 1500 Ctrls (Fig. 1).

Statistical analysis

Statistical analyses of the clinical data were carried out using SPSS version 24.0 (IBM Corporation, Armonk, NY, USA), GraphPad Prism 5.03 (GraphPad Software, San Diego, CA, USA), BellCurve for Excel (Social Survey Research Information, Tokyo, Japan) and R version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were compared using the Fisher's exact or χ^2-test. Quantitative variables were expressed as the mean ± standard deviation or the median with the IQR. The differences among groups were compared using the Student's t-test for normally distributed data. The Mann–Whitney U-test was used for non-normally-distributed data. A multivariate logistic regression analysis was used to construct a model for predicting the probability of urolithiasis. Based on the regression coefficients of the independent variables, we established the individualized nomogram model for predicting episodes of urolithiasis.[20] The OR and 95% CI were also derived. A nomogram for the probability of a stone episode was developed based on the final logistic regression model. The predictive ability of the nomogram was evaluated using the AUC of the ROC curve. An AUC >0.75 indicated that the model shows excellent discrimination. A calibration plot was applied to assess the prediction accuracy of the nomogram by plotting the actual probabilities against the nomogram-predicted probabilities of a stone episode. Multicollinearity among covariates was assessed through a VIF.[21] The differences were considered statistically significant at $P < 0.05$.

Results

Patient characteristics

Table 1 provides a list of the characteristics of the enrolled study population. Significant differences were observed among all clinical parameters between the Ctrl and Stone groups in both the training and validation tests, except for BMI (P = 0.075) in the training set.

Nomogram development

VIF values among covariates were between 1.00 and 1.30. High VIF value was observed between the sex and UA (1.30), followed by between age and HTN (1.24), the age and eGFR (1.23), the eGFR and UA (1.15), and the age and Alb (1.13; Table S1). Table 2 provides a list of the significant predictors that discriminate the Ctrl group from the Stone group. Based on the multivariate logistic analysis carried out on the training test, age, sex, DM, eGFR, Alb and UA were found to be significantly associated with urolithiasis (Table 2). Using these seven independent predictors, we constructed the STEP nomogram model to predict stone episodes (Fig. 2a). The estimated probability was calculated using the following formula:

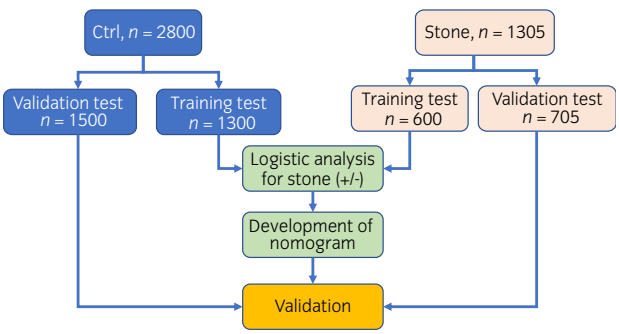

Fig. 1 Patient selection and classification. Eligible patients with urinary stones and Ctrl participants were randomly selected from the database. The schematic shows the steps taken using the Ctrl and Stone groups to develop the STEP nomogram.

$$1/(1+e^{p}),\ p = 1 \times (\text{age} \times -0.0363 + \text{sex} \times 0.3562 + \text{DM} \times 1.4229 + \text{eGFR} \times -0.2226 + \text{Alb} \times -4.4019 + \text{UA} \times 0.24145 + 20.4964)$$

A web-based application for the STEP nomogram calculator (Fig. 2b) was posted at https://www.calconic.com/calculator-widgets/step-nomogram/5ccadea344587d0026d93c0d.

