*Retrospective Clinical Research Report*

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(3) 1–11

DOI: 10.1177/0300060521997661
journals.sagepub.com/home/imr

SAGE

# A new risk-scoring system to predict Xp11.2 translocation renal cell carcinoma in adults

**Qiancheng Shi[1]*, Ning Liu[1]*, Yiqi Zhu[1], Feng Qu[1], Linfeng Xu[1], Xiaogong Li[1], Gutian Zhang[1], Hongqian Guo[1], Dongmei Li[2,3] and Weidong Gan[1,4]**

## Abstract

**Objective:** The objective was to derive and validate a practical scoring system for preoperative diagnosis of Xp11.2 translocation renal cell carcinoma (RCC) in adults.

**Methods:** Epidemiology, symptomatology, and imaging methods were correlated between patients with common RCC and those with Xp11.2 translocation RCC using a derivation study (N = 6352) and a validation study (N = 127). Univariate analysis of risk factors was performed to derive a scoring system to predict the occurrence of Xp11.2 translocation RCC in adults. The Hosmer–Lemeshow goodness-of-fit test and receiver operating characteristic (ROC) curve were used to validate the scoring system.

**Results:** Based on odd ratios, three low-risk factors (sex, gross haematuria, and intratumoural calcification) and three high-risk factors (age, unenhanced computed tomography density, and enhancement pattern) were given weighted scores of 1 and 2, respectively. Patients who scored 3 to 5 points underwent an additional magnetic resonance imaging examination. The final scoring system had a sensitivity of 81.0% and a specificity of 98.0%.

**Conclusion:** We established a practical scoring system for the preoperative diagnosis of Xp11.2 translocation RCC in adults, which can be optimised through further clinical findings in the future.

[1]Department of Urology, Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, Jiangsu, China
[2]Immunology and Reproduction Biology Laboratory & State Key Laboratory of Analytical Chemistry for Life Science, Medical School, Nanjing University, Nanjing, Jiangsu, China
[3]Jiangsu Key Laboratory of Molecular Medicine, Nanjing University, Nanjing, Jiangsu, China
[4]Department of Urology, Drum Tower Clinical Medical School of Nanjing Medical University, Nanjing, Jiangsu, China

*These authors contributed equally to this work.

**Corresponding author:**
Weidong Gan, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, 321 Zhongshan Road, Nanjing, Jiangsu 210008, China.
Email: gwd@nju.edu.cn

**Keywords**
Renal cell carcinoma, translocation, Xp11.2, scoring system, preoperative diagnosis, risk factors

Date received: 18 January 2021; accepted: 3 February 2021

## Introduction

Renal cell carcinoma (RCC) with an Xp11.2 translocation is a distinct entity of renal tumours, and it is associated with Xp11.2 translocation/transcription factor E3 (*TFE3*) gene fusions that result in overexpression of the TFE3 fusion protein.[1] This type of RCC is more likely to develop in children and young adults, affecting 46.7% of paediatric patients, 15% of patients aged <45 years, and 1% to 1.6% of adult patients with RCC.[2–5] Although the incidence of Xp11.2 translocation RCC in paediatric patients is higher, the number of paediatric patients is much lower than the number of adult patients with RCC.[6]

Xp11.2 translocation RCC is different from common RCCs and has a poor prognosis because a large number of cases involve local invasive disease or distant metastases.[7–10] Although there is no consensus regarding the treatment of Xp11.2 translocation RCC, some experienced researchers have contended that radical therapies should be adopted to reduce the risk of residual or recurrent tumours.[5] However, owing to the lack of preoperative prediction methods, treatment options for Xp11.2 translocation RCC are extrapolated from the European Association of Urology (EAU) guidelines for common RCCs.[11] Given the rarity and distinctive features of paediatric Xp11.2 translocation RCC, no paediatric cases were included in our study.[12] Thus, our study was designed to derive and validate a practical scoring system to predict the outcome of latent Xp11.2 translocation RCC in adults before surgery.

## Methods

### *Ethics statement*

This study was approved by the Ethics Committee of Nanjing Drum Tower Hospital, The Affiliated Hospital of Medical School of Nanjing University. This study involved a retrospective review of medical records only; therefore, no informed consent was necessary.

### *Derivation study by literature search*

We conducted an electronic search in PubMed for literature published between January 2010 and December 2018 to increase the sample size of the derivation study. The initial search term for the negative group was "renal cell carcinoma," and the initial search keywords for the positive group were "TFE3" or "Xp11.2 translocation RCC."

