INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2022) 29, 641–645 doi: 10.1111/iju.14859

Original Article: Clinical Investigation

GRade, Age, Nodes, and Tumor (GRANT) compared with Leibovich score to predict survival in localized renal cell carcinoma: A nationwide study

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Abbreviations & Acronyms
ccRCC = clear cell renal cell carcinoma
CI = confidence interval
CT = computed tomography
GRANT = GRade, Age, Nodes, and Tumor
IQR = interquartile range
OS = overall survival
RCC = renal cell carcinoma
RFS = recurrence-free survival

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Received 9 January 2022; accepted 24 February 2022.
Online publication 1 April 2022

Objective: To examine the performance of Leibovich score *versus* GRade, Age, Nodes, and Tumor score in predicting disease recurrence in renal cell carcinoma.

Methods: In total, 7653 patients diagnosed with renal cell carcinoma from 2010 to 2018 were captured in the nationwide DaRenCa database; 2652 underwent radical or partial nephrectomy and had full datasets regarding the GRade, Age, Nodes, and Tumor score and Leibovich score. Discrimination was assessed with a Cox regression model. The results were evaluated with concordance index analysis.

Results: Median follow-up was 40 months (interquartile range 24–56). Recurrence occurred in 17%, and 15% died. A significant proportion of patients (36%) had missing data for the calculation of the Leibovich score. Among 1957 clear cell renal cell carcinoma patients the distribution of GRade, Age, Nodes, and Tumor score of 0, 1, 2, or 3/4 was 21%, 56%, 21% and 1.4%, respectively, and for Leibovich score of low/intermediate/high this was 47%, 36% and 18%, respectively. A similar distribution was seen in 655 non-clear cell patients. Both Leibovich and GRade, Age, Nodes, and Tumor scores performed well in predicting outcomes for the favorable patient risk groups. The Leibovich score was better at predicting recurrence-free survival (concordance index 0.736 *versus* 0.643), but not overall survival (concordance index 0.657 *versus* 0.648). Similar results were obtained in non-clear cell renal cell carcinoma.

Conclusion: GRade, Age, Nodes, and Tumor and Leibovich scores were validated in clear cell and non-clear cell renal cell carcinoma. Leibovich score outperformed the GRade, Age, Nodes, and Tumor score in predicting recurrence-free survival and should remain the standard approach to risk stratify patients during follow-up when all data are available.

Key words: disease free survival, GRANT, Leibovich, overall survival, RCC.

Introduction

RCC is the 13th most common cancer in the world and is the most lethal genitourinary cancer.[1–3] The main therapeutic approach for early stage RCC is radical or partial nephrectomy. About 20–40% of patients have metastatic disease (metastatic RCC) at initial diagnosis.[4,5] In addition, about 20% of patients experience recurrence after attempted curative surgery, which mainly develops within the first 5 years after surgery.[6–8]

The Leibovich score is a risk stratification tool to assess the risk of metastasis or recurrence after surgical treatment; the nomogram was developed in a cohort of localized, unilateral ccRCC patients who underwent radical nephrectomy between 1970 and 2000.[9] The nomogram includes pathologic features; tumor stage, regional lymph node status, tumor size, nuclear grade and histologic tumor necrosis. It is the most widely used clinical nomogram in Denmark for scheduling the postoperative follow-up program after nephrectomy for RCC.

A new risk stratification tool for RCC was recently developed: the GRANT score.[10] The score is easy to use and has been validated.[11,12] The GRANT score was based on patient age, and pathologic features; Fuhrman grade, nodal status (pN) and tumor size (pT). GRANT has demonstrated excellent discrimination for predicting recurrence in both ccRCC and non-

ccRCC patients and may therefore be an acceptable and simpler alternative to the Leibovich score.

The aim of this study was to compare the performance of the GRANT with the Leibovich score in a nationwide renal cell carcinoma cohort.