For example, a 60-year-old man with diabetes was treated at the outpatient clinic after presenting with DM, eGFR 60 mL/min/1.73 m^2, Alb 4.5 g/dL and UA 7.0 mg/dL. Based on these parameters, his probability of a stone episode was 65%. The waterfall plot showed a significantly higher probability of a stone episode in the Stone group than in the Ctrl group (median probability 13% [95% CI 6.4–27] *vs* 59% [95% CI 31–86], respectively, $P < 0.001$; Fig. 3a). According to the ROC curve analysis, the optimal cut-off value for the probability of a stone episode using the STEP nomogram model was set at >28% in the training test with a sensitivity of 79%, specificity of 76% and AUC of 0.860 (blue line, Fig. 3b). In this model, the positive and negative predictive values were 60% and 89%, respectively. In the validation test, the waterfall plot shows a significantly higher value of probability in the Stone group (median probability: 21% [95% CI 10–38] *vs* 65% [95% CI 35–90], respectively, $P < 0.001$; Fig. 3c), and AUC for the probability of a stone episode was 0.815 with a sensitivity of 81% and specificity of 63% (red line, Fig. 3b). The positive and negative predictive values were 60% and 85%, respectively, in the validation test. The calibration plots showed that the actual probability corresponded closely to the nomogram-predicted probability. A slight overestimation was observed in participants with an actual probability between 20% and 40% (Fig. 3d).

Discussion

In the present study, we developed and validated the STEP nomogram to predict the individual probability of symptomatic urolithiasis based on a comparison of patients with urolithiasis with a general healthy population without urolithiasis. To the best of our knowledge, this is the first report to develop the nomogram that compares an individual who had symptomatic stones to those who never had stones. The present results suggest that the STEP nomogram can predict a potential "stone former" who develops symptomatic stone colic. Urolithiasis has been linked to a wide variety of comorbidities, such as chronic kidney disease, HTN, DM, metabolic syndrome and CVD.[22–25] Although these disorders share common risk factors, the multivariate analysis showed that renal function and DM were significantly associated with urolithiasis. In addition, we included Alb and UA in the model that distinguished the Stone group from the Ctrl group. These parameters were consistent with those of previous studies that suggested an association among urolithiasis, hyperuricemia and chronic inflammation.[11,12,26–28] We excluded

Table 1 Background of patients

	Training dataset			Validation dataset		
	Ctrl	Stone	*P*-value	Ctrl	Stone	*P*-value
n	1300	600		1500	705	
Age, years (IQR)	60 (46–69)	61 (50–72)	<0.001	58 (45–67)	62 (51–73)	<0.001
Sex, male (*n*)	642 (51%)	396 (66%)	<0.001	761 (51%)	426 (60%)	0.357
BMI, kg/m^2 (IQR)	23.0 (21.2–25.2)	22.8 (21.2–25.8)	0.075	22.9 (20.9–25.2)	23.1 (21.2–25.8)	0.022
HTN (*n*)	469 (36%)	266 (44%)	<0.001	339 (23%)	298 (42%)	<0.001
CVD (*n*)	95 (7.3%)	72 (12%)	0.003	132 (8.8%)	100 (14%)	<0.001
DM (*n*)	74 (5.7%)	122 (20%)	<0.001	101 (6.7%)	147 (21%)	<0.001
eGFR, mL/min/1.73 m^2 (IQR)	79 (69–89)	67 (51–82)	<0.001	79 (69–89)	65 (49–80)	<0.001
Alb, g/dL (IQR)	4.5 (4.4–4.7)	4.0 (3.9–4.4)	<0.001	4.4 (4.2–4.6)	4.0 (3.7–4.3)	<0.001
UA, mg/dL (IQR)	4.9 (4.0–5.9)	6.0 (4.5–6.6)	<0.001	5.2 (4.2–6.2)	5.0 (4.4–6.3)	0.008

Table 2 Multivariate logistic regression analysis of the training test

	First model					Final model		
	Factor	*P*-value	OR	95% CI		*P*-value	OR	95% CI
Age	Continuous	<0.001	0.97	0.96–0.98	Age	<0.001	0.95	0.95–0.97
Sex	Male	<0.001	1.72	1.28–2.32	Sex	<0.001	1.07	1.07–1.91
BMI	Continuous	0.126	0.97	0.94–1.01				
HTN	Positive	0.756	1.05	0.78–1.41				
CVD	Positive	0.557	1.15	0.72–1.84				
DM	Positive	<0.001	4.11	2.73–6.21	DM	<0.001	4.15	2.80–6.15
eGFR	Continuous	<0.001	0.98	0.97–0.98	eGFR	<0.001	0.98	0.97–0.99
Alb	Continuous	<0.001	0.01	0.01–0.02	Alb	<0.001	0.01	0.01–0.02
UA	Continuous	<0.001	1.27	1.14–1.42	UA	<0.001	1.15	1.15–1.41

