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ORIGINAL RESEARCH

Preoperative β2 Microglobulin Is a Prognostic Factor in Patients with Renal Cell Carcinoma and Normal Kidney Function

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Introduction: β2 microglobulin is a non-glycosylated protein synthesized by all nucleated cells. It has been utilized as a tumor marker in several different malignancies, however, studies examining its role in renal cell carcinoma (RCC) are limited.

Methods: Using the Emory kidney cancer database, patients with any stage or histology RCC who underwent partial or radical nephrectomy from 2014 to 2022 and had an available β2 microglobulin within 90 days before surgery were included. Following manufacturer's recommendation, β2 microglobulin ≥ 2.34 mg/L was considered elevated. Patient and surgical characteristics were recorded. Kaplan Meier curves and multivariable Cox Hazards models were used to assess the association between an elevated β2 microglobulin and overall and cancer-specific survival. Subgroup analysis was performed between patients with and without renal dysfunction (defined as an estimated glomerular filtration rate (eGFR) of ≤ or > 60 mL/min/1.73m^2) and with and without metastatic disease.

Results: Of 429 patients who met inclusion criteria, 178 (41.5%) had an elevated preoperative β2 microglobulin. After adjusting for confounders, an elevated β2 microglobulin was independently associated with worse CSS (HR 2.08 [95% CI 1.20–3.60]; p = 0.009) and OS (HR 1.58 [95% CI 1.03–2.41]; p = 0.035) compared to a normal β2 microglobulin. On subgroup analysis, elevations in β2 microglobulin levels remained significantly associated with OS and CSS in patients with normal renal function and non-metastatic disease.

Conclusion: Preoperatively elevated β2 microglobulin levels are independently associated with worse OS and CSS in patients with RCC undergoing nephrectomy. The utility of β2 microglobulin as a prognostic indicator is most relevant for patients with normal renal function and non-metastatic disease.

Keywords: β2 microglobulin, eGFR, overall survival, cancer-specific survival, RCC

Introduction

Overall survival in renal cell carcinoma (RCC) is highly dependent on stage at diagnosis, with a 5-year survival of 93% for localized disease, 75% for regional disease, and 18% for metastatic disease.[1] Several prognostic nomograms exist for risk stratification and patient counseling, which rely on a combination of patient, oncologic, and laboratory characteristics.[2–5] Unfortunately, the laboratory results currently used in these nomograms lack specificity to RCC. In fact, there is currently no agreement on a single biomarker suitable for either prognostication or treatment response of localized or metastatic RCC. As such, there have been tremendous efforts to identify reliable urine and serum biomarkers to incorporate into the treatment paradigm for RCC. While some markers have shown promise, their clinical utility remains limited due to insufficient validation and standardization.[6]

β2 microglobulin is a non-glycosylated protein synthesized by all nucleated cells.[7] It forms an invariable light chain subunit which stabilizes the tertiary structure of the major histocompatibility complex (MHC) class I antigen, which is an

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essential component of the adaptive immune system.[7,8] β2 microglobulin is renally excreted; thus, impaired kidney function can independently increase serum levels.[9] Serum β2 microglobulin has successfully been used as a prognostic tumor marker in patients with hematological malignancies; however, its prognostic utility in other cancers is not well understood.[8,9]

Emory was among the first institutions to study β2 microglobulin as a potential target for cancer therapy in RCC.[9,10] To date, the largest study examining β2 microglobulin (among other biomarkers) in patients with RCC was performed in Italy by Lucarelli et al.[11] They found that an elevated preoperative β2 microglobulin level was associated with worse cancer specific survival (CSS) in 332 patients who underwent nephrectomy for RCC, but this relationship was not maintained on multivariable logistic regression. This study, like many others, excluded patients with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2. As such, the prognostic value of β2 microglobulin in RCC patients with reduced kidney function is even more poorly understood than in the general RCC population. Additionally, it has been demonstrated that elevated β2 microglobulin is more common in patients with metastatic disease as well as those with higher grade disease.[11,12] However, the impact of metastasis on the prognostic utility of β2 microglobulin in RCC has yet to be definitively determined. The primary aim of our study was to assess the prognostic utility of elevated preoperative serum β2 microglobulin for overall and cancer-specific survival at five years in patients with any stage any histology RCC who underwent extirpative surgery. Our secondary aim was to determine whether poor kidney function or the presence of metastatic disease reduces the prognostic utility of this biomarker.