Methods

Data source

A total of 7653 patients diagnosed with RCC from August 2010 to August 2018 were identified in the nationwide DaRenCa database;[13] of these 4331 patients underwent radical or partial nephrectomy (Fig. 1). Date of initial diagnosis, Fuhrman grade, age, tumor and lymph node stage, tumor size, Leibovich score, date of metastasis, and vital status (dead or alive) were all collected from the DaRenCa database. Patients with synchronous metastasis, defined in the DaRenCa database as patients who presented with metastasis, or metastasis appeared within the first 120 days from the time of diagnosis, were omitted from the analysis. Patients were classified with a GRANT score of 0–4; according to the original paper by Buti *et al.*;[10] patients were given one point for each of the following parameters: age >60; Fuhrman grade >2; a pathologic T-stage of T3b, T3c or T4;[14] and a pathologic N-stage other than N0 or NX. There were only three patients with GRANT 4 in this cohort; therefore, this group was combined with the GRANT score of 3 cohort. Patients were also classified with a Leibovich score of 0–11 according to original classification by Leibovich *et al.* which stratifies patients with low (0–2), intermediate (3–5) or high (>5) risk.[15] All aspects of this study followed the principles in the Declaration of Helsinki. The study was approved by the Danish Health Data Board (jr. no. 3-3013-2056/1).

Statistical analyses

RFS was defined as the length of time between date of nephrectomy and date of recurrence. OS was defined as the time between nephrectomy and death. Discrimination was investigated at 60 months after surgery with the concordance index (C-index), which is the area under the receiver operating characteristic curve for survival time in the presence of censored data. A C-index of 0·5 represented no predictive discrimination and an index of 1 represents perfect ability to distinguish patients. Calibration was assessed with a calibration curve for the GRANT score 60 months after surgery, in which the diagonal line indicated perfect calibration. A Kaplan-Meier plot was used to inspect the OS curves for death and recurrence according to the GRANT and Leibovich scores. Statistical analyses were performed using RStudio version 1.3.1056 (Boston, MA, USA).

Results

In the nationwide cohort, 4155 patients underwent radical or partial nephrectomy and were evaluable for GRANT criteria; of which 1503 patients (36%) had missing necrosis status in the database regarding Leibovich score criteria (Fig. 1). Therefore, we included 2652 patients with complete data in the study. The median age of the cohort was 66 years (IQR 57–72) years. There were 1728 (65%) male patients, and the median follow-up time of patients alive at last follow up was 40 (IQR 24–56) months. A total of 1717 (65%) patients underwent radical nephrectomy, while 935 (35%) underwent partial nephrectomy. Recurrence was diagnosed in 450 (17%) of the patients; of them, 348/1957 (17.8%) in patients with ccRCC, 105/695 (15.1%) in patients with non-ccRCC, and 398 (15%) of the cohort died. The median time to recurrence was 41 (95% CI 39–43) months, and the median time to death was 43 (95% CI 42–45) months.

Clear cell renal cell carcinoma

There were 1957 patients who were diagnosed with ccRCC. According to the GRANT criteria, 414 (21.2%) had score 0, 1096 (56.0%) score 1, 419 (21.4%) score 2 and 28 (1.4%) score 3/4. Stratifying the cohort by Leibovich score, 910 (46.6%) were at low risk, 699 (35.7%) were at intermediate risk and 347 (17.7%) were at high risk. The 5-year overall OS was 93%, 82%, 63%, and 37% for GRANT 0–3/4, compared to 89%, 80%, and 57% for Leibovich low-risk, intermediate-risk, and high-risk groups, respectively (Fig. S1). The 5-year overall RFS stratified by GRANT score 0–3/4 was 85%, 79%, 57%, and 19%, respectively, compared to 90%, 75%, and 39% for Leibovich score low-risk, intermediate-risk, and high-risk groups, respectively (Fig. S2).

Accuracy of prognostic models for ccRCC

Analyzing the agreement between GRANT and Leibovich scores, patients with score 0 by the GRANT method were largely (96%) categorized as low- or intermediate-risk by the Leibovich score. Patients with GRANT score 3/4 were largely (93%) categorized as high risk by Leibovich score. GRANT score 2 and 3 captured 66% of the patients categorized as Leibovich score high-risk (Table 1).

We assessed GRANT and Leibovich scores for prognostic accuracy. Using C-index statistics, the Leibovich score was better at predicting RFS (0.736 *vs* 0.643), but not OS (Table 2). The predictive model utilizing the Leibovich score outperformed the model with the GRANT score for all levels of risk, whereas the model using the GRANT score was better at discriminating intermediate-risk patients (0.93 *vs* 0.84); see Table 3.