Subsequently, two authors (Qiancheng Shi and Ning Liu) independently reviewed the abstracts of all candidate articles; full-text review was considered when the articles could not be categorised based on the title and abstract alone. Studies that fulfilled the following criteria were included. (1) Studies that contained at least one case of Xp11.2 translocation RCC or two types of common RCC. The selection criteria for the common RCC included clear cell RCC, papillary RCC, chromophobe RCC, and eosinophilic RCC, following the 2019 EAU guidelines.[11] (2) Studies that reported imaging findings (including computed tomography [CT], magnetic resonance imaging [MRI], or urinary ultrasound) or clinical manifestations (including sex, age,

and symptoms) of the patients. (3) Studies in which the diagnosis of all cases with Xp11.2 translocation RCC was confirmed using an immunohistochemical (IHC) assay for TFE3, fluorescence in situ hybridisation (FISH) assay, or other strict criteria. The exclusion criteria included patients <18 years of age and duplicate studies by the same institution.

In total, the derivation study comprised 6352 cases, including 532 cases of Xp11.2 translocation RCC and 5820 cases of common RCCs from 88 studies (Figure 1). The list specifying all included studies can be found in Supplementary Table 1.

### Validation study by clinical review

Clinical data from consecutive patients who underwent radical or partial nephrectomy at the Nanjing Drum Tower Hospital from January 2010 to December 2018 were retrospectively reviewed. After excluding cases with insufficient medical records or severe systemic disease, 27 cases of Xp11.2 translocation RCC and 100 cases of common RCC were randomly selected to constitute the validation group (Figure 1). All cases with Xp11.2 translocation RCC were diagnosed using IHC for TFE3 and FISH assay.[13,14] The complete clinical data of those patients can be found in the Supplementary Table 2.

### Statistical analyses

Statistical analyses were conducted using SPSS Statistics software (version 24.0.0.0; IBM Corp., Armonk, NY, USA). For univariate analysis, continuous variables were analysed using Student's *t*-test, and categorical variables were analysed using the $\chi^2$ test or Fisher's exact test. Covariates showing a significant association in the univariate analysis underwent additional binary logistic regression analysis to identify possible covariates as significant predictors of Xp11.2 translocation RCC. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated to estimate the relative risks. The calibration of this system was evaluated using the Hosmer–Lemeshow goodness-of-fit test. The cut-off value for total score was defined based on the receiver operating characteristic curve, and $p < 0.05$ was considered to indicate statistical significance. Statistical values described as mean ± standard deviations.