Methods

Patient Selection and Data Acquisition

We retrospectively reviewed the prospectively maintained Emory University kidney cancer database for patients who underwent partial or radical nephrectomy for RCC from 2014 to 2022. Patients with any stage or histology RCC were included. Exclusion criteria included patients who had previously undergone nephrectomy, those missing stage data, or those with no available preoperative β2 microglobulin measurement within 90 days of surgery. For patients with multiple β2 microglobulin measurements available, the one closest to the date of surgery was used. There are no established abnormal β2 microglobulin serum thresholds in RCC. Like previous studies, the upper limit of normal for serum β2 microglobulin was set to 2.34 mg/L based on manufacturer recommendation (Optilite® Beta-2 microglobulin assay).[12] All measurements were performed within Emory Medical Laboratory utilizing the above assay. Patient characteristics including age, sex, race, smoking history, eGFR as defined by the Chronic Kidney Disease Epidemiology Cooperative (CKD-EPI) 2021, Eastern Cooperative Oncology Group (ECOG) performance status (PS), Charlson Comorbidity Index (CCI), American Society of Anesthesiology (ASA) classification, obesity (defined as body mass index [BMI] ≥ 30 kg/m^2), diabetes, and hypertension were recorded. Oncologic characteristics including pathologic tumor size, histology, pathologic T (pT) stage, Furhman nuclear grade, nodal status, presence of inferior vena cava (IVC) thrombus, and presence of necrosis were recorded. Histology was recorded as clear cell, papillary, chromophobe, or other. For patients with metastatic disease undergoing cytoreductive nephrectomy, details on any administered adjuvant systemic therapy were collected. All patients were followed until death or last follow-up, with a collection cutoff of April 2024. Patients with no further follow-up were censored at the time of last clinical contact. The primary outcomes of interest were overall survival (OS) and CSS at 5 years. Outcomes were cross referenced using the electronic medical record, the state of Georgia death registry, and the national (United States) death index.

Statistical Analysis

Continuous variables were calculated as median values with interquartile ranges (IQR), and categorical variables as counts and percentages. ANOVA and chi-square tests were used to compare differences between groups. Kaplan-Meier curves were used to estimate 5-year OS and CSS rates. The association between an abnormal β2 microglobulin with OS and CSS after nephrectomy was determined utilizing a multivariable Cox proportional hazards model. Patients were divided by those with metastatic disease at the time of surgery (cytoreductive) versus those who did not (curative intent). The variables used in this model included β2 microglobulin, age, sex, race, eGFR, ECOG PS, smoking, obesity, CCI,

pathologic stage, clear cell histology, RCC grade, tumor size, presence of IVC thrombus, and any systemic treatment following nephrectomy. Backward selection was performed to arrive at final models. Subgroup analyses were performed utilizing the same covariants in the final models. For this, patients were divided into two groups: patients with an eGFR between 15–60 mL/min/1.73m^2 and patients with an eGFR > 60 mL/min/1.73m^2. Collinearity and interaction were assessed and Harrell's concordance statistic estimates were calculated for each model. All statistical tests were two-sided with type 1 error set at 0.05. All analyses were performed using SAS version 9.4 (Cary, NC, USA).