Non-clear cell renal cell carcinoma

There were 695 patients diagnosed with non-ccRCC. According to the GRANT criteria, 146 (21.0%) had score 0, 405 (58.3%) had score 1, 128 (18.4%) had score 2, and 16 (2.3%) had score 3/4. Stratification by the Leibovich score showed 360 (51.8%) were at low risk, 229 (32.9%) were at intermediate risk, and 106 (15.3%) were at high risk.

The 5-year overall OS for GRANT score 0–3/4 was 93%, 82%, 65%, and 55%, respectively, and for Leibovich score low-risk, intermediate-risk, and high-risk groups was 86%, 82%, and 59%, respectively (Fig. S3). The 5-year RFS for

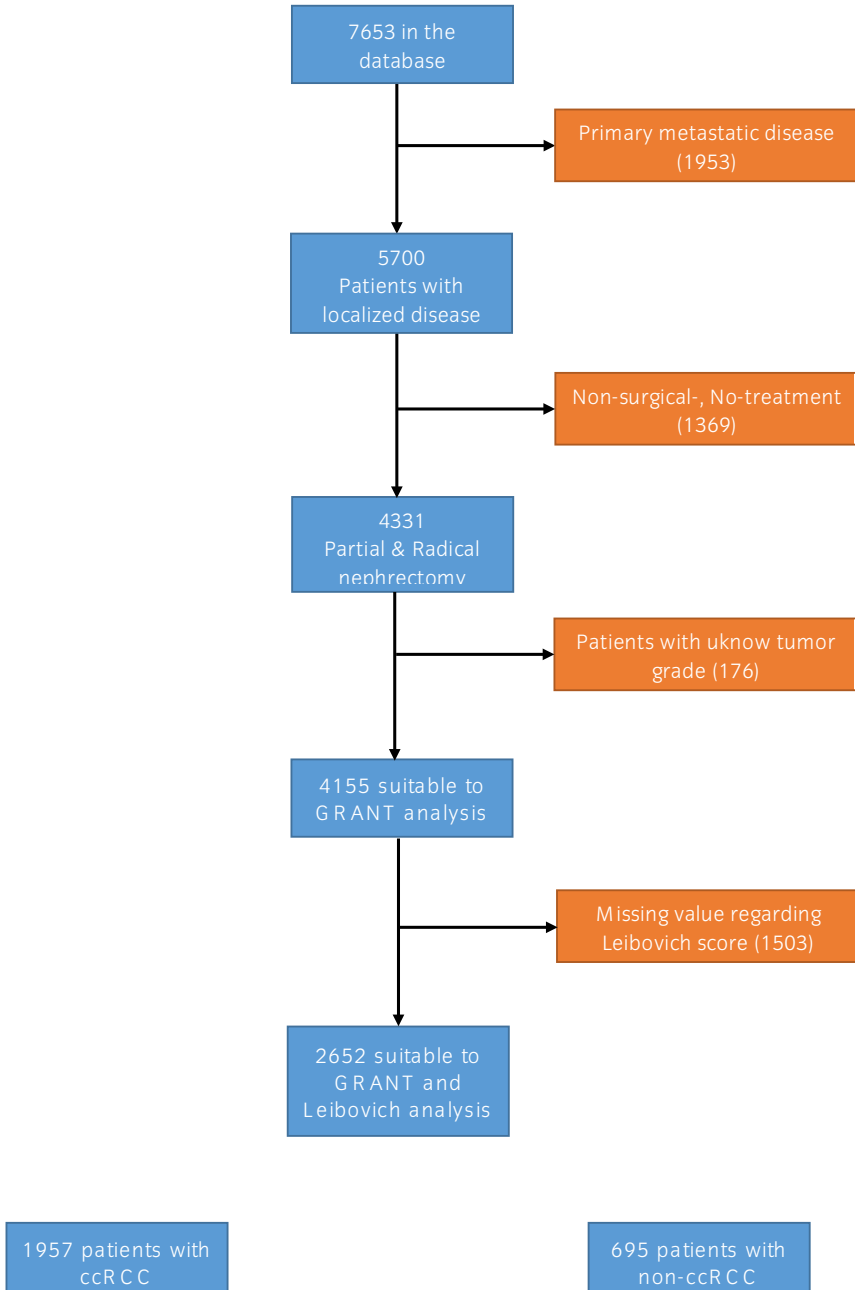

Fig. 1 Diagram flowchart of inclusion and exclusion criteria of the study.