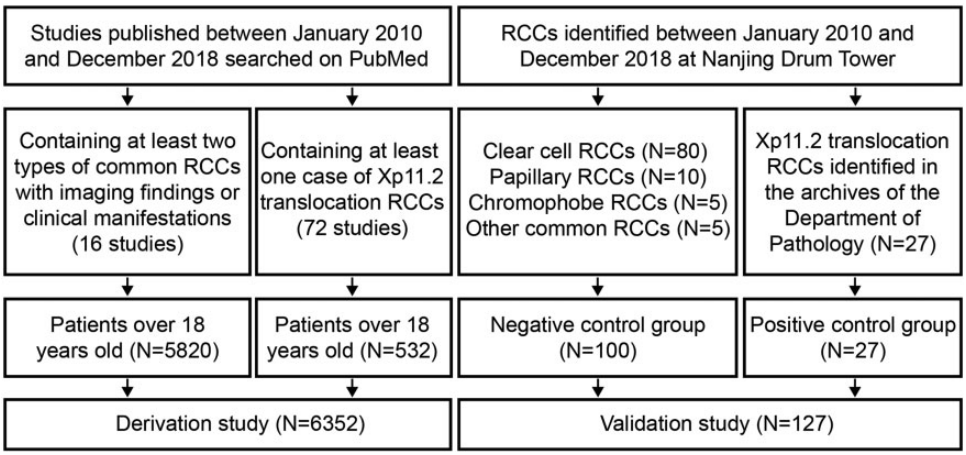


**Figure 1.** Patient selection flowchart of the derivation study and the validation group.
RCC, renal cell carcinoma.

## Results

### Clinical manifestations

Of 6352 cases, 63.6% were men and 36.4% were women (Table 1). The age of onset ranged from 18 to 84 years (mean 57.77 ± 12.3 years). Regarding the clinical manifestations, 79.5% of patients presented with gross haematuria. Based on imaging findings, 25.2% of RCCs showed intratumoural calcification, 51.9% showed heterogeneity, and 49.7% showed high attenuation in unenhanced CT. Persistent enhancement could be seen in 36.0% of RCCs. Xp11.2 translocation RCC tumours demonstrated mildly increasing attenuation in the corticomedullary phase and prolonged enhancement in the nephrographic and excretory phase, as described in our previous study.[15] We named this "less in and slow out," which was different from the "fast in and fast out" pattern of clear cell RCC. MRI revealed that 64.6% of RCCs showed T1-hypointensity, whereas 60.2% showed hyperechogenicity by urinary ultrasound. Additionally, 82.4% of RCCs showed early phase enhancement, and 60.4% of RCCs showed delayed phase enhancement in urinary contrast-enhanced ultrasound.

**Table 1.** Baseline characteristics of 6352 patients with RCC.

| Characteristic | No. (%) |
|---|---|
| Age (years) | 57.77 ± 12.3 |
| Sex | |
| Male | 4039 (63.6) |
| Female | 2313 (36.4) |
| Gross haematuria | |
| No | 153 (20.5) |
| Yes | 595 (79.5) |
| CT | |
| Intratumoural calcification | |
| No | 1256 (74.8) |
| Yes | 317 (25.2) |
| Heterogeneous | |
| No | 291 (48.1) |
| Yes | 314 (51.9) |
| Unenhanced CT density | |
| High attenuation | 82 (49.7) |
| Iso-, hypoattenuation | 83 (50.3) |
| Enhancement pattern | |
| Less in and slow out | 76 (36.0) |
| Other | 211 (64.0) |
| MRI | |
| T1-hypointensity | |
| No | 102 (35.4) |
| Yes | 186 (64.6) |
| Urinary ultrasound | |
| Hyperechogenicity | 245 (60.2) |
| Other | 162 (39.8) |
| Urinary contrast-enhanced ultrasound | |
| Early phase enhancement | |
| No | 72 (17.6) |
| Yes | 337 (82.4) |
| Delayed phase enhancement | |
| No | 162 (39.6) |
| Yes | 247 (60.4) |

RCC, renal cell carcinoma; CT, computed tomography; MRI, magnetic resonance imaging.

### Risk factors for adult Xp11.2 translocation RCC

Univariate analysis revealed the following seven independent risk factors for adult Xp11.2 translocation RCC: age, sex, gross haematuria, intratumoural calcification, unenhanced CT density, CT enhancement pattern, and MRI T1 unenhanced signal (all $p < 0.01$) (Table 2). Based on ORs, these factors were divided into low-risk factors (OR $<10$) and high-risk factors (OR $\geq 10$).

### Scoring to predict adult Xp11.2 translocation RCC

Low-risk factors were given a score of +1, and high-risk factors were given a score of +2 (Supplementary Table 3). We named this the G Scoring System, wherein "G" refers to the first letter of the Nanjing Drum Tower Hospital (Gu Lou) in Chinese.

**Table 2.** Univariate analysis of risk factors for Xp11.2 translocation RCCs

| Risk factor | Common RCCs | Xp11.2 translocation RCCs | Odds ratio | 95% CI | *p*-value |
|---|---|---|---|---|---|
| Age (years) | | | 26.16 | 20.87–32.79 | <0.001 |
| <50 | 775 | 426 | | | |
| ≥50 | 5045 | 106 | | | |
| Sex | | | 2.47 | 2.06–2.95 | <0.001 |
| Male | 3808 | 231 | | | |
| Female | 2012 | 301 | | | |
| Gross haematuria | | | 2.39 | 1.66–3.46 | <0.001 |
| No | 440 | 155 | | | |
| Yes | 83 | 70 | | | |
| CT | | | | | |
| Intratumoural calcification | | | 4.74 | 3.23–6.95 | <0.001 |
| No | 1197 | 59 | | | |
| Yes | 257 | 60 | | | |
| Heterogeneous | | | 1.06 | 0.63–1.78 | 0.836 |
| No | 261 | 30 | | | |
| Yes | 280 | 34 | | | |
| Unenhanced CT density | | | 33.76 | 12.22–93.30 | <0.001 |
| High attenuation | 5 | 77 | | | |
| Iso-, hypoattenuation | 57 | 26 | | | |
| Enhancement pattern | | | 43.16 | 19.03–97.88 | <0.001 |
| Less in and slow out | 26 | 50 | | | |
| Other | 202 | 9 | | | |
| MRI | | | | | |
| T1-hypointensity | | | 5.66 | 2.16–14.81 | <0.001 |
| No | 97 | 5 | | | |
| Yes | 144 | 42 | | | |
| Urinary ultrasound | | | 1.08 | 0.44–2.66 | 0.870 |
| Hyperechogenicity | 154 | 8 | | | |
| Other | 232 | 13 | | | |
| Urinary contrast-enhanced ultrasound | | | | | |
| Early phase enhancement | | | — | — | — |
| No | 71 | 0 | | | |
| Yes | 315 | 22 | | | |
| Delayed phase enhancement | | | 0.84 | 0.36–1.97 | 0.696 |
| No | 152 | 10 | | | |
| Yes | 234 | 13 | | | |