Results

Cohort Characteristics

A total of 429 patients met inclusion criteria. The median follow-up time was 31.6 months (IQR 13.9–58 months) during which there were 76 mortality events. An elevated preoperative β2 microglobulin level ≥ 2.34 mg/L was observed in 178 (41.5%) patients. The median preoperative β2 microglobulin level for the cohort was 2.2 mg/L (IQR 1.7–3), and 1.9 mg/L (IQR 1.6–2.6) and 2.7 mg/L (IQR 2.1–3.5) for non-metastatic and metastatic patients, respectively. Patient and oncologic characteristics are reported in Table 1. In all, 162 (37.4%) patients underwent cytoreductive nephrectomy. Patients with an elevated β2 microglobulin tended to be older (median age 68.8 vs 60.8 years, p < 0.001), white (75.8% vs 65.7%, p = 0.016), and with more comorbidities (CCI 4+, 91.0% vs 59.8%, p < 0.001) compared to patients with normal β2 microglobulin levels. Additionally, patients with elevated β2 microglobulin levels were more likely to have advanced oncologic characteristics such as larger tumor size (median size 10.4 vs 5.3 cm, p < 0.001), higher T stage (pT3, 74.7% vs 43.0%; T4, 9% vs 1.2%, p < 0.001), higher nuclear grade (G3–G4, 92.9% vs 70.6%, p < 0.001), and metastatic disease (57.3% vs 23.9%, p < 0.001) compared to patients with normal β2 microglobulin levels.

β2 Microglobulin and Survival

Regarding to our primary outcome, patients with an elevated preoperative β2 microglobulin had worse 5-year OS (29.3% vs 56.9%, p < 0.0001) and CSS (61.2% vs 70.8%, p = 0.0005) compared to patients with a normal preoperative β2 microglobulin, respectively (Figure 1). After adjusting for potential confounders, an elevated β2 microglobulin remained independently associated with worse 5-year OS (HR 1.58 [95% CI 1.03–2.41], p = 0.035; Table 2) and CSS (HR 2.08 [95% CI 1.20–3.60], p = 0.009; Table 3).

β2 Microglobulin and Survival According to Kidney Function

An elevated β2 microglobulin was associated with worse 5-year OS (27.8% vs 44.4%; p = 0.0366) but not CSS (58.6% vs 66.4%, p = 0.4904) in patients with kidney dysfunction. In patients with normal kidney function, an elevated β2 microglobulin was associated with worse 5-year OS (33.6% vs 60.6%, p < 0.001) and CSS (53.3% vs.74.2%, p < 0.001) compared to those with normal β2 microglobulin levels. On multivariable analysis, an elevated β2 microglobulin level was independently associated with worse OS (HR 2.00 [95% CI 1.19–3.36], p = 0.009; Table 2) and CSS (HR 2.90 [95% CI 1.54–5.44], p < 0.001; Table 3) in patients with normal kidney function only.

β2 Microglobulin and Survival According to Metastatic Disease Status

In the subgroup analysis of patients undergoing curative intent surgery (non-metastatic), an elevated β2 microglobulin was associated with worse 5-year OS (57% vs 85.5%, p < 0.001) and CSS (80.7% vs 95.5%, p = 0.002) compared to those with a normal β2 microglobulin. Conversely, in the subgroup of patients undergoing cytoreductive nephrectomy (metastatic), an elevated β2 microglobulin was not significantly associated with worse 5-year OS (35.6% vs 45.7%, p = 0.023) or CSS (63% vs 80.5%, p = 0.548) compared to patients with a normal β2 microglobulin level (Figure 2). In multivariable Cox hazards model, an elevated β2 microglobulin was independently associated with worse OS (HR 2.99 [95% CI 1.37–6.54], p = 0.006; Table 4) and CSS (HR 4.55 [95% CI 1.24–16.77], p = 0.023; Table 5) in patients with non-metastatic disease only.

