

External Validation of the GRade, Age, Nodes and Tumor (GRANT) Score for Patients with Surgically Treated Papillary Renal Cell Carcinoma

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Abstract

Introduction: Stratifying the risk of recurrence for surgically treated papillary renal cell carcinoma (pRCC) could be challenging. Prognostic models are crucial for patient counselling and individualized surveillance. The GRANT score is one of the models suggested by guidelines to predict prognosis of surgically treated pRCC. This study aims to externally validate the GRANT score using a three-risk group stratification in a large cohort of pRCC patients.

Materials and Methods: The present analysis utilized retrospective data from pRCC patients who underwent radical or partial nephrectomy. The GRANT score parameters included tumor grade, age, pathological T-stage, and N-stage. Patients were stratified into three risk groups (0-1 vs 2 vs 3-4 risk factors). Cancer-specific survival (CSS) was assessed using the Kaplan-Meier method, and differences between groups were evaluated using the log-rank test. Harrell's c-index was used to measure model accuracy, and restricted mean survival time (RMST) was calculated for up to 120 months.

Results: A total of 1942 patients were included. The median follow-up was 64.6 months. At 60 months, CSS was 93.2% (95%CI 91.7%-94.6%) for group 1, 60.8% (95%CI 54.0%-78.6%) for group 2, and 26% (95%CI 15.7%-42.9%) for group 3, with significant differences between each group ($p < 0.001$). The median CSS was not reached for group 1 (95%CI NR-NR), 86.0 months in group 2 (95%CI 65-NR), and 22.8 months in group 3 (95%CI 16.4-48.0). The c-index for CSS was 0.732. The RMST at 120 months was 113.3 months for group 1, 75.9 months for group 2, and 56.6 months for group 3, with a statistically significant difference ($p < 0.001$).

Conclusion: The GRANT score effectively stratified surgically treated pRCC patients into three risk groups, demonstrating good prognostic accuracy. This validation supports the GRANT score's utility as a reliable and easy-to-use prognostic tool.

Keywords

prognostic factors, papillary, renal cancer, surgical treatment, prognosis, surgery

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Introduction

Papillary renal cell carcinoma (pRCC) accounts for 10%–15% of all renal cell carcinoma (RCC) cases and is the second most common histology among RCCs. Typically, pRCC has been classified as Type 1 and Type 2, primarily based on morphological features, although mixed types are common.¹ In 2022, the World Health Organization (WHO) integrated immunophenotypic and molecular characteristics into the pRCC classification.¹ Localized pRCC tends to have a more favorable prognosis compared with clear-cell RCC (ccRCC), whereas patients with metastatic pRCC generally

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have poorer survival, possibly due to the lack of effective targeted agents.²

Partial and total nephrectomy represent the standard curative treatments for both localized and locally advanced RCC, although up to 30% of patients may experience tumor recurrence. In this scenario, prognostic models are essential tools for counselling patients, individualizing surveillance, and selecting those who may benefit from potential adjuvant therapy.³ Different clinical and pathological factors have been identified for surgically treated RCC. These include Eastern Cooperative Oncology Group (ECOG) performance status (PS), tumor stage, tumor size, regional lymph node involvement, nuclear grade, presence of necrosis, and vascular invasion.⁴ These factors have been incorporated into several prognostic models and nomograms, which differ in the type and number of clinical and pathological variables included, as well as the endpoints considered (overall survival, cancer-specific survival, and recurrence-free survival).

All International guidelines provide a strong recommendation for the use of these prognostic models. However, both the European Society for Medical Oncology (ESMO) and European Association of Urology (EAU) state that there is insufficient evidence to recommend one prognostic model over another.⁵

