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Research Article

Comparison of the Outcome between the Mayo Clinic Stage, Size, Grade, and Necrosis (SSIGN) Score and the Leibovich Score in Non-Metastatic Renal Cancer

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Keywords

- Leibovich score
- Renal cancer
- SSIGN score

Abstract

Introduction: Renal cell carcinoma (RCC) is associated with a significantly higher ratio of annual mortality-to-incidence. Prognostic tools like SSIGN and Leibovich score have been developed to evaluate the progression free survival (PFS), overall survival (OS) and cancer specific survival (CSS).

Purpose: To compare the prognostic accuracy of the SSIGN score and the Leibovich score regarding PFS, OS and CSS in a cohort of Danish RCC patients.

Materials and methods: Data from 289 consecutive patients diagnosed with localized or locally advanced RCC who underwent renal surgerybetween January 2005 to December 2013 were retrospectively collected from patient charts and analyzed.

Results: The mean age was 64 years. The median follow-up was 31 months (range 6 – 60 months). For PFS, Harrell's c concordance for the SSIGN score was 0.76, 95% CL [0.69-0.82] and 0.77, 95% CL [0.69-0.83] for the Leibovich score (p= 0.64). Likewise, there was no statistically significant difference of the two scoring systems regarding CSS, as the SSIGN score and the Leibovich score had Harrell's c concordance of 0.64, 95% CL [0.53-0.72] and 0.62, 95% CL [0.50-0.71], p= 0.36, respectively. Finally, the Harrell's c concordance of the SSIGN score regarding OS was 0.67, 95% CL [0.59-0.74] and 0.69, 95% CL [0.59-0.74] for the Leibovich score (p=0.85).

Conclusion: The SSIGN and the Leibovich scoring systems are good nomograms for prediction of PFS and show similar accuracy. More studies are needed to evaluate the accuracy of the models in predicting CSS and to better understand the risk factors regarding survival in Danish patients with non-metastatic renal cancer.

ABBREVIATIONS

RCC: Renal Cell Carcinoma; PFS: Progression Free Survival; OS: Overall Survival; CSS: Cancer Specific Survival; SSIGN: Mayo Clinic Stage, Size, Grade, and Necrosis Score

INTRODUCTION

Renal cell carcinoma (RCC) is associated with a significantly higher ratio of annual mortality-to-incidence compared with other common urological malignancies [1]. Overall, the 5-year survival following surgical resection in patients with RCC is approximately 60%. TNM stage and Fuhrman nuclear grade provide important information regarding prognosis, but other predictive algorithms for overall and cancer specific survival among patients with RCC have also been reported using a number of clinical and pathological features [2-8]. Prognostic tools have been developed to evaluate the progression free survival (PFS), overall survival (OS) and cancer specific survival (CSS), which are all clinically important measures of patient outcomes. These tools include the Mayo clinic stage, size, grade, and necrosis (SSIGN) score and the Leibovich score [3,5,8,9], which were developed to predict CSS and metastasis free survival, respectively. Both tools are widely used and are the basis of the current study.

Purpose

To compare the prognostic accuracy of the SSIGN score and the Leibovich score regarding PFS, OS and CSS in a cohort of Danish RCC patients.

MATERIALS AND METHODS

Data from 289 consecutive patients diagnosed with localized or locally advanced RCC who underwent radical or partial nephrectomy at the Department of Urology, Zealand University Hospital, Roskilde from January 2005 to December 2013 were retrospectively collected from patient charts and analyzed. Permission from the Danish Health and Medicines Authority in accordance with Danish legislation was obtained.

All patients had undergone a CT urography as well as either a thoracic x-ray or CT scan as part of their diagnostic work-up. Pathological T-stage was assigned according to the 2009 TNM classification [10]. Patients who underwent surgery before this

time were re-classified accordingly by their histological features. N0 was assigned to patients with no evidence of clinical or pathological involvement of regional lymph nodes, and N1 was assigned when histological examination of the nephrectomy sample showed lymph nodes with malignant cells. Patients with clinical or pathological evidence of metastasis were excluded from the study. None of the patients received neoadjuvant treatment and all surgical specimens were evaluated by pathologists with extensive experience in assessment of renal cancer.