Table 1 Cohort Distribution of Patient and Surgical Characteristics

Covariant		**Preoperative β2 Microglobulin ≥ 2.34 mg/L**			
		No (N = 251)	**Yes (N = 178)**	**Total (N = 429)**	**p-value**
Age*		60.8 (50.8–67.7)	68.8 (59.8–74.3)	63.7 (55–71.1)	**< 0.001**
Male Sex		169 (67.3)	117 (65.7)	286 (66.67)	0.729
Race					**0.016**
	White	165 (65.7)	135 (75.8)	300 (69.93)	
	Black	69 (27.5)	28 (15.7)	97 (22.61)	
	Other	17 (6.8)	15 (8.4)	32 (7.46)	
Smoking history					0.652
	Current	19 (7.6)	16 (9)	35 (8.16)	
	Former	102 (40.6)	65 (36.5)	167 (38.93)	
	Never	130 (51.8)	97 (54.5)	227 (52.91)	
BMI ≥ 30		106 (42.2)	78 (43.8)	184 (42.89)	0.743
Diabetes		70 (27.9)	74 (41.6)	144 (33.57)	**0.003**
Hypertension		173 (68.9)	148 (83.1)	321 (74.83)	**< 0.001**
Charlson Comorbidity Index					**< 0.001**
	0–3	101 (40.2)	16 (9)	117 (27.27)	
	4+	150 (59.8)	162 (91)	312 (72.73)	
ASA Score					**< 0.001**
	1–2	71 (28.3)	18 (10.1)	89 (20.75)	
	3–4	176 (70.1)	157 (88.2)	333 (77.62)	
	Unknown	4 (1.6)	3 (1.7)	7 (1.63)	
ECOG Status ≥1					**< 0.001**
	0	238 (95.2)	140 (79.1)	378 (88.52)	
	≥1	12 (4.8)	37 (20.9)	49 (11.48)	
eGFR according to CKD-EPI 2021 (mL/min/ 1.73m2)*		76 (63–88)	59 (47–72)	68 (56–83)	**< 0.001**
RCC Tumor Histology					0.079
	Clear cell	184 (73.3)	144 (80.9)	328 (76.46)	
	Papillary	19 (7.6)	11 (6.2)	30 (6.99)	
	Chromophobe	24 (9.6)	6 (3.4)	30 (6.99)	
	Other	24 (9.6)	17 (9.6)	41 (9.56)	
Tumor size (cm)*		5.3 (3.3–8.5)	10.4 (7.4–13)	7.5 (4–11)	**< 0.001**

(*Continued*)

Table 1 (Continued).

Covariant		Preoperative β2 Microglobulin ≥ 2.34 mg/L			
		No (N = 251)	Yes (N = 178)	Total (N = 429)	p-value
pT-stage					**< 0.001**
	T1	117 (46.6)	23 (12.9)	140 (32.63)	
	T2	23 (9.2)	6 (3.4)	29 (6.76)	
	T3	108 (43)	133 (74.7)	241 (56.18)	
	T4	3 (1.2)	16 (9)	19 (4.43)	
Furhman grade					**< 0.001**
	G1-G2	65 (29.4)	12 (7.1)	77 (19.69)	
	G3-G4	156 (70.6)	158 (92.9)	314 (80.31)	
Nodal involvement**					**< 0.001**
	pN0	40 (15.9)	64 (36)	104 (24.24)	
	pN1	18 (7.2)	43 (24.2)	61 (14.22)	
	pNx	193 (76.9)	71 (39.9)	264 (61.54)	
IVC thrombus		37 (14.7)	91 (51.1)	128 (29.84)	**< 0.001**
Necrosis		86 (34.3)	132 (74.2)	218 (50.82)	**< 0.001**
Cytoreductive nephrectomy		60 (23.9)	102 (57.3)	162 (37.76)	**< 0.001**
Receipt of neoadjuvant systemic treatment		8 (3.2)	7 (3.9)	15 (3.5)	0.679
Receipt of any systemic treatment		55 (21.9)	65 (36.5)	120 (27.97)	**< 0.001**
Systemic treatment within 1 year of surgery		37 (14.7)	46 (25.8)	83 (19.35)	**0.004**

Notes: Frequencies reported as No. (%). Parametric p-value by ANOVA for numerical and chi-square test for categorical covariates. Statistically significant parametric p-values (< 0.05) are bolded. *Median (interquartile range). **Based on 2010 pN-classification, pNx denotes no dissection performed.

Abbreviations: BMI, Body Mass Index; ASA Score, American Society of Anesthesiologists' Score; ECOG Status, Eastern Cooperative Oncology Group Status; eGFR, estimated glomerular function; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; RCC, Renal Cell Carcinoma; IVC, inferior vena cava.