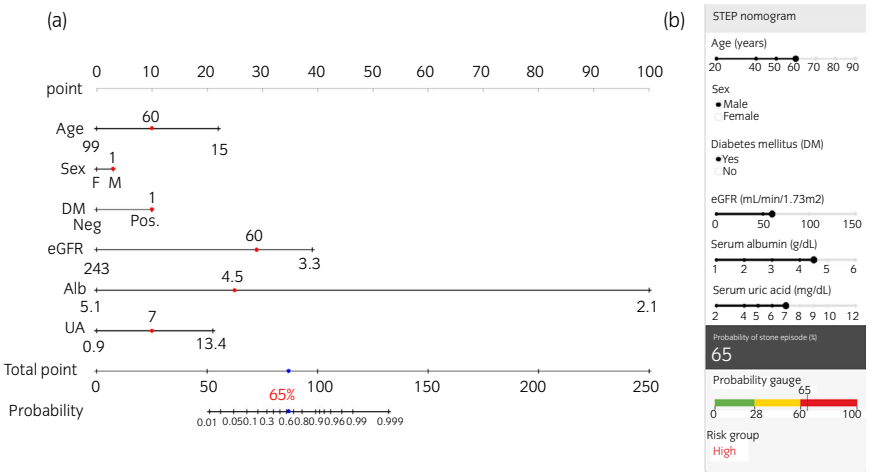

Fig. 2 The STEP nomogram for predicting the probability of a stone episode. (a) The STEP nomogram was developed to predict the probability of a stone episode. (b) A web-based application for the STEP nomogram calculator was posted at https://www.calconic.com/calculator-widgets/step-nomogram/5ccadea344587d0026d93c0d. For example, a 60-year-old man with diabetes who was treated at the outpatient clinic after presenting with DM, eGFR 60 mL/min/1.73 m^2, Alb 4.5 g/dL and UA 7.0 mg/dL had a probability of a stone disease/episode of 65%.

CRP in this model, because it is not evaluated in all patients, and acute inflammation, including pyelonephritis, can influence its measured result. Multivariate analysis showed that age, sex, eGFR, Alb and UA were significantly associated with urolithiasis, and these were included in the final model. As a result, high AUC values were observed in the training and validation tests (0.860 and 0.815, respectively). However, calibration plots showed an overestimation in patients with estimated probability between 20–100% (Fig. 3d). To resolve this problem, the use of the median value of probability (≥60% in the stone group, sensitivity 49% and specificity 96% in the training set) might be better to exclude the probability overestimation. We believe that the STEP nomogram model efficiently predicts potential candidates for stone formation; however, a prospective validation study is necessary to show its usefulness in a clinical setting. Our ongoing study (UMIN 000033964) will address these issues.

The relationship between urolithiasis and CVD also requires further studies. Given that several studies have shown an association between urolithiasis and increased cardiovascular risk,[24,29] we expected a similar association between CVD and urolithiasis; however, the present results showed that CVD was not significantly associated with the episodes of stone formation. A previous study suggested that the impact of CVD on