RCC, renal cell carcinoma; CT, computed tomography; MRI, magnetic resonance imaging.

### *Verification and optimisation of the G Scoring System*

The calibration and discrimination ability of the initial scoring system was examined using the validation study. The Hosmer–Lemeshow goodness-of-fit test showed that $R^2 = 0.725$ and $p > 0.05$, confirming that the difference between the predicted and actual probability of the system was not significant (Figure 2a). These results confirmed that the initial scoring system was reliable in terms of calibration ability.

The total score of the seven indicators ranged from 0 to 10, and the sensitivity and specificity of the prediction for the G Scoring System within this range were analysed to determine the minimum total score by which Xp11.2 translocation RCC could be diagnosed. When the cut-off score was set at 4, sensitivity of 88.9% and specificity of 93.0% were obtained (Figure 2b). The area under the curve (AUC) was 0.962, and the 95% CI ranged from 0.930 to 0.994. We then compared two other scoring methods, one where each factor was given a score of +1 equally (score=1) and another in which each factor was given a score corresponding to the ORs (score=Od). The AUCs for score=1 and score=Od were 0.944 and 0.968, respectively, as shown in Figure 2. Although score=Od had a larger AUC, its total score ranged from 0 to 111.21, which is more complicated and inconvenient for clinical application. Therefore, we concluded that the G Scoring System had a higher diagnostic value under the existing conditions.