The University of California Los Angeles Integrated Staging System (UISS), the Stage, Size, Grade and Necrosis (SSIGN) score, the Leibovich score, and the GGrade, Age, Nodes and Tumor (GRANT) score are recommended risk stratification tools for surgically treated RCC.^{5,6} Recently, the risk stratification model of the KEYNOTE-564 has been widely used to select patients who may be eligible for adjuvant treatment.^{5,7} The EAU guidelines currently recommend the use of the UISS score, the 2018 Leibovich score, the VENous tumour thrombus, NUclear grade, Size, T and N Stage (VENUSS), and the GRANT models to specifically guide the prognosis of surgically treated pRCC.⁶ These models are primarily derived from retrospective studies, with only a few validated using prospective data.⁴ Additionally, most of these models are based on studies including patients with ccRCC, and the relatively low prevalence of pRCC makes it challenging to develop a specific risk stratification tool.⁸

The UISS score was initially developed in 2002 by Zisman et al⁹ and subsequently externally validated in a cohort of 4202 patients, demonstrating accurate survival prediction for localized RCC, with *c*-indices ranging from 0.76 to 0.86.¹⁰ However, the score lacks specific validation for pRCC.^{9,10}

The 2018 Leibovich model was developed to specifically assess relapse-free survival (RFS) and cancer-specific survival (CSS) for ccRCC, pRCC and chromophobe RCC. The model, for the 607 patients with pRCC included in the study, demonstrated a *c*-index of 0.77 for RFS and 0.83 for CSS.¹¹

Klatte et al developed the VENUSS model for predicting disease recurrence in 556 patients with non-metastatic pRCC.¹² The *c*-index at 1 year, 2 years and 5 years was 89.8, 84.2 and 81.1%, respectively.¹² The score was externally validated in a cohort of 980 patients with non-metastatic pRCC,

with *c*-indices comparable to those from the original development.¹³

The GRANT model stratified patients into favorable and unfavorable risk categories based on the presence of 0–1 and 2–4 risk factors, which were Fuhrman's grade, age, pathological tumor size, and nodal status.¹⁴ The score was validated in 2019, using a five-risk group stratification (0 vs 1 vs 2 vs 3 vs 4 risk factors) in 12,317 patients with resected pRCC from the Surveillance, Epidemiology, and End Results (SEER) database. The *c*-index for OS at 60 months were 0.650.¹⁵ Despite its relatively low *c*-index, the GRANT score was easy to calculate, included routine histopathological features and age, and has been validated in a large pRCC population with a long follow-up.¹⁶

Recently, Wagener et al collected clinical and pathological data from 2325 patients with pRCC who underwent radical or partial nephrectomy at European and North American centers between 1984 and 2015. They compared cancer-specific mortality (CSM) between pRCC and ccRCC, taking into account age at surgery, sex, stage, grade, and lymph node involvement in a multivariate Cox model. The study reported a significantly reduced risk of cancer specific death for non-metastatic pRCC when compared with ccRCC.¹⁷

In this study, we aimed to further validate the GRANT score in a large cohort of pRCC patients, using a three-group risk stratification (0-1 vs 2 vs 3-4 risk factors) to explore the accuracy of the model in predicting cancer-specific survival (CSS).

Methods

The study cohort consisted of patients with pRCC included in the freely available dataset published by Wagener et al.¹⁷ This retrospective database collected clinical and pathological data from patients (*n*=2325) who underwent radical or partial nephrectomy for pRCC at 17 centers worldwide (14 European and three North American centers) between 1984 and 2015. Only patients with unilateral pRCC, aged ≥18 years, treated with partial or radical nephrectomy between 1984 and 2015, were included. Patients under 18 years of age and patients with bilateral disease were excluded. Data regarding follow-up time, death from disease, metastatic disease, center, age at surgery, sex, pRCC subtype (where available), T classification, lymph node involvement (according to TNM 2009), and grade (G1, G2, G3, and G4) were collected. 383 patients with missing data (stage or grade) were excluded. Ultimately, 1942 patients were included in the final analysis.

Surgical specimens were evaluated by genitourinary pathologists at each institution, without central pathology review. Tumor stage was adjusted according to the 2009 TNM classification of malignant tumors. Preoperative staging of patients included abdominal CT or MRI, chest imaging, and serum chemistry; bone scans and/or brain imaging were performed when indicated by symptoms. No patient received (neo)adjuvant therapy. Cause of death was determined by treating physicians, chart review, or death certificate.