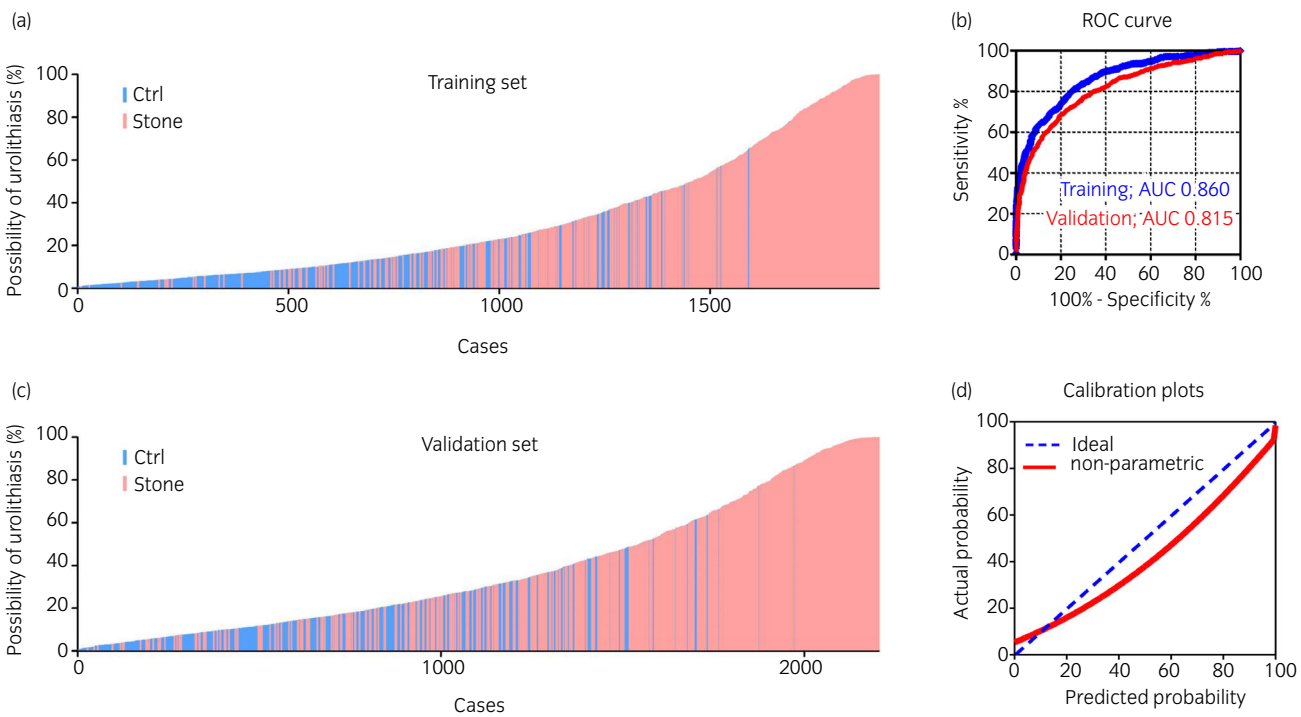

Fig. 3 Predictive ability of the STEP nomogram. (a) The waterfall plot shows a significantly higher value of probability in the Stone group than in the Ctrl group (median probability 13% *vs* 59%, respectively; $P < 0.001$). (b) The optimal cut-off value set at >28% in the training test with the AUC of 0.860 (blue line, $P < 0.001$). The AUC for the prediction of a Stone episode was 0.815 (red line, $P < 0.001$). (c) In the validation test, the waterfall plot shows a significantly higher value of probability in the Stone group (median probability 21% *vs* 65%, respectively; $P < 0.001$). (d) The calibration plots show that the actual probability corresponds closely to the nomogram-predicted probability. A slight overestimation was observed in participants with an actual probability between 20% and 100%.

urolithiasis might not be simple, and different between women and men.[24] A meta-analysis comprising 49 597 patients with kidney stones and 3 558 053 Ctrls suggested a different profile between men and women for urolithiasis and cardiovascular risk.[24] Kidney stones were associated with an increased risk of CVD; however, only in the female cohorts (HR 1.49, 95% CI 1.21–1.82); the male cohorts showed no such association (HR 1.15; 95% CI 0.89–1.50). The other potential explanation is the profile of CVD in Japanese patients. Compared with Western nations, Japanese patients have a higher mortality from stroke and a lower mortality from coronary heart disease.[30] These observations suggest that identifying an independent relationship between CVD and urolithiasis is challenging because of population bias in the present study.