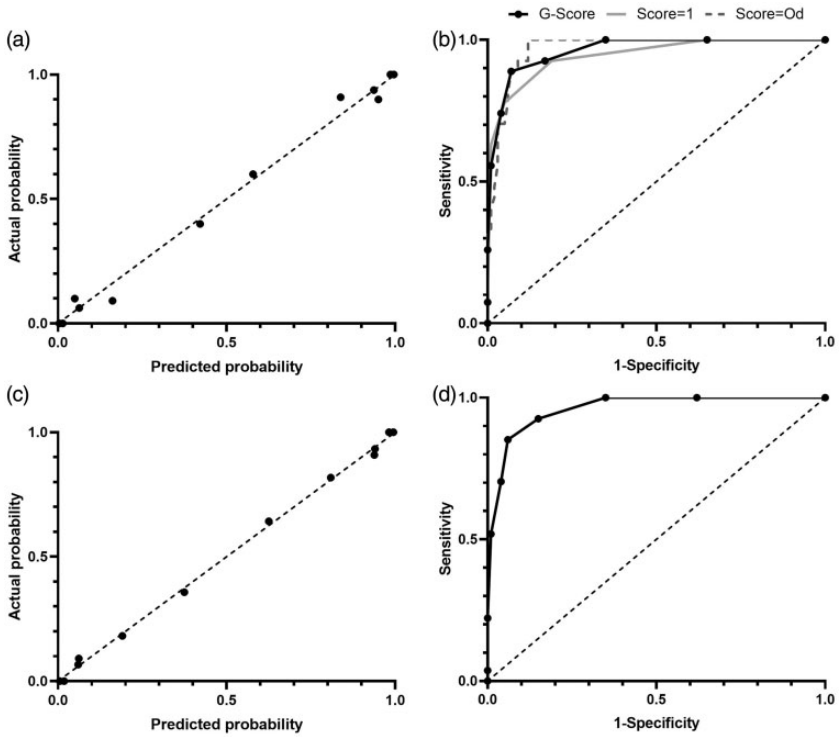


**Figure 2.** Statistical analysis of the initial and revised G Scoring System. (a) Calibration plot of the Hosmer–Lemeshow goodness-of-fit test for the initial G Scoring System ($R^2 = 0.725$, $p = 0.734$); (b) ROC curve of the initial G Scoring System and 2 other criteria (AUC of the G-Score: 0.962, and 95% CI: 0.930–0.994); (c) calibration plot of the Hosmer–Lemeshow goodness-of-fit test for the revised G Scoring System ($R^2 = 0.902$, $p = 0.721$); (d) ROC curve of the revised G Scoring System (AUC = 0.960, 95% CI: 0.927–0.993).

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; Score=1, each factor was given a score of +1 equally; Score=Od, each factor was given a score corresponding to the odds ratio.

Because the EAU guidelines do not recommend MRI as an efficient diagnostic procedure for RCC, we expected a lower score without MRI findings. Therefore, MRI findings were removed from the initial scoring system and changed into a secondary indicator to identify the critical-risk group; three low-risk factors (female sex, gross haematuria, and intratumoural calcification) were given a score of +1, and three high-risk factors (age <50 years, high attenuation on unenhanced CT density, and "less in and slow out" CT enhancement pattern) were given a score of +2. The total score of the new system ranged from 0 to 9. The Hosmer–Lemeshow goodness-of-fit test indicated that $R^2 = 0.902$ and $p > 0.05$, demonstrating that the revised system was more reliable for calibration (Figure 2c). When the cut-off score was set at 4, we obtained a sensitivity of 85.2% and a specificity of 94.0% (Figure 2d).

The final scoring system was applied in the following manner: cases with a score $\leq 2$ points were classified into the low-risk group; cases with a score >6 points and the hypointense T1 cases were classified into the high-risk group; and cases with scores between 3 and 5 were defined as a critical-risk group that required an additional MRI examination. Under the final scoring system, we achieved a sensitivity of 81.0% and a specificity of 98.0%.

## Discussion

Xp11.2 translocation RCC was first reported in 1988 and formally described as a distinct clinicopathologic entity in 2001.[16,17] Unlike the common RCCs, which are more prevalent in male patients and older people, Xp11.2 translocation RCC tends to affect children and female patients aged between 18 and 45 years, which reduces the social labour force.[18] It is currently understood that Xp11.2 translocation RCC has an aggressive behaviour and an invasive course, and it is common for patients to present at an advanced stage with lymph node involvement.[9] However, there is no consensus on a surgical strategy for this type of renal tumour. Complete resection appears to be the best option for those who present with localised disease. Given the tendency of even small tumours (<7 cm) towards local invasion and metastasis to regional lymph nodes, some researchers have suggested that more aggressive surgical resection, including lymphadenectomy, is warranted.[5,12] Our recent multicentre study showed that surgical margin positivity and pelvicalyceal, vascular, and region lymphatic involvement were more likely to occur in Xp11.2 translocation RCC at the cT1b stage ($p < 0.05$), and that patients with cT1b tumours who underwent radical nephrectomy had more favourable progression-free survival than those who underwent partial nephrectomy ($p < 0.05$), which emphasises that partial nephrectomy is not recommended for cT1b tumours because of the increased risk of postoperative recurrence and metastasis.[19] Therefore, the need for discriminative therapy for Xp11.2 translocation RCC increases the importance of predictive diagnosis before surgery.

The current study is the first to describe a simple and non-invasive method to predict Xp11.2 translocation RCC in adults. Using epidemiological, symptomatological, and imaging data, the scoring system allowed us to obtain a preoperative diagnosis in an efficient and convenient manner, but also guided the pathologists to perform a differential diagnosis, which is a complex process. Inexperienced pathologists often misdiagnose Xp11.2 translocation RCC because of its unusual morphology and its similarity to other RCC types, such as clear cell or papillary RCC.[2]

Scoring systems are widely used to assess risk and provide guidance for the treatment of other types of tumours. For instance, the

Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B model (REACH-B model) is used to evaluate the risk of hepatocellular carcinoma in patients with chronic hepatitis B; the AUCs using that model were 0.811 at 3 years, 0.796 at 5 years, and 0.769 at 10 years.[20] Using the Assessment of Different NEoplasias in the adnexa (ADNEX) model to evaluate the risk of ovarian cancer results in 96.5% sensitivity and 71.3% specificity.[21] Scoring systems for identification of endometrial cancer or atypical hyperplasia can likewise provide a high diagnostic value.[22] Concerning RCC, however, no scoring system is yet available for any of the subtypes. The discriminating features between the common RCC subtypes that enable easy diagnosis through routine imaging might explain this.[23] The median sensitivity and specificity, respectively, were 88% and 75% for CT and 87.5% and 89% for MRI.[23] Moreover, the current surgical method is established for clear cell RCC, but it can be applied to non-clear cell cancer as well. The rate of malignancy of clear cell RCC is higher than that of the other common RCCs except Xp11.2 translocation RCC, but there is no evidence of increased recurrence rate with the current surgical methods. However, Xp11.2 translocation RCC has more aggressive clinicopathologic features at diagnosis and a significantly worse prognosis than the common RCCs.[24] At initial diagnosis, Xp11.2 translocation RCC tends to present with stage III/IV regional tumours, accompanied by lymph node metastasis, and several patients develop recurrent or hematogenous metastases within 3 years of follow-up.[7,9,10] Hence, the conventional surgical protocol is not suitable for Xp11.2 translocation RCC, and it is essential to identify the type of RCC before surgery.

Since the first reported case of gene arrangement 46,XY,t(X;1)(p11.2;q21.2) in a 2.4-year-old boy with renal adenocarcinoma (Grawitz tumour), several paediatric Xp11.2 translocation RCC cases have been reported in recent decades.[25] We noted previously that Xp11.2 translocation RCC accounts for 47% of paediatric cases of RCC, 15% of RCC cases in adults between 15 and 45 years, and 1% to 1.6% of the entire population with RCC.[2–5] However, the actual number of paediatric patients with RCCs is much lower than the number of adult patients with RCCs. Although paediatric patients have a higher incidence of regional lymph node positivity, they have a better prognosis than adult patients.[18] The high incidence rate and favourable prognosis have limited the predictive value of paediatric Xp11.2 translocation RCC. To avoid any bias resulting from the high number of paediatric cases with Xp11.2 translocation RCC, only adult patients were enrolled in the current study.

Xp11.2 translocation RCCs mainly affect paediatric and younger adults; the age distribution of Xp11.2 translocation RCC cases is bimodal, with a mean age of 17 years in the paediatric population[26] and 37 years in the adult population.[7] When a mixed cohort of paediatric and adult patients was considered, the peak age of onset was 20 to 29 years, and the average age of onset was 40 years.[27] Generally, a low onset age with a high degree of malignancy inflicts harm to both affected families and to society. Epidemiologically, the prevalence of Xp11.2 translocation RCC in female patients is another important feature.[9] A meta-analysis by Cheng et al.[28] found that the number of female patients of all ages was 3.93 times higher than the number of male patients (95% CI: 1.66–9.34), and the ratio was 5.13 (95% CI: 1.67–15.72) when children (aged $\leq$14 years) were excluded. The present study indicated a female-to-male ratio of 1.30. Although Xp11 translocation RCC was found to be negative for the oestrogen receptor, we are investigating whether

oestrogen or oestrogen receptors play a role in the progression of Xp11.2 translocation RCC, based on the high incidence in young women; the role of such receptors in common RCCs has been reported.[29] The presence of two X chromosomes in females compared with one X chromosome in males explains the sex difference. Although females have two X chromosomes, translocations might only occur on the active X chromosome and not on the inactive X chromosome (Barr body). In addition, the expression of genes located on the X chromosome in females could be affected by random inactivation,[30] which may further influence sex differences in the incidence of Xp11.2 translocation RCC.

The clinical presentation of Xp11.2 translocation RCC is different from that of other renal tumours. Patients with common RCCs are usually asymptomatic at presentation and are incidentally diagnosed through abdominal imaging. However, the typical symptoms of gross haematuria, flank pain, or abdominal mass are commonly present in Xp11.2 translocation RCC, especially in paediatric and young adult patients. In our study, haematuria was seen in 31.1% of cases with Xp11.2 translocation RCC compared with 15.9% of cases with common RCCs. In some cases of Xp11.2 translocation RCC, haematuria may be the only presentation; it is a manifestation of the tumour invading the renal pelvis and progressing to haemorrhage,[31] which also indicates an advanced degree of at least the T3 stage. Thus, kidney masses with gross haematuria indicate the probability of advanced Xp11.2 translocation RCC, and nephron-sparing surgery should be considered in the treatment of such tumours. Currently, a retrospective study focusing on the invasion rate of the intrarenal collecting system of Xp11.2 translocation RCC is in progress.