Recurrence was defined as tumor relapse in the operative field, regional lymph nodes, and/or distant metastasis as diagnosed either by a CT scan or histologically by biopsies or resection of metastases.

The duration of follow-up was defined as the period between the time of diagnosis and the last follow-up or death. Data collection was performed in January 2016. In order to reduce bias in attribution of the cause of death and to clearly distinguish between cancer-specific death and death from other causes, the cause of death was specifically confirmed in each deceased individual using the patient charts. Leibovich scores were assigned according to the original paper by Leibovich et al., [5]. SSIGN scores were assigned according to Frank et al., [3].

Due to the limited number of patients in each SSIGN score category, patients were stratified by collapsing scores into fewer categories. Patients were divided into four categories consisting of scores 0-2; 3-4; 5-7; and ≥8 to analyze PFS, (Figure1). This was termed the SSIGN for progression model (SSIGNp). To analyze CSS and OS, the SSIGN scores were collapsed into two categories consisting of scores 1-4 and ≥5, respectively. This was termed the SSIGN for survival model (SSIGNs).

Regarding the Leibovich model, patients were stratified according to the original collapsing model for PFS (Leibovich_p) and by collapsing low and intermediate risk groups to one group for CSS and OS (Leibovich_s) again due to limited number of patients in each group.

Statistical methods

The PFS, CSS, and OS were estimated using Kaplan-Meier methods. For estimation of PFS, patients who were recurrence-free at their last date of follow-up or at death were censored.

Differences in the PFS and survival probabilities by various histological features were tested by the log rank test. Harrell's c concordance and Receiver operating characteristic (ROC) curve analysis was used to compare the concordance of the Leibovich model versus the SSIGN model. A p-value below 0.05 was considered statistically significant. Statistical analyses were performed using Statistical Analysis Software (SAS) version 9.4 (Institute Inc., Cary, NC, USA).

RESULTS AND DISCUSSION

Overall, 289 patients were diagnosed with localized or locally advanced renal cancer in the period. The mean age was 64 years (range 38 – 89 years). Males represented 188 patients (65%), and females represented 101 patients (35%). Radical nephrectomy was performed in 230 patients (79%), while partial nephrectomy was performed in 59 patients (21%). The median follow-up period for all patients was 31 months (range 6 – 60 months), 95% CI [38–44]. Distribution of the pathological features used for the SSIGN and Leibovich models are described in table 1. The mean tumor size was 61.43 ± 44.72 cm, 12 patients had a Sarcomatoid growth, 13 patients had non-free surgical resection margin, 20 patients had tumor involvement of lympho-vascular structures. Fifty-two patients experienced late metastasis and 72 died during the follow up period of 5 years.

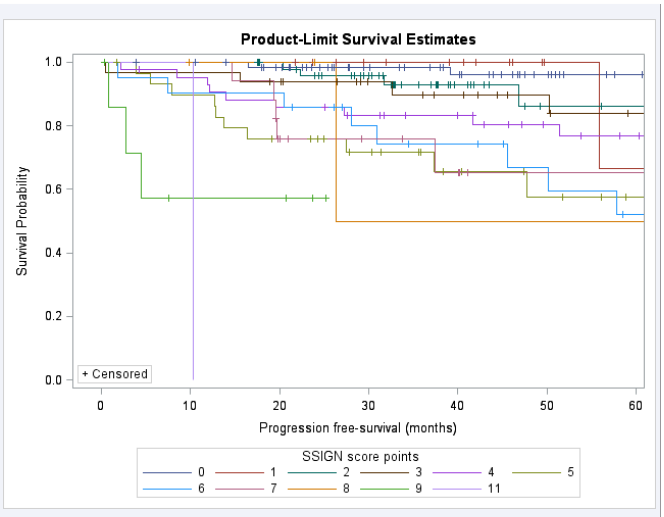

Figure 1a SSIGN score over PFS.

