

External validation of the modified Glasgow prognostic score for renal cancer

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ABSTRACT

Purpose: The modified Glasgow prognostic Score (mGPS) incorporates C-reactive protein and albumin as a clinically useful marker of tumor behavior. The ability of the mGPS to predict metastasis in localized renal cell carcinoma (RCC) remains unknown in an external validation cohort.

Patients and Methods: Patients with clinically localized clear cell RCC were followed for 1 year post-operatively. Metastases were identified radiologically. Patients were categorized by mGPS score as low-risk (mGPS = 0 points), intermediate-risk (mGPS = 1 point) and high-risk (mGPS = 2 points). Univariate, Kaplan-Meier and multivariate Cox regression analyses examined Recurrence-free survival (RFS) across patient and disease characteristics.

Results: Of the 129 patients in this study, 23.3% developed metastases. Of low, intermediate and high risk patients, 10.1%, 38.9% and 89.9% recurred during the study. After accounting for various patient and tumor characteristics in multivariate analysis including stage and grade, only mGPS was significantly associated with RFS. Compared with low-risk patients, intermediate- and high-risk patients experienced a 4-fold (hazard ratios [HR]: 4.035, 95% confidence interval [CI]: 1.312-12.415, $P = 0.015$) and 7-fold (HR: 7.012, 95% CI: 2.126-23.123 $P < 0.001$) risk of metastasis, respectively.

Conclusions: mGPS is a robust predictor of metastasis following potentially curative nephrectomy for localized RCC. Clinicians may consider mGPS as an adjunct to identify high-risk patients for possible enrollment into clinical trials or for patient counseling.

Key words: Albumin, biological markers, C-reactive protein, metastasis, renal cell carcinoma

INTRODUCTION

Over 50,000 Americans are diagnosed with renal cell carcinoma (RCC) annually.^[1] This number has increased significantly over the last three decades, in part due to increased radiologically-diagnosed tumors.^[2] Of these patients, the majority present with localized disease: Approximately 75% of patients with

radiologically-diagnosed tumors and approximately 50% with symptomatic tumors.^[2] Approximately, one-third of patients presenting with localized RCC will eventually experience either a local or distant recurrence following therapy.^[3,4]

Several studies have focused on systemic inflammatory markers, in particular C-reactive protein (CRP).^[2,5-9] CRP, an acute-phase reactant, primarily stimulates the innate immune system by facilitating phagocytosis, but also modulates the adaptive immunity.^[8,10] Elevated CRP levels reflect systemic inflammation and are associated with poor outcomes in heart disease, depression and nearly all malignancies.^[10-12] In RCC, tumor progression typically involves local production of proinflammatory molecules such as interleukin-6 (IL-6), which upregulate hepatic and intratumoral CRP production.^[10] Consequently, in RCC elevated pre-operative CRP is associated with poor outcomes (metastasis and mortality).^[2,5,7,8,13,14] While CRP remains a potent predictor of outcomes, several studies have noted the added benefit of considering hypoalbuminemia

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with CRP as measured by the Glasgow prognostic score (mGPS) as first described by McMillan *et al.*^[15-20] The mGPS scores patients based on CRP (CRP > 10 mg/L = 1 point) and albumin (albumin < 3.5 g/dL = 1 point) and categorizes them as low-risk (0 points), intermediate-risk (1 point) and high-risk (2 points). Patients with a CRP concentration elevation (>10 mg/L) and a decreased serum albumin concentration (< 3.5 mg/L) score 2. Those patients with an elevated CRP concentration (>10 mg/L) score 1 and finally patients with a CRP concentration of < 10 mg/L and any albumin level score 0.

Ramsey *et al.* noted the mGPS's potential for predicting outcomes in patients with metastatic RCC.^[21] In a study of 119 patients, intermediate and high-risk mGPS scores were associated with significantly poorer cancer-specific survival. However, the mGPS's prognostic potential for the development of metastases in patients with localized RCC has not been reported and not with an external validation study. Therefore, we conducted a prospective study to assess the mGPS's value in predicting 1 year Recurrence-free survival (RFS) among patients treated surgically for localized RCC. We hypothesized that increasing mGPS score would correlate with increased risk of recurrence.

PATIENTS AND METHODS

Patients

This prospective cohort study followed 129 patients for 1 year following potentially curative radical nephrectomy with negative surgical margins for clear cell RCC. Patients were recruited at Emory University Hospital between November 2006 and January 2008. Inclusion criteria consisted of clear cell histology and exclusion criteria consisted of T4, nodal or metastatic disease or age less than 18 years. No patients received systemic therapy following nephrectomy. The Emory University Institutional Review Board approved this protocol. Written informed consent was obtained from all participants prior to inclusion into the study registry.