The parameters used to calculate the GRANT score were as follows: tumor grade 1–2 versus 3–4, age ≤ 60 years versus > 60 years, pN0-NX versus pN1, pT1-T3a versus all others (any pT3b, pT3c, pT4). Patients were assigned one point for each of the following: age > 60 years, tumor grade > 2 , pathologic T-stage of pT3b, pT3c, or pT4, and pathologic N-stage other than N0 or NX, resulting in a score range of 0 to 4. We validated the GRANT score using a three-risk group stratification (0-1 vs 2 vs 3-4 risk factors) in the pRCC population.

The Kaplan-Meier method was used to estimate CSS rates by risk group and assess differences between GRANT groups. Survival was calculated from the time of surgery. The log-rank test (Mantel-Cox) was used to assess the association between CSS rates and the GRANT score, with a level of significance set at $p < 0.05$. Model performance was evaluated in terms of discrimination using Harrell's c-index.¹⁸ Since the proportional hazards assumption was violated by visual inspection, hazard-ratios were not reported. Instead, the restricted mean survival time (RMST) from 0 to 120 months was assessed as an alternative measure. RMST for each group was measured as the area under the survival curve from 0 to 120 months, indicating the mean survival time free from an event over a fixed time horizon. The log-rank test was used to assess differences between curves in the three groups, with a level of significance set at $p < 0.05$ and 95% confidence intervals (95% CI). The software JAMOVI version 2.3.21 (www.jamovi.org) and Stata (v.16; StataCorp) were used to perform all the computational analyses and to draw the survival curves.

Results

Out of the 2325 patients included in the original database, 383 patients were excluded due to missing data necessary for the GRANT score (stage and grade). A total of 1942 patients were included in the final analysis. Clinical and pathological characteristics of the patients are reported in Table 1. The median follow-up was 64.6 months (95%CI 63.0-67.0), with a mean patient age of 61.6 years (range: 19.6-93.2). Patients aged > 60 years represented 58% of the population, and 75.6% were male. Approximately 94.1% of patients had initial stage disease (pT1-T2-T3a), and 92.7% had no lymph node involvement at surgery. Around 415 (21.3%) patients had high grade tumors (G3-G4). Within the overall population, 151 (7.8%) patients presented with metastatic disease.

Overall, 1584 (81.5%) patients were in the GRANT group 1 (0-1 risk factors), 275 (14.2%) in group 2 (2 risk factors), and 83 (4.3%) in group 3 (3-4 risk factors).

At 60 months, CSS rates differed significantly (log-rank test; $p < 0.001$) across the three risk groups determined by the GRANT score and were 93.2% (95%CI 91.7%-94.6%) for group 1, 60.8% (95%CI 54.0%-78.6%) for group 2, and 26% (95%CI 15.7%-42.9%) for group 3.

The median CSS was not reached for group 1 (95%CI NR-NR), 86.0 months in group 2 (95%CI 65-NR), and 22.8 months in group 3 (95%CI 16.4-48.0), as shown in Figure 1. The CSS c-index value was 0.732.

Table 1. Summary of Clinical and Pathological Features of Patients with pRCC.

	Overall (n = 1942)
<i>Age at surgery</i>	
Mean (SD)	61.6 (11.7)
Range	19.6–93.2
<i>Age</i>	
≤ 60 years	816 (42.0%)
> 60 years	1126 (58.0%)
<i>Sex</i>	
Male	1468 (75.6%)
Female	474 (24.4%)
<i>T classification</i>	
pT1a	862 (44.4%)
pT1b	433 (22.3%)
pT2a	163 (8.4%)
pT2b	82 (4.2%)
pT3a	288 (14.8%)
pT3b	75 (3.9%)
pT3c	8 (0.4%)
pT4	31 (1.6%)
<i>T group</i>	
pT1-T2-T3a	1828 (94.1%)
pT3b-T3c-T4	114 (5.9%)
<i>Lymph node metastasis</i>	
pN0/pNx	1800 (92.7%)
pN+	142 (7.3%)
<i>Grade</i>	
1	279 (14.4%)
2	1248 (64.3%)
3	358 (18.4%)
4	57 (2.9%)
<i>GRANT group</i>	
1	1584 (81.6%)
2	275 (14.2%)
3	83 (4.3%)
<i>Metastatic disease</i>	
cM0	1791 (92.2%)
cM1	151 (7.8%)