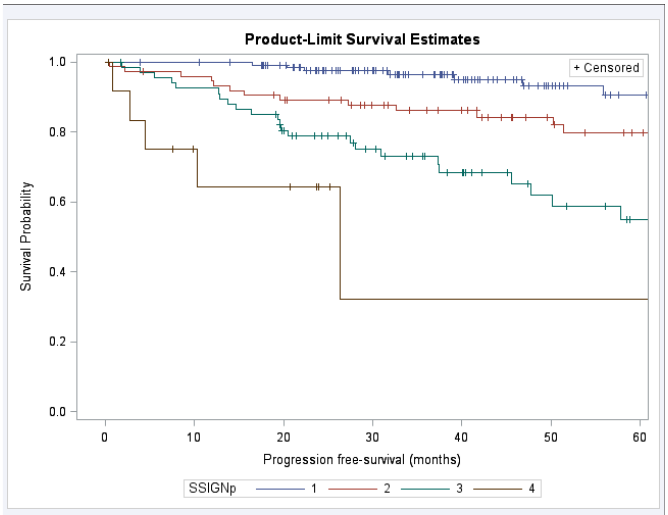

Figure 1b SSIGN collapsed according using the adjustment for multiple comparison for log rank test.

The mean PFS was 95.43%, 86.42% and 77.62% at 1, 3 and 5 years, respectively. There were significant differences in the subgroups of both the SSIGNp and Leibovich_p models regarding PFS ($p<0.0001$) (Figure 2A, 2B).

The CSS was 96.50%, 89.04% and 83% at 1, 3 and 5 years, respectively. There were significant differences between subgroups in both the SSIGNs and the Leibovich_s models regarding CSS, (Figure 2C, 2D). This tendency could not be recognized using neither the SSIGN scores/SSIGNp model nor Leibovich scores/Leibovich_p model.

The OS was 94.09%, 83.92% and 74.18% at 1, 3 and 5 years, respectively. There were significant differences between subgroups in both SSIGNs and Leibovich_s models regarding OS (Figure 2E, 2F). This tendency could not be recognized using neither SSIGN scores/SSIGNp model nor Leibovich scores/ Leibovich_p model.

For PFS, Harrell's c concordance for the SSIGN score was 0.76, 95% CL [0.69-0.82], while Harrell's c concordance was 0.77, 95% CL [0.69-0.83] for the Leibovich score. This difference

Table 1: **Distribution of the data.**

	Frequency (%)
T-stage	
pT1a	97 (33.56)
pT1b	66 (22.84)
pT2a	31 (10.73)
pT2b	21 (7.27)
pT3a	54 (18.69)
pT3b	18 (6.22)
pT4	2 (0.69)
Necrosis status	
Non-Necrosis	159 (55.02)
Necrosis	130 (44.98)
Lymph node status	
Negative lymph node	279 (96.54)
Positive lymph node	10 (3.46)
Sarcomatoid growth	
Non-Sarcomatoid Growth	277 (95.85)
Sarcomatoid Growth	12 (4.15)
Fuhrman grade	
Fuhrman I	14 (6.60)
Fuhrman II	113 (53.30)
Fuhrman III	69 (32.55)
Fuhrman IV	16 (7.55)
Numberof patientsdeceased due to anycause	**72 (24.91)**
Number of patients deceased due to RCC	**40 (13.84)**
Number of patients with recurrences	**52 (17.99)**

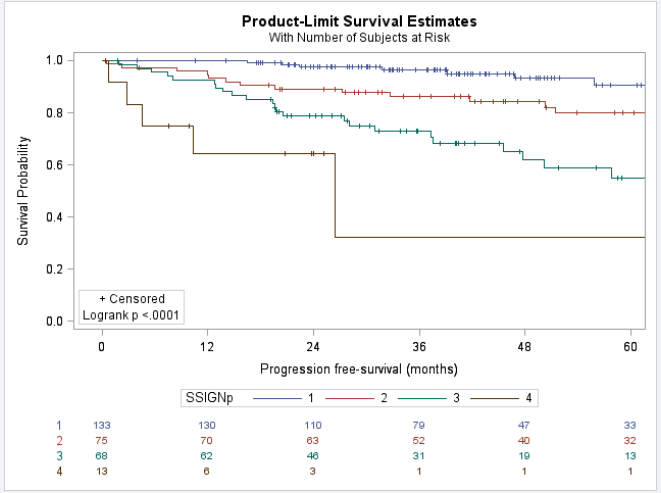

Figure 2a Estimated progression free-survival stratified by SSIGNp model.