The utility of the STEP nomogram needs to debated. Our nomogram was developed using metabolic factors (such as DM, renal function decline, hypoalbuminemia or uric acid level abnormality) comparing the individuals who had symptomatic stones and those who never had stones. However, our nomogram could not detect the actual risk of the existence of stone and symptomatic episodes because of the cross-sectional study. Also, our model has limitations in use for urolithiasis patients without symptoms, because we developed this model using the clinical difference between the patients with symptoms and healthy individuals without urolithiasis. Ideally, data comparison between the urolithiasis patients before symptomatic events and healthy individuals without urolithiasis, or between the urolithiasis patients "at symptoms" and "after removal of stones and inflammations" might provide a useful nomogram in clinical practice. Also, we could not exclude the potential of other diseases, such as malignancy and systemic inflammatory disease. Despite the limitations, our model might be useful for the first step of discussion for the possibility of urolithiasis in individuals with lifestyle-related diseases and the opportunity for non-invasive screening, such as an abdominal X-ray and ultrasonography, as there is a no stone attack prediction tool.

Also, further studies are required to assess the usefulness of the STEP nomogram for recurrent stone formation. Although a few nomograms for predicting stone formation have been reported, they mainly predicted recurrent stones.[5,6] The Recurrence of Kidney Stones nomogram was reported to predict a second symptomatic stone episode by including 11 risk factors in the model.[6] Of those, the top six factors for symptomatic stone recurrence were as follows: (i) young age; (ii) composition of uric acid stone; (iii) symptomatic renal pelvic or lower-pole stone on imaging; (iv) episode of previous suspected stone event; (v) asymptomatic stone on imaging; and (vi) family history of kidney stones. Unfortunately, our database did not include information on previous suspected stone events or the family history of stones, which will be a key factor in improving the predictability of the nomogram. Our future study must include these non-invasive and easy-access parameters.

The limitations of the present study were its asynchronous cross-sectional nature, which causes selection bias that included unmeasurable confounding factors. The patients in the Stone group were older than the Ctrl group in the present study. Also, the key values for inflammation (C-reactive protein) and metabolic syndrome (triglyceride and cholesterol) were not evaluated in all patients. We could not control the contamination of a silent stone former in the Ctrl individuals. We could not address the influence of acute inflammation at the time of a stone episode in the laboratory data, especially for eGFR and Alb values. A history of previous stone episodes, family history of urolithiasis, types of treatment and stone composition were lacking in the data. In addition, the present results could not be generalized to other populations because of regional bias. Finally, our nomogram might not be useful for patients who have no symptoms, because we could not evaluate the utility of this nomogram for patients without symptoms.

Despite these limitations, to our knowledge, the present study is the first and largest of its kind to investigate the clinical implications of a nomogram for stone episodes. Considering the link between urolithiasis and key comorbidities, not only urologists, but general internists and primary care practitioners as well, must be involved in the prevention of these painful events. Although further studies are required on the model, the present findings enhance the clinical importance of screening of potential urolithiasis candidates in general practice. We believe that our simple nomogram will support the first step of stone screening, and can lead to a more concerted effort to prevent stone episodes.

In conclusion, we developed the STEP nomogram to predict potential candidates for episodes of urolithiasis based on a practical dataset. Although the present study is preliminary, this nomogram might be beneficial for both patients and clinicians as a first step in stone screening.

Acknowledgments

We thank Ippei Takahashi, Yuriko Terayama, Megumi Tsushima, Mihoko Sutoh Yoneyama, Saori Araya, Kanemitsu Yamaya, Hisao Saitoh, Naoki Fujita, Hiromichi Iwamura, Teppei Okamoto, Teppei Matsumoto, Osamu Soma, Kazuhisa Hagiwara, Sakae Konishi, Yuki Fujita, Yukie Nishizawa, Satomi Sakamoto and the entire staff of the Department of Urology of Hirosaki University for their invaluable help with data collection. The authors also thank Enago (www.enago.jp) for the English language review. This work was supported by Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 15H02563, 17K11119 and 19H05556.

Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Variance inflation factor among covariates.