Imaging techniques such as urinary ultrasound, CT, and MRI are routinely applied in preoperative differential diagnoses. In a previous study, we reported the sensitivity of CT imaging: 59.3% for high attenuation on unenhanced CT density, 59.3% for the "less in and slow out" enhancement pattern, and 33.3% for intratumoural calcification. Moreover, the sensitivity of MRI (hypointense on T1) was shown to be 50.0%. In comparison, our scoring system, which combines imaging with epidemiological and symptomatological analysis, attained a sensitivity of 81.0%. An MRI is not routinely performed in clinical practice; in our scoring system, an MRI scan is additionally required to reach a conclusion only when the patient has a score from 3 to 5. In such patients, T1-hypointensity is considered strong evidence for the presence of Xp11.2 translocation RCC.

This is the first study to propose a scoring system with high sensitivity and high specificity for Xp11.2 translocation RCC in adults. By collecting epidemiology, symptomatology, and imaging data, preoperative predictions can be made noninvasively. With a score $>6$ points, the G Scoring System could identify 93.3% of Xp11.2 translocation RCC cases in adults. Moreover, using a score of 3 to 5 points and T1-hypointensity in MRI, the G Scoring System could identify 75% of Xp11.2 translocation RCC cases in adults. Because this system was established using a single-centre retrospective study, our results might be biased; further studies with more clinical cases are required for verification and optimisation of the scoring system. Like other scoring systems for tumours, our system cannot replace pathological diagnosis, but it can, at least, provide a preoperative prediction for Xp11.2 translocation RCC in adults. This improves our ability to consider patients with Xp11.2 translocation RCC as unique individuals when choosing initial treatment methods and thus greatly improves the overall treatment and prognosis for these patients.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by the State Key Laboratory of Analytical Chemistry for Life Science (5431ZZXM2004), and Beijing Ronghe Medical Development Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## ORCID iDs

Xiaogong Li https://orcid.org/0000-0003-0297-2244
Weidong Gan https://orcid.org/0000-0001-7144-3106

## Supplemental Material

Supplemental material for this article is available online.

## References

1. Argani P. MiT family translocation renal cell carcinoma. *Semin Diagn Pathol* 2015; 32: 103–113.
2. Kuroda N, Mikami S, Pan CC, et al. Review of renal carcinoma associated with Xp11.2 translocations/TFE3 gene fusions with focus on pathobiological aspect. *Histol Histopathol* 2012; 27: 133–140.
3. Komai Y, Fujiwara M, Fujii Y, et al. Adult Xp11 translocation renal cell carcinoma diagnosed by cytogenetics and immunohistochemistry. *Clin Cancer Res* 2009; 15: 1170–1176.
4. Sukov WR, Hodge JC, Lohse CM, et al. TFE3 rearrangements in adult renal cell carcinoma: clinical and pathologic features with outcome in a large series of consecutively treated patients. *Am J Surg Pathol* 2012; 36: 663–670.
5. Geller JI, Ehrlich PF, Cost NG, et al. Characterization of adolescent and pediatric renal cell carcinoma: A report from the Children's Oncology Group study AREN03B2. *Cancer* 2015; 121: 2457–2464.
6. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; 70: 7–30.
7. Argani P, Olgac S, Tickoo SK, et al. Xp11 translocation renal cell carcinoma in adults: expanded clinical, pathologic, and genetic spectrum. *Am J Surg Pathol* 2007; 31: 1149–1160.
8. Mir MC, Trilla E, De Torres IM, et al. Altered transcription factor E3 expression in unclassified adult renal cell carcinoma indicates adverse pathological features and poor outcome. *BJU Int* 2011; 108: E71–E76.
9. Ellis CL, Eble JN, Subhawong AP, et al. Clinical heterogeneity of Xp11 translocation renal cell carcinoma: impact of fusion subtype, age, and stage. *Mod Pathol* 2014; 27: 875–886.
10. He J, Chen X, Gan W, et al. Renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusions: clinical experience and literature review. *Future Oncol* 2015; 11: 3243–3252.
11. Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. *Eur Urol* 2019; 75: 799–810.
12. Geller JI, Argani P, Adeniran A, et al. Translocation renal cell carcinoma: lack of negative impact due to lymph node spread. *Cancer* 2008; 112: 1607–1616.
13. Argani P, Lal P, Hutchinson B, et al. Aberrant nuclear immunoreactivity for TFE3 in neoplasms with TFE3 gene fusions: a sensitive and specific immunohistochemical assay. *Am J Surg Pathol* 2003; 27: 750–761.
14. Green WM, Yonescu R, Morsberger L, et al. Utilization of a TFE3 break-apart FISH assay in a renal tumor consultation service. *Am J Surg Pathol* 2013; 37: 1150–1163.
15. He J, Gan W, Liu S, et al. Dynamic computed tomographic features of adult renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusions: comparison with clear cell renal cell carcinoma. *J Comput Assist Tomogr* 2015; 39: 730–736.