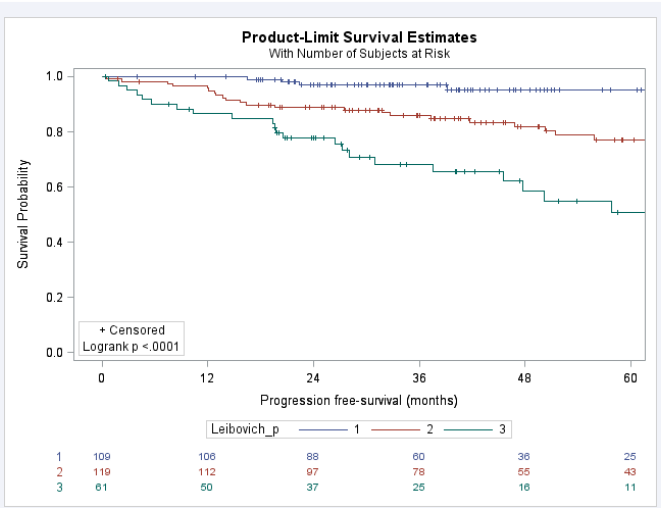

Figure 2b Estimated progression free-survival stratified by Leibovich_p model.

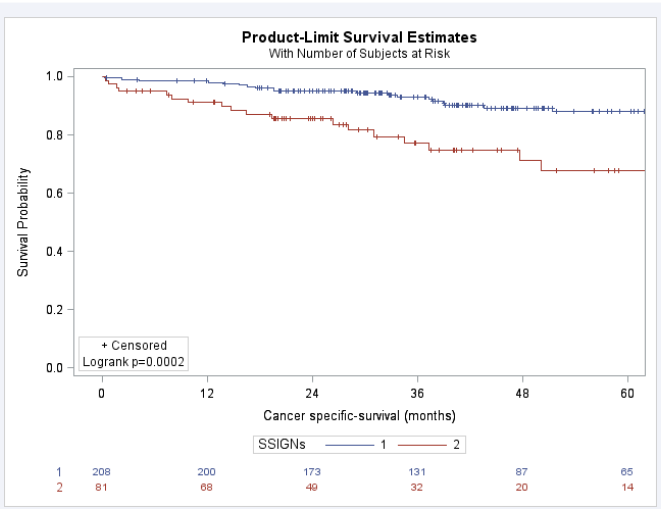

Figure 2c Estimated cancer specific-survival by SSIGNs model.

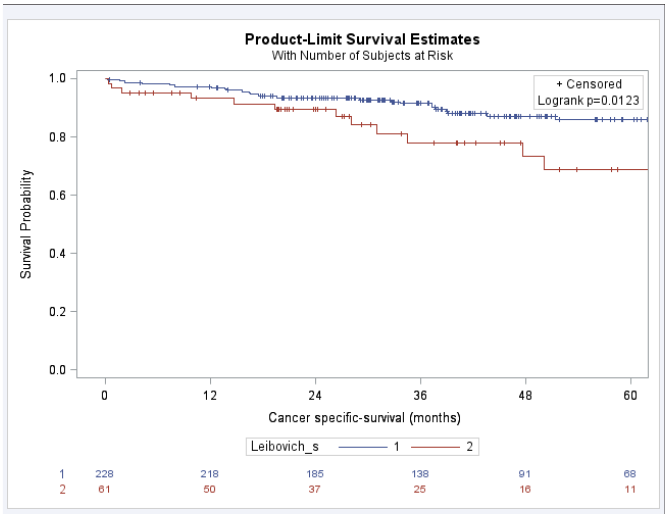

Figure 2d Estimated cancer specific-survival stratified by Leibovich_s model.

was not statistically significant (p= 0.64). Likewise, there was no statistically significant difference in the concordance test of the two scoring systems regarding CSS, as the SSIGN score and the Leibovich score had Harrell's c concordance of 0.64, 95% CL [0.53-0.72] and 0.62, 95% CL [0.50-0.71], p= 0.36, respectively. Finally, the Harrell's c concordance of the SSIGN score regarding OS was 0.67, 95% CL [0.59-0.74] and 0.69, 95% CL [0.59-0.74] for the Leibovich score. As for PFS and CSS, this did not amount to a statistically significant difference (p=0.85), (Figure 3).