Clinical and laboratory assessment

Patients were staged pathologically according to the 1997 TNM staging system for renal tumor classification^[22] and tumors were graded based on Fuhrman criteria.^[23] Staging was initially based on six stages (T1a, T1b, T2, T3a, T3b and T3c). However, one-way analysis of variance demonstrated no significant difference in outcomes between T1a and T1b and between T3a, T3b and T3c.

Prior to surgery, clinical stage, Eastern Cooperative Oncology Group-performance status, (ECOG-PS), routine laboratory measurements and CRP levels were assessed. The limit of detection of the assay for CRP was < 0.2 mg/L. The inter- and intra-assay variability for all laboratory values were < 10%. Post-operatively we assessed patients using the UCLA integrated staging system (UISS) (based on stage,

grade and ECOG-PS),^[24] the Mayo Clinic stage, size, grade, and necrosis (SSIGN) score (based on stage, nodal disease, tumor size, grade, tumor necrosis and metastases),^[25] and the Kattan clinical score (presenting symptoms, histology, tumor size and stage).^[26]

Outcome measures

This study employed assessed RFS. Metastases were diagnosed radiologically using computerized tomography and magnetic resonance imaging at routine follow-up visits.

Statistical analysis

Demographic and clinicopathological variables (except age and tumor size) were treated as categorical variables. All laboratory variables, age and tumor size were treated as continuous variables. Univariate analyses were performed to identify variables associated with 1 year RFS, Mann-Whitney U and Chi-squared analysis for categorical variables and *t*-test for continuous variables. Kaplan-Meier analyses were conducted to assess the impact of mGPS on RFS. Variables in univariate analysis with *P* ≤ 0.100 were included in multivariate analysis. Cox regression analyses with simultaneous entry regression were used to assess the association between potential contributing factors [Table 1] and RFS. The hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were obtained. Statistical

Table 1: Patient characteristics; univariate analysis of recurrence-free survival

Variables	All patients (N=129)	Univariate analysis RFS
Patient characteristics		
Age (year)-median (IQR)	62.0 (54.0-70.0)	<i>P</i> =0.622
Race (% white/black)	70.8/29.2	<i>P</i> =0.302
Sex (% male/female)	64.3/35.7	<i>P</i> =0.600
% developing metastasis	23.3	N/A
Clinical staging		
T-stage (% T1/T2/T3)	63.6/8.5/27.9	<i>P</i> <0.001
ECOG PS (% 0/1/2-4)	38.0/17.1/45.0	<i>P</i> =0.006
UISS (% 1-2/3-5)	17.8/82.2	<i>P</i> =0.044
SSIGN (% 0-2/3-5/□6)	55.0/27.1/17.8	<i>P</i> <0.001
Kattan (% <70/70-100/>100)	54.3/27.9/17.8	<i>P</i> <0.001
Pathology		
Tumor size (cm)-median (IQR)	4.5 (2.9-7.0)	<i>P</i> <0.001
Fuhrman grade (1/2/3/4)	5.4/35.7/45.7/13.2	<i>P</i> <0.001
% tumor necrosis	24.2	<i>P</i> =0.035
Pre-operative lab values		
Glasgow prognostic score (low-0/moderate-1/high-risk-2)	68.5/14.0/17.1	<i>P</i> <0.001

RFS=Recurrence-free survival, IQR=Interquartile range, ECOG=Eastern co-operative oncology group, PS=Performance status, UISS=UCLA integrated staging system, SSIGN=Mayo clinic stage, size, grade, and necrosis score, N/A=Not available

significance in this study was set at $P < 0.05$. Models were assessed for co-linearity and interaction. All analyses were performed using SPSS version 16.0 (SPSS Inc, Chicago, IL). Harrell's C was calculated using R Statistical Software.

RESULTS

Patient demographics

This study cohort consisted of 129 consecutive patients who underwent potentially curative nephrectomy for localized clear cell RCC. The majority of patients were male and white, with a median interquartile range (IQR) age of 62.0 (54.0-70.0) years [Table 1]. Of all patients, 63.6% presented with T-stage 1 disease, 8.5% with T2 disease and 27.9% presented with T3 disease. In addition, 5.4% presented with grade 1 disease, 35.7% presented with grade 2 disease and 45.7% presented with grade 3 disease and 13.2% presented with grade 4 disease. Of all patients, 23.3% developed metastases within 1 year of surgery. Median IQR follow-up period was 25.5 (12.0-32.4) months. Median IQR pre-operative CRP values for patients who did and did not develop metastases were 58.4 (8.8-132.2) and 2.9 (1.4-6.9) mg/L, respectively. Median IQR pre-operative albumin values for patients who did and did not develop metastases were 3.4 (2.7-3.6) and 3.7 (3.6-3.9) mg/L, respectively. Of the cohort, 62.0% were categorized by the mGPS as low-risk, 20.9% as intermediate-risk and 17.1% as high-risk.