GRANT score 0–3/4 was 93%, 82%, 61%, and 51%, respectively (Fig. S4). The 5-year RFS was 91%, 80%, and 44% for Leibovich score low-risk, intermediate-risk, and high-risk groups, respectively.

Accuracy of prognostic models in non-ccRCC

Patients with GRANT score 0 were largely (97%) categorized as low- or intermediate-risk by Leibovich score criteria. Patients with a GRANT 3/4 score were largely (87%) categorized as Leibovich score high-risk. GRANT 2–3 were mainly (58%) categorized as Leibovich score high-risk patients (Table 1).

There was almost no difference in performance between Leibovich and GRANT score as measured by C-index metrics for OS (Table 2). There was no difference in model accuracy for OS using either score for unfavorable risk patients. For RFS, the Leibovich score outperformed the GRANT score in predicting outcomes for patients at the highest risk (Table 3).

Discussion

In our database, there were 4155 patients with full data available to assign a GRANT score but only 2652 (64%) patients who had the additional data needed to assign a Leibovich score due to missing data on necrosis. Several prognostic models have been developed to improve survival prediction for patients with RCC. Although the Leibovich score and the SSIGN score use the same pathological features to predict

Table 1 Distribution of patients diagnosed with ccRCC and non-ccRCC comparing GRANT score and Leibovich score

ccRCC				
Leibovich score	Overall (*n* = 1957)	Low-risk 911 (47%)	Intermediate-risk 699 (36%)	High-risk 347 (18%)
GRANT				
GRANT 0	414 (21.2%)	277 (67%)	121 (29%)	16 (4%)
GRANT 1	1096 (56%)	579 (53%)	415 (38%)	102 (9%)
GRANT 2	419 (21.4%)	55 (13%)	161 (38%)	203 (49%)
GRANT 3/4	28 (1.4%)	0 (0%)	2 (7%)	26 (93%)
Non-ccRCC				
Leibovich score	Overall (*n* = 695)	Low-risk 360 (52%)	Intermediate-risk 229 (33%)	High-risk 106 (15%)
GRANT				
GRANT 0	146 (21.0%)	103 (70%)	39 (27%)	4 (3%)
GRANT 1	405 (58.3%)	225 (56%)	139 (34%)	41 (10%)
GRANT 2	128 (18.4%)	32 (25%)	49 (38%)	47 (37%)
GRANT 3/4	16 (2.3%)	0 (0%)	2 (13%)	14 (87%)

Table 2 The 5-year OS and RFS C-index for patients with ccRCC and non-ccRCC

Survival	C-index (GRANT)	C-index (Leibovich)	*P*-value
ccRCC			
OS	0.648	0.657	0.78
RFS	0.643	0.736	<0.0001
Non-ccRCC			
OS	0.659	0.647	0.41
RFS	0.662	0.737	0.007

Table 3 Model performance regarding risk groups in patients with ccRCC and non-ccRCC

Survival	GRANT score	AUC ccRCC	AUC non-ccRCC
OS	GRANT 3	0.67	0.50
OS	GRANT 2	0.75	0.55
OS	GRANT 1	0.71	0.69
OS	GRANT 0	0.50	0.57
RFS	GRANT 3	0.83	0.50
RFS	GRANT 2	0.99	0.61
RFS	GRANT 1	0.93	0.78
RFS	GRANT 0	0.59	NA†
Survival	Leibovich score	AUC ccRCC	AUC non-ccRCC
OS	High-risk	0.72	0.50
OS	Intermediate-risk	0.89	0.69
OS	Low-risk	0.71	0.78
RFS	High-risk	0.98	0.75
RFS	Intermediate-risk	0.84	0.62
RFS	Low-risk	0.7	0.61

†The area under the curve is less than 0.5.

the outcome of RCC, both were designed to predict RFS. These prognostic models have the benefit of a customized follow-up schedule, while the limitations of these nomograms are related to frequently missing data, particularly tumor necrosis.