The restricted mean survival time at 120 months was 113.3 months in group 1, 75.9 months in group 2, and 56.6 months in group 3. This resulted in a shorter time free from the death event for the groups 2 and 3, with an estimated difference of 37.4 months (95%CI 30.3-44.4; $p < 0.001$) between group 2 and group 1, and 66.7 months (95%CI 53.5-79.9; $p < 0.001$) between group 3 and group 1.

The population also included 151 (7.8%) metastatic patients. However, these patients were equally represented in the three GRANT groups. When these patients were excluded from the analysis, the differences in CSS rates and group comparisons remained consistent (Supplementary Figure 1).

Discussion

Recurrence after curative intent remains a significant issue in renal cell carcinoma.⁴ An intensive follow-up schedule applied to unselected patients can be stressful and increase healthcare

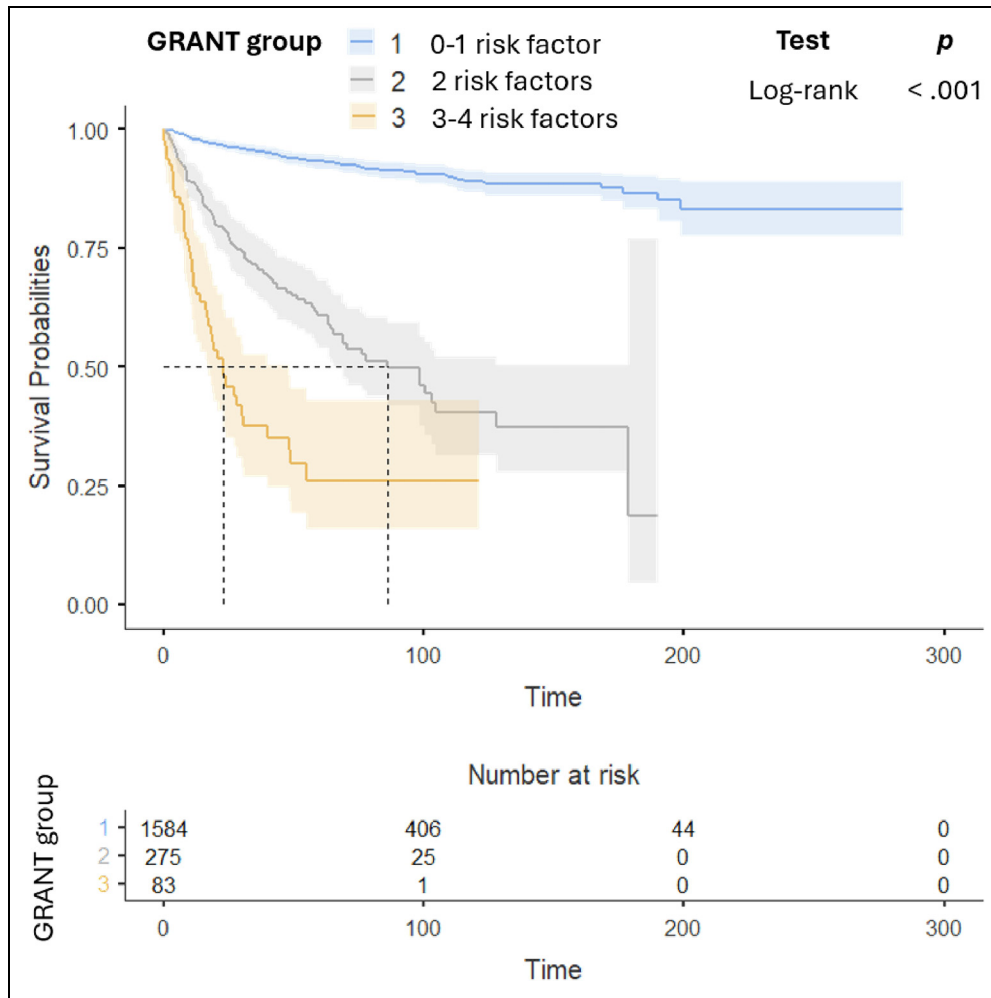


Figure 1. Representative kaplan-meier curve illustrating cancer-specific survival for each GRANT group.