Cox regression analysis of 1 year RFS

In all, 30 (23.3%) patients developed metastases. Univariate analysis identified several variables significantly associated with RFS: T-Stage and Fuhrman Grade; tumor size; tumor necrosis; UISS, SSIGN and Kattan clinical scores; and mGPS [Table 1]. These variables were included in multivariate analysis. After accounting for these variables, only, mGPS was significantly associated with 1 year RFS [Table 2]. Compared with low-risk patients, intermediate- and high-risk patients experienced a 4-fold (HR: 4.035, 95% CI: 1.312-12.415, $P = 0.015$) and 7-fold (HR: 7.012, 95% CI: 2.126-23.123 $P < 0.001$) risk of metastasis within 1 year of surgery, respectively. Harrell's C indicated that the model has good predictive ability ($C = 0.887$ 95% CI: 0.787, 0.987).

Kaplan-Meier analysis of 1 year RFS

Along with multivariate Cox regression, the relationship between mGPS and 1 year RFS was assessed using Kaplan-Meier analysis [Figure 1]. Of low-, intermediate- and

high-risk patients, 10.1%, 38.9% and 89.9% recurred. Mean (95% CI) RFS for low-, intermediate- and high-risk groups was 38.4 (36.4-40.4), 22.9 (15.6-30.2) and 6.5 (2.9-10.1), respectively. Compared with low-risk patients, intermediate- and high-risk patients suffered significantly higher probability of recurrence (log rank, $P < 0.001$).

DISCUSSION

Given the diversity in outcomes, investigators have sought prognostic markers of metastasis and mortality in RCC. These markers include hemoglobin, calcium and lactate dehydrogenase, platelets and CRP.^[2,5,7,8,9,14] Recent studies have improved prognostic potential through novel scores that combine these factors. In particular, the mGPS carries significant prognostic potential of poor outcomes in metastatic RCC and other diseases including pancreas, lung, liver and ovarian cancer, in a robust and clinically easy to use calculation.^[16-22] However, the mGPS's utility in localized RCC has not been assessed. Therefore, we conducted this prospective study. We hypothesized that increasing mGPS score would correlate with increased risk of recurrence.

Many currently use prediction models for survival after a diagnosis of renal cancer rely on post-operative pathological factors, including factors, which may not always be consistently measured, such as coagulative necrosis. Some

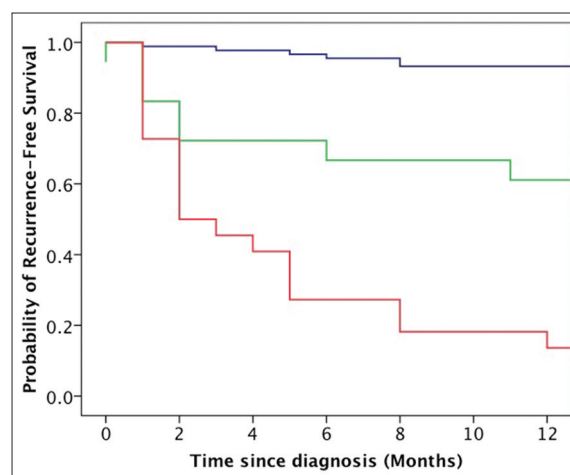


Figure 1: Kaplan-Meier curve of likelihood of developing metastases. Blue line is Glasgow prognostic Score (mGPS = 0), Green Line is mGPS = 1 and Red Line is mGPS = 2

Table 2: Multivariate cox regression analyses of predictors of recurrence-free survival among patients with localized renal cell carcinoma

Glasgow prognostic score	Crude HR	95% CI	P value	Adjusted HR*	95% CI	P value
Low-risk mGPS=0	Reference			Reference		
Moderate risk mGPS=1	5.458	2.019-14.752	0.001	4.035	1.312-12.415	0.015
High-risk mGPS=2	19.973	8.780-45.436	<0.001	7.012	2.126-23.123	0.001

*Adjusted for T-stage and Fuhrman grade; tumor size; tumor necrosis; ECOG-PS, UISS, SSIGN and Kattan clinical scores; pre-operative CRP and albumin, all with a $P > 0.100$. HR=Hazard ratio, CI=Confidence interval, mGPS=Modified Glasgow prognostic score, CRP=C-reactive protein

have to be plotted on a nomogram and all involve multiple factors. mGPS is a simple model, with only two factors to calculate, CRP and albumin. No knowledge of pathologic factors is required. Both of these tests can be performed world-wide and are inexpensive. For instance, a patient with mGPS score of 2, is unlikely to benefit from radical therapy and may be counseled as such and indeed choice of therapy may be goal directed toward palliation for example, depending upon the wishes of the patient and the treating physician.