We found the OS C-index values for the GRANT score in patients with ccRCC and non-ccRCC were 0.648 and 0.659, respectively; similar to those presented by Buti *et al.*[11] This suggests that the GRANT score has the same prognostic accuracy for patients in the DaRenCa database as those in the SEER database.

We found that in general, for both ccRCC and non-ccRCC patients, models that utilized the Leibovich score outperformed those utilizing the GRANT score regarding RFS (Table 3). We found that the RFS C-index value was 0.737 for patients with non-ccRCC when modeled using the Leibovich score, similar to the result (C-index of 0.83) first reported by Leibovich *et al.*[15]

We validated the performance of the GRANT score for those with a higher score by showing a similar C-index of 0.65, when compared to the original paper 0.61.[10,11]

All the patients with non-metastatic RCC were offered follow-up after surgical treatment that had financial implications and radiation exposure; thus, the need for nomograms is critical to individualize follow-up depending on the patient's risk. There is no consensus on a unique follow-up program in the urological community. In the DaRenCa guidelines, the follow-up program is based on CT images from every 6 months to annually in the first 3 years and then once every 2 years depending on the Leibovich score risk group. We found that 36% of the patients cannot be assigned a Leibovich score due to missing data in our database and thus lack proper risk stratification for RFS and OS. A report by Dabestani *et al.*[16] has suggested that increasing the number of CT images during follow-up does not improve postrecurrence survival, which may be related to improper scheduling of cross-sectional imaging due to inaccurate risk-stratification. Thus, there is a need for better nomograms to improve risk-adjusted follow up programs.

The strength of our study is based on the large national cohort, in which we found the GRANT score more widely applicable because of fewer missing variables, most commonly related to tumor necrosis, such that more patients could be accurately assigned. A limitation of this study is that it was a retrospective study, and the data were not collected with the purpose of conducting this study. In the database, 36% of the patients were missing due to missing details in the Leibovich score model, which may have affected the results.

Both the GRANT and Leibovich scores were useful in assigning recurrence and survival risk groups in ccRCC and non-ccRCC. However, overall models utilizing the Leibovich score outperformed those using the GRANT score for both ccRCC and non-ccRCC when data is available. A smaller fraction of patients were categorized as GRANT score high risk. The Leibovich score should remain the standard for assessing risk and driving follow-up care when data is available and the GRANT score can be an alternative prognostic tool.

Author contributions

Simon Juul: Writing – original draft; Writing – review & editing. Frede Donskov: Writing – review & editing. Peter E Clark: Writing – original draft; Writing – review & editing. Lars Lund: Writing – original draft; Writing – review & editing. Nessn H Azawi: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Conflict of interest

None declared.

Approval of the research protocol by an Institutional Reviewer Board

Approval of the research protocol by an Institutional Reviewer Board: Danish Health Data Board (jr. no. 3-3013-2056/1).

Informed consent

Not applicable.

Registry and the Registration No. of the study/trial

Not applicable.

Animal studies

Not applicable.

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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:

Figure S1. (a) Distribution of overall survival probability for patients who diagnosed with ccRCC determined by GRANT score at 60 months. (b) Distribution of overall survival probability for patients who diagnosed with ccRCC determined by Leibovich score at 60 months.
Figure S2. (a) Distribution of disease free survival probability for patients who diagnosed with ccRCC determined by GRANT score at 60 months. (b) Distribution of disease free survival probability for patients who diagnosed with ccRCC determined by Leibovich score at 60 months.
Figure S3. (a) ROC curve in patient who diagnosed with ccRCC represented 60 month OS regarding GRANT score. (b) ROC curve in patient who diagnosed with ccRCC represented 60 month OS regarding Leibovich score.
Figure S4. (a) ROC curve in patient who diagnosed with ccRCC represented 60 month DFS regarding GRANT score. (b) ROC curve in patient who diagnosed with ccRCC represented 60 month DFS regarding Leibovich score.