On multivariate analyses controlling for pathological features (SSIGN and Leibovich),the presence of Sarcomatoid growth and a positive surgical margin were independent predictors for poor OS with hazard ratios of 2.9, 95% CL [1.2 – 7.0], p=0.01 and 2.2, 95% CL 0.98 – 4.88], p=0.05, respectively. Sarcomatoid growth and positive surgical margin were not significant predictors of PFS and CSS.

DISCUSSION

Several prognostic models have been developed to improve survival prediction in patients with RCC. Although the Leibovich score and the SSIGN score use the same pathological features in predicting the outcome of RCC, the Leibovich score is designed to predict PFS while the SSIGN score is designed to predict CSS. In our study, we tested the ability of both scoring systems to predict PFS, CSS, and OS and we compared the accuracy of the two systems for each outcome.

In our population from a single regional area in Denmark both the SSIGN and the Leibovich score system provided good estimates of PFS, and there were no significant differences in the accuracy between the systems. Meanwhile, the accuracy of the systems regarding CSS and OS were not optimal in our cohort. This is contradictory to previous studies in which the accuracy of the SSIGN score is reported to be up to 80% regarding CSS [11]. This could be due to the relatively small number of patients included in our study, or it could be due to inherent differences in the study populations. More studies with a greater number

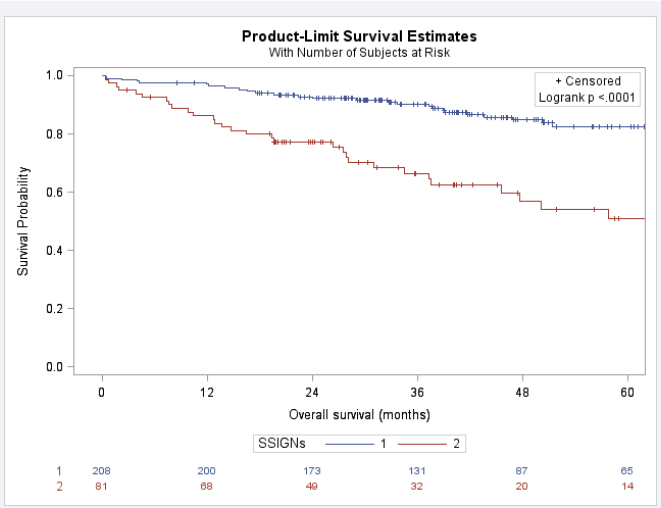

Figure 2e Estimated overall survival by SSIGNs model

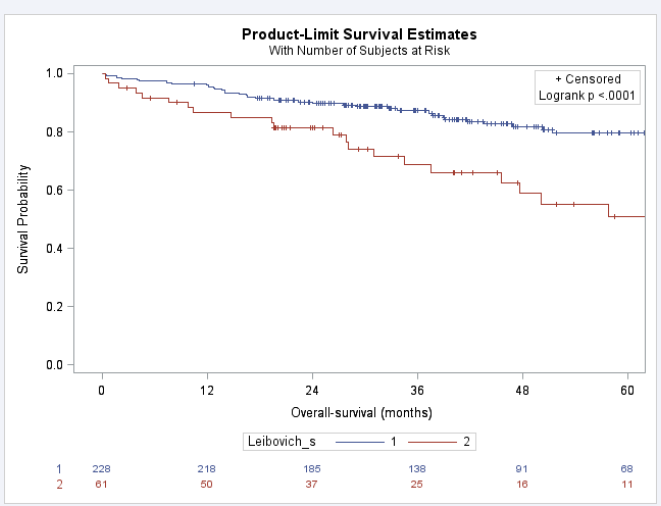

Figure 2f Estimated overall survival by Leibovich model.