costs.¹⁹ Measuring the risk of relapse for each patient and tailoring the follow-up schedule is crucial to improve the management of potentially cured patients.¹⁹

For resected pRCC, different prognostic tools have been developed in recent years, incorporating clinical and pathological features to accurately estimate relapse risk.^{4,16} While adding variables to these models could improve their accuracy, it may also increase their complexity, potentially limiting their applicability in clinical practice.¹⁵ Therefore, balancing predictive accuracy and ease of use is essential for these models to be effectively applied in clinical practice.^{15,16}

Among the models recommended by international guidelines for pRCC, the GRANT score is an easy-to-use tool for predicting prognosis in resected pRCC.^{14,15} The score includes routine histopathological features as well as age, and has been validated in a large cohort of pRCC patients.¹⁵

In this study, we aimed to further validate the GRANT score in a cohort of 1942 pRCC patients included in the dataset collected by Wagener et al,¹⁷ using a three-risk group stratification (differing from the original GRANT score validation). The score showed to accurately predict CSS, exhibiting a

statistically significant difference between each GRANT group. Similarly, the RMST was significantly different in each group. The *c*-index for CSS was 0.732, reflecting good prognostic accuracy and aligning with the performance of other established models.^{4,8,10–15,20–23}

The primary limitation of this study lies in its retrospective design. The population included also 151 metastatic patients, but it was unclear whether metastatic disease was synchronous or metachronous with respect to surgery or if metastatic lesions were resected. However, the CSS was not different, when these patients were removed from the analysis.

The primary objective of this analysis was merely to externally validate an existing prognostic score using a freely accessible database. Unfortunately, the lack of additional data points limited the scope for further insights. Furthermore, the lack of available data on other known prognostic factors prevented us from performing a multivariable analysis using the Cox proportional hazards model. As a result, we could not adjust for potential confounders, which represents a key limitation of our study.

A notable limitation is that the dataset is not recent. However, when retrospectively evaluating time-dependent

outcomes, older datasets are often necessary to ensure sufficient follow-up. Additionally, treatment options for pRCC have remained largely unchanged over the years, particularly in the adjuvant setting where effective therapies are still lacking. Therefore, the lack of significant advancements in the therapeutic scenario of pRCC may maintain the applicability of our score. Nonetheless, our team is actively working on validating the score using more recent cohorts treated with immunotherapy within clinical trials.

Future studies should aim to incorporate additional prognostic variables to enable a more comprehensive multivariable analysis. Additionally, future models should be prospectively validated and incorporate molecular, genetic, and transcriptomic data to further improve risk stratification and personalize care for resected patients.⁴ In light of this, our team is trying to enhance the accuracy of the GRANT score by integrating additional parameters (eg neutrophil-to-lymphocyte ratio) while maintaining its ease of use.

Machine learning applied to real-world prospective data from patients undergoing surgery for localized RCC can provide accurate individual recurrence prediction, eventually outperforming traditional prognostic scores.²⁴

Conclusion

The GRANT score was successfully validated using a three-risk group stratification in a large population of patients with resected pRCC from a real-world database. This successful application of the GRANT model represents an additional demonstration of its validity and accuracy, combining ease of calculation with reliable prognostication for surgically treated patients with pRCC.

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Author Contributions

Michele Maffezzoli, Sebastiano Buti, Davide Campobasso and Alessio Signori have given substantial contributions to the study conception and design, data analysis and drafting of the manuscript. All Authors contributed to the conception of the study, editing and revising the manuscript critically. All authors read and approved the final version of the manuscript. All authors have sufficiently participated to the study and agreed to be accountable for all aspects of the work.

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Statements and declarations

The authors have no other competing interests or relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Supplemental Material

Supplemental material for this article is available online.

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