Pre-operative mGPS predicts 1 year recurrence risk in localized RCC

The minority of patients presented with intermediate (14.0%) and high-risk (17.1%) disease [Table 1]. However, these patients accounted for the majority of metastases. Overall 23% of our cohort developed metastases within 1 year of potentially curative nephrectomy. While approximately 10.1% of low-risk patients relapsed with metastatic disease, approximately 38.9% and 89.9% of intermediate and high-risk patients developed metastases, respectively. It is important to understand that these patients likely had micrometastatic disease at diagnosis.

Consequently, univariate and multivariate analyses demonstrate mGPS's prognostic potential. Kaplan-Meier curves reveal the significant decline in RFS experienced by intermediate- and high- risk patients (log rank, $P < 0.001$) [Figure 1]. In multivariate analysis, after controlling for various patient and disease characteristics, only mGPS was significantly associated with RFS ($P < 0.001$) [Table 2]. Compared with low-risk patients, intermediate-risk patients exhibited 10-fold increased risk of metastasis (OR: 4.035, 95% CI: 1.312-12.415, $P = 0.015$). Most importantly, high-risk patients exhibited a 90-fold increased risk of metastasis (HR: 7.012, 95% CI: 2.126-23.123 $P < 0.001$). Overall, these findings suggest the robust potential of mGPS to predict recurrence in patients undergoing potentially curative nephrectomy for localized RCC.

Tumor aggression or host inadequacy?

RCC metastatic progression has been linked to inflammatory pathways such as the IL-6/CRP network.^[11] IL-6, produced in part by RCC cells, is a known mediator of inflammation and the primary inducer of CRP production in both hepatocytes and RCC tumor cells.^[11] Consequently, elevations in the IL-6/CRP axis have been strongly linked to tumor grade, tumor size and metastases.^[9] These correlations confirm the attribution of poor outcomes to the tumor.^[16]

However, the findings of the present study suggest that additional processes might contribute to disease recurrence. Specifically, mGPS consists of albumin, along with CRP. Previous studies have linked hypoalbuminemia with inflammation and cachexia of cancer.^[27] These studies suggest that low albumin reflects a catabolic state in which patients

lose muscle mass and experience metabolic disturbances.^[27,28] Muscle atrophy occurs through complex processes involving proteolytic systems, including lysosomes, proteasomes, calcium-dependent systems and caspases.^[29] These and other proteolytic processes also play critical roles in immune surveillance of cancer.^[30-32] Perhaps these systems have a finite capacity, such that cachectic emphasis on muscle catabolism de-emphasizes surveillance of tumor cells; thus, increasing the risk of metastasis. Alternatively, perhaps cachexia itself weakens the immune system, possibly even before other clinical wasting symptoms.^[33] Weakened immune function might also reduce immune surveillance to tumor cells, thereby predisposing cachectic patients with localized RCC to a higher risk of recurrence.

Study limitations

CRP and albumin were only measured once prior to surgery as part of a standard pre-operative laboratory panel at our institution. Future studies should achieve a larger pre-operative baseline to account for this stressor. In addition, only patients with clear cell RCC were included in this study as opposed to other histologies. We also did not account for socio-economic and lifestyle variables, such as BMI, smoking and diet, which can affect CRP and therefore be confounding variables.^[34] Our study also had a higher rate of recurrence than one might expect. This may reflect a selection bias. Though we studied consecutive patients, the patient population at our academic center may have more significant disease than the general population. Another concern is that our findings reflect a follow-up of only 1 year. Future studies should confirm this relationship over a longer period of time, although we wish to emphasize these short-term findings are striking, in terms of the early development of metastases and survival.

CONCLUSIONS

Despite a brief follow-up window, these findings suggest the clinical potential for the mGPS in the prediction of metastases in patients with localized clear cell RCC undergoing potentially curative nephrectomy. Given the increased risk of metastasis among patients, especially with high risk mGPS scores, clinicians should consider increasing the frequency of surveillance with increased mGPS score or potentially counsel patients about their high-risk of metastasis and potential enrollment into a clinical trial.

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