Discussion

Here, we show that an elevated preoperative β2 microglobulin is independently associated with worse 5-year OS and CSS in patients with RCC. These results continue to build upon previous research on β2 microglobulin in RCC, which has previously been only significantly associated with survival on univariable analysis.[11,12] Additionally, the subgroup analyses undertaken in the present study demonstrated that a β2 microglobulin ≥ 2.34 mg/L has prognostic utility specifically in patients with an eGFR > 60 and no metastatic disease at the time of surgery. This is also a novel finding, as most other studies examining β2 microglobulin in RCC have excluded patients with renal dysfunction. While it is true that β2 microglobulin elevations can result from kidney dysfunction, our results demonstrate elevations in β2 microglobulin are independently associated with poor survival.

β2 Microglobulin and Disease Severity

Within our cohort, we observed that elevated β2 microglobulin correlated with both poor health status and worse pathology. This correlation has been described previously.[9,11] Rapid cell-turnover, a characteristic of more aggressive pathology, increases the amount of β2 microglobulin (a cell-surface protein) in serum. Additionally, proinflammatory

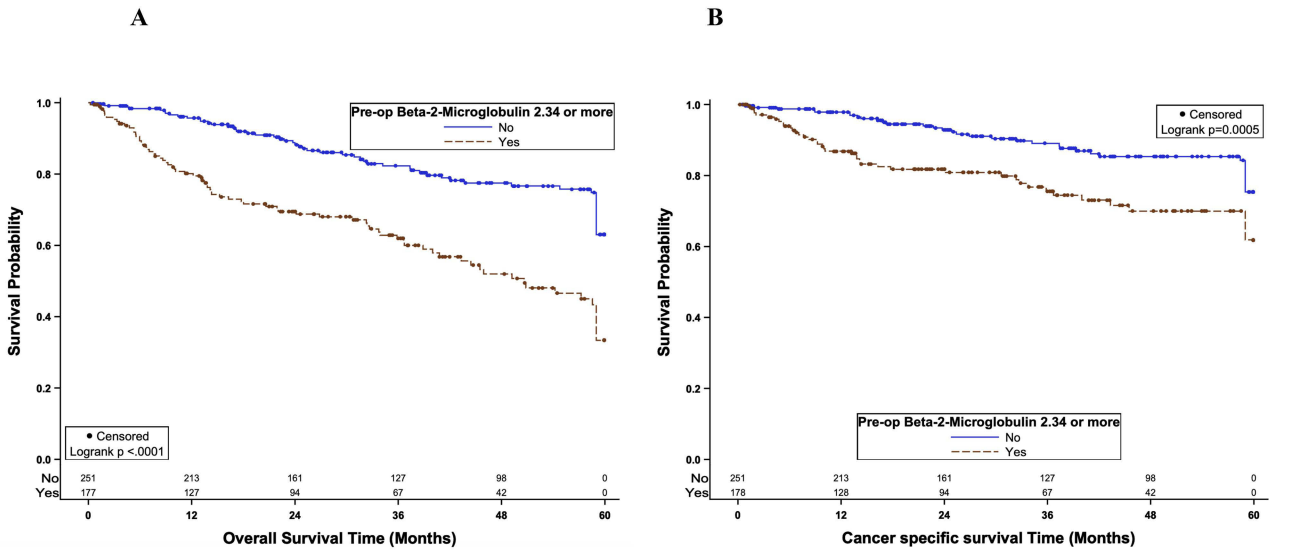

Figure 1 Kaplan-Meier curves for overall survival (**A**) and cancer-specific survival (**B**) in patients with any RCC and a β2 microglobulin ≥ 2.34 mg/L.

cytokines such as interferon alpha (IFN-α) and gamma (IFN-γ), are frequently elevated in RCC, and known to induce β2 microglobulin expression.[13–16] In examinations of β2 microglobulin in other common urologic malignancies, metastatic prostate cancer cell lines have been observed to shed higher levels of β2 microglobulin as compared to local/regional prostate cancer cell lines.[15] In an in vitro mouse model of prostate cancer, β2 microglobulin has demonstrated element binding protein (CREB) activation, which is considered to be an important molecular pathway for the development of metastasis.[9,17,18] This study is particularly notable for demonstrating a causative relationship between β2 microglobulin and metastatic potential. Our current study additionally demonstrated association of elevated β2 microglobulin and metastasis. More research is still needed to determine the exact nature of the relationship between β2 microglobulin and malignancy.