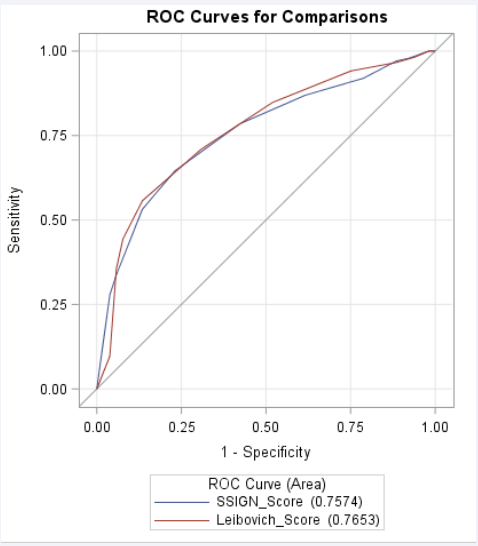

Figure 3a SSIGN versus Leibovich score regarding PFS.

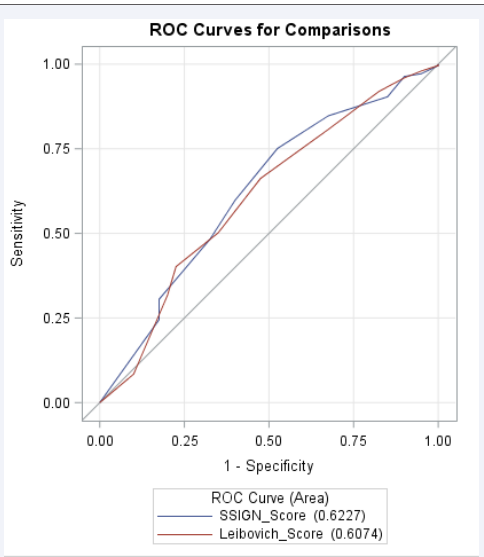

Figure 3b SSIGN versus Leibovich score regarding CCS.

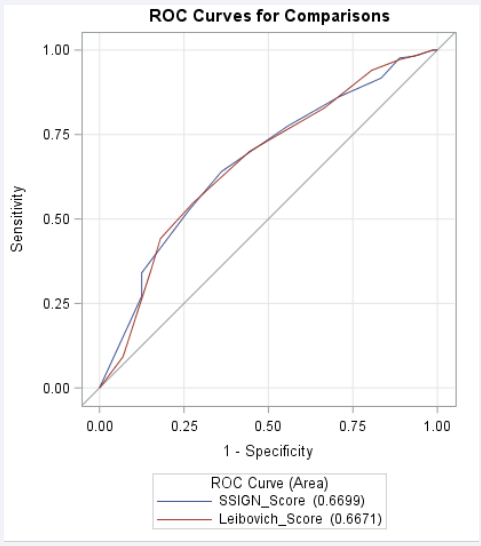

Figure 3c SSIGN versus Leibovich score regarding OS.

of Danish patients with localized and locally advanced RCC are needed to resolve this issue.

Accurate prediction of patient outcomes using some type of score model is an important instrument used for counseling and scheduling the postoperative follow up program after surgical treatment of localized and locally advanced RCC. The survival rate can be improved by early detection of recurrences, but on the other hand, many follow-up appointments may be associated with expenses and a poor quality of life. Therefore, development of a good predictive scoring model is essential to keep the balance between safety, feasibility and cost of any follow-up program [12].

The presence of Sarcomatoid growth and a positive surgical margin were significant predictors of poorer OS. Adding new pathological feature to these score systems may increase the accuracy of the models to predict the outcome of patients with RCC after surgery. Some studies have used multimodal linking biomarkers and pathological features to improve the accuracy of the model to predict the postoperative outcome for patients with RCC with promising results, such model have yet to be validated in large multicenter studies [13-15].

The limitations of our study include its retrospective nature, and the inclusion of a single regional area in Denmark with a relatively small number of patients.

CONCLUSION

The SSIGN and the Leibovich scoring systems are good nomograms for prediction of PFS and show similar accuracy. More studies are needed to evaluate the accuracy of the models in predicting CSS and to better understand the risk factors regarding survival in Danish patients with non-metastatic renal cancer.

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