16. De Jong B, Oosterhuis JW, Idenburg VJ, et al. Cytogenetics of 12 cases of renal adenocarcinoma. *Cancer Genet Cytogenet* 1988; 30: 53–61.
17. Argani P, Antonescu CR, Illei PB, et al. Primary renal neoplasms with the ASPL-TFE3 gene fusion of alveolar soft part sarcoma: a distinctive tumor entity previously included among renal cell carcinomas of children and adolescents. *Am J Pathol* 2001; 159: 179–192.
18. Ma W, Liu N, Zhuang W, et al. Comparative clinicopathologic characteristics and outcomes of paediatric and adult Xp11 translocation renal cell carcinomas: a retrospective multicentre study in China. *Sci Rep* 2020; 10: 2249.
19. Liu N, Qu F, Shi Q, et al. Nephron-sparing surgery for adult Xp11.2 translocation renal cell carcinoma at clinical T1 stage: a multicenter study in China. *Ann Surg Oncol* 2020.
20. Yang HI, Yuen MF, Chan HLY, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol* 2011; 12: 568–574.
21. Van Calster B, Van Hoorde K, Valentin L, et al. Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicentre diagnostic study. *BMJ* 2014; 349: g5920.
22. Dueholm M, Hjorth IMD, Dahl K, et al. Identification of endometrial cancers and atypical hyperplasia: development and validation of a simplified system for ultrasound scoring of endometrial pattern. *Maturitas* 2019; 123: 15–24.
23. Vogel C, Ziegelmuller B, Ljungberg B, et al. Imaging in suspected renal-cell carcinoma: systematic review. *Clin Genitourin Cancer* 2019; 17: e345–e55.
24. Choo MS, Jeong CW, Song C, et al. Clinicopathologic characteristics and prognosis of Xp11.2 translocation renal cell carcinoma: multicenter, propensity score matching analysis. *Clin Genitourin Cancer* 2017; 15: e819–e825.
25. De Jong B, Molenaar IM, Leeuw JA, et al. Cytogenetics of a renal adenocarcinoma in a 2-year-old child. *Cancer Genet Cytogenet* 1986; 21: 165–169.
26. Wu A, Kunju LP, Cheng L, et al. Renal cell carcinoma in children and young adults: analysis of clinicopathological, immunohistochemical and molecular characteristics with an emphasis on the spectrum of Xp11.2 translocation-associated and unusual clear cell subtypes. *Histopathology* 2008; 53: 533–544.
27. Caliò A, Segala D, Munari E, et al. MiT family translocation renal cell carcinoma: from the early descriptions to the current knowledge. *Cancers (Basel)* 2019; 11: 1110.
28. Cheng X, Gan W, Zhang G, et al. Clinical characteristics of XP11.2 translocation/TFE3 gene fusion renal cell carcinoma: a systematic review and meta-analysis of observational studies. *BMC Urol* 2016; 16: 40.
29. Yu CP, Ho JY, Huang YT, et al. Estrogen inhibits renal cell carcinoma cell progression through estrogen receptor-$\beta$ activation. *PLoS One* 2013; 8: e56667.
30. Syrett CM, Paneru B, Sandoval-Heglund D, et al. Altered X-chromosome inactivation in T cells may promote sex-biased autoimmune diseases. *JCI Insight* 2019; 4: e126751.
31. Suzigan S, Drut R, Faria P, et al. Xp11 translocation carcinoma of the kidney presenting with multilocular cystic renal cell carcinoma-like features. *Int J Surg Pathol* 2007; 15: 199–203.