Table 2 Multivariable Cox Proportional Hazards Model for Overall Survival in Patients Undergoing Nephrectomy for Renal Cell Carcinoma with Number of Observations in the Original Data Set of 429

Covariates		n (%)	Hazard Ratio (95% CI)	p-value
β2 microglobulin ≥ 2.34 mg/L		178 (41.5)	1.58 (1.03–2.41)	**0.035**
Male sex		286 (66.7)	1.27 (0.83–1.93)	0.273
Race				
	Black	97 (22.6)	1.07 (0.67–1.71)	0.78
	Other	32 (7.5)	1.24 (0.59–2.61)	0.576
	White	300 (69.9)	Ref	
eGFR ≤ 60*		149 (34.7)	0.92 (0.62–1.38)	0.701
BMI ≥ 30		184 (42.9)	0.84 (0.58–1.22)	0.358
Charlson Comorbidity Index				
	CCI 4+	312 (72.7)	4.44 (1.73–11.45)	**0.002**
	CCI 0–3	117 (27.3)	Ref	

(*Continued*)

Table 2 (Continued).

Covariates		n (%)	Hazard Ratio (95% CI)	p-value
pT stage				
	III–IV	266 (62)	3.87 (1.94–7.70)	**< 0.001**
	I–II	163 (38)	Ref	
Clear cell histology		328 (76.5)	0.42 (0.27–0.66)	**< 0.001**
Furhman grade				
	G3-G4	314 (80.3)	0.80 (0.42–1.51)	0.487
	G1-G2	77 (19.7)	Ref	
IVC tumor thrombus		128 (29.8)	1.60 (1.08–2.37)	**0.019**
Any systemic treatment after nephrectomy		120 (28)	0.93 (0.64–1.36)	0.705
Subgroup analysis**				
β2 microglobulin ≥ 2.34 mg/L	eGFR ≤ 60*	99 (23.1)	1.51 (0.95–2.41)	0.083
	eGFR > 60*	79 (18.4)	2.00 (1.19–3.36)	**0.009**
β2 microglobulin < 2.34 mg/L	eGFR ≤ 60*	50 (11.7)	1.39 (0.74–2.60)	0.309
	eGFR > 60*	201 (46.9)	Ref	

Notes: *eGFR calculated using Chronic Kidney Disease Epidemiology Collaboration 2021 equation. Values displayed as mL/min/1.73m2. Frequencies reported as No. (%). Statistically significant parametric p-values (< 0.05) are bolded. Number of observations in the original data set = 429. Number of observations used = 390. Harrell's Concordance statistic estimate = 0.7724. **Subgroup analysis performed adjusting for the covariants above. Harrell's Concordance statistic estimate = 0.7728.
Abbreviations: eGFR, estimated glomerular function; BMI, Body Mass Index; IVC, Inferior Vena Cava.

Table 3 Multivariable Cox Proportional Hazards Model for Cancer-Specific Survival in Patients Undergoing Nephrectomy for Renal Cell Carcinoma

Covariates		n (%)	Hazard Ratio (95% CI)	p-value
β2 microglobulin ≥ 2.34 mg/L		178 (41.5)	2.08 (1.20–3.60)	**0.009**
Age 60+		262 (61.1)	0.98 (0.58–1.63)	0.923
Male sex		286 (66.7)	1.36 (0.78–2.37)	0.284
eGFR ≤ 60*		149 (34.7)	0.65 (0.37–1.14)	0.134
Race				
	Black	97 (22.6)	1.13 (0.62–2.08)	0.683
	Other	32 (7.5)	0.74 (0.26–2.09)	0.568
	White	300 (69.9)	Ref	
Clear cell histology		328 (76.5)	0.40 (0.23–0.71)	**0.002**
WHO/ISUP grade				
	G3-G4	314 (80.3)	2.25 (0.78–6.44)	0.132
	G1-G2	77 (19.7)	Ref	

(*Continued*)

Table 3 (Continued).

Covariates		n (%)	Hazard Ratio (95% CI)	p-value
Any systemic treatment post-nephrectomy or metastatic treatment		120 (28)	2.69 (1.64–4.40)	**< 0.001**
Subgroup analysis**				
β2 microglobulin ≥ 2.34 mg/L	eGFR ≤ 60*	99 (23.1)	1.31 (0.69–2.49)	0.410
	eGFR > 60*	79 (18.4)	2.90 (1.54–5.44)	**< 0.001**
β2 microglobulin < 2.34 mg/L	eGFR ≤ 60*	50 (11.7)	1.24 (0.55–2.78)	0.600
	eGFR > 60*	201 (46.9)	Ref	

Notes: *eGFR calculated using Chronic Kidney Disease Epidemiology Collaboration 2021 equation. Values displayed as mL/min/1.73m2. Frequencies reported as No. (%). Statistically significant parametric p-values (< 0.05) are bolded. Number of observations in the original data set = 429. Number of observations used = 391. Harrell's Concordance statistic estimate = 0.7029. **Subgroup analysis performed adjusting for the covariants above. Harrell's Concordance statistic estimate = 0.7055.

Abbreviations: eGFR, estimated glomerular function; WHO/ISUP, World Health Organization/International Society of Urological Pathology.

β2 Microglobulin and Survival in Previous Studies

Our findings affirm that patients with an elevated β2 microglobulin have worse survival. We show β2 microglobulin is an independent predictor of OS and CSS. A full summary of the previously cited studies examining beta2 microglobulin in RCC can be found in Supplementary Table 1.[11,12] Compared to Lucarelli et al and Rasmuson et al, our study consisted of a larger cohort with larger tumors and a higher proportion of patients with high nuclear grade and metastasis.[11,12] As such, our study was better powered to assess the relationship between β2 microglobulin and survival. Median β2 microglobulin levels among nonmetastatic RCC patients within our own study were comparable to those reported by Lucarelli et al (1.90 mg/L vs 1.85 mg/L).[11] Despite this, patients in their study had less advanced (pT1-2: 76.2% vs 58.1%) and less aggressive (G3-G4: 36.6% vs 70.5%) RCC pathology when compared to patients in our non-metastatic subgroup.[11] These differences may explain why an elevated β2 microglobulin was independently associated with worse survival in our cohort but not in the study by Lucerelli et al. While Rasmuson et al possessed a cohort of patients with tumor features more similar to our own, they did not stratify patients by metastatic disease status in their analysis and were likely underpowered with a smaller patient cohort. While none of these studies examined race, one previous study examining patients with HIV reported decreased levels of β2 microglobulin in black patients compared to white patients.[19] This correlation was also observed in our study, however, there was no significant difference in survival according to race.

β2 Microglobulin and Survival within Subgroups

Reduced kidney function increases β2 microglobulin levels regardless of cancer status. Thus, in our cohort CKD limits the prognostic ability of β2 microglobulin. Additionally, our results demonstrate that the prognostic ability of β2 microglobulin is seen in patients with non-metastatic disease. A majority of patients in our cohort with metastatic disease had β2 microglobulin levels greater than 2.34 mg/L; thus, the discriminative ability of this threshold may be inadequate for patients with metastatic disease or decreased renal function. Factors such as decreased renal clearance, increased tumor burden, and greater overall systemic inflammation can lead to an elevated baseline β2 microglobulin level. Increasing the upper limit of normal may help address this limitation; however, further research is required. In previous studies, abnormal β2 microglobulin thresholds were determined based on the manufacturer's recommendation in Rasmuson et al, while Lucerelli et al used a threshold of 2.6 mg/L without providing justification for its selection.[11,12] Given the lack of standardized β2 microglobulin thresholds, establishing clinically validated thresholds for RCC remains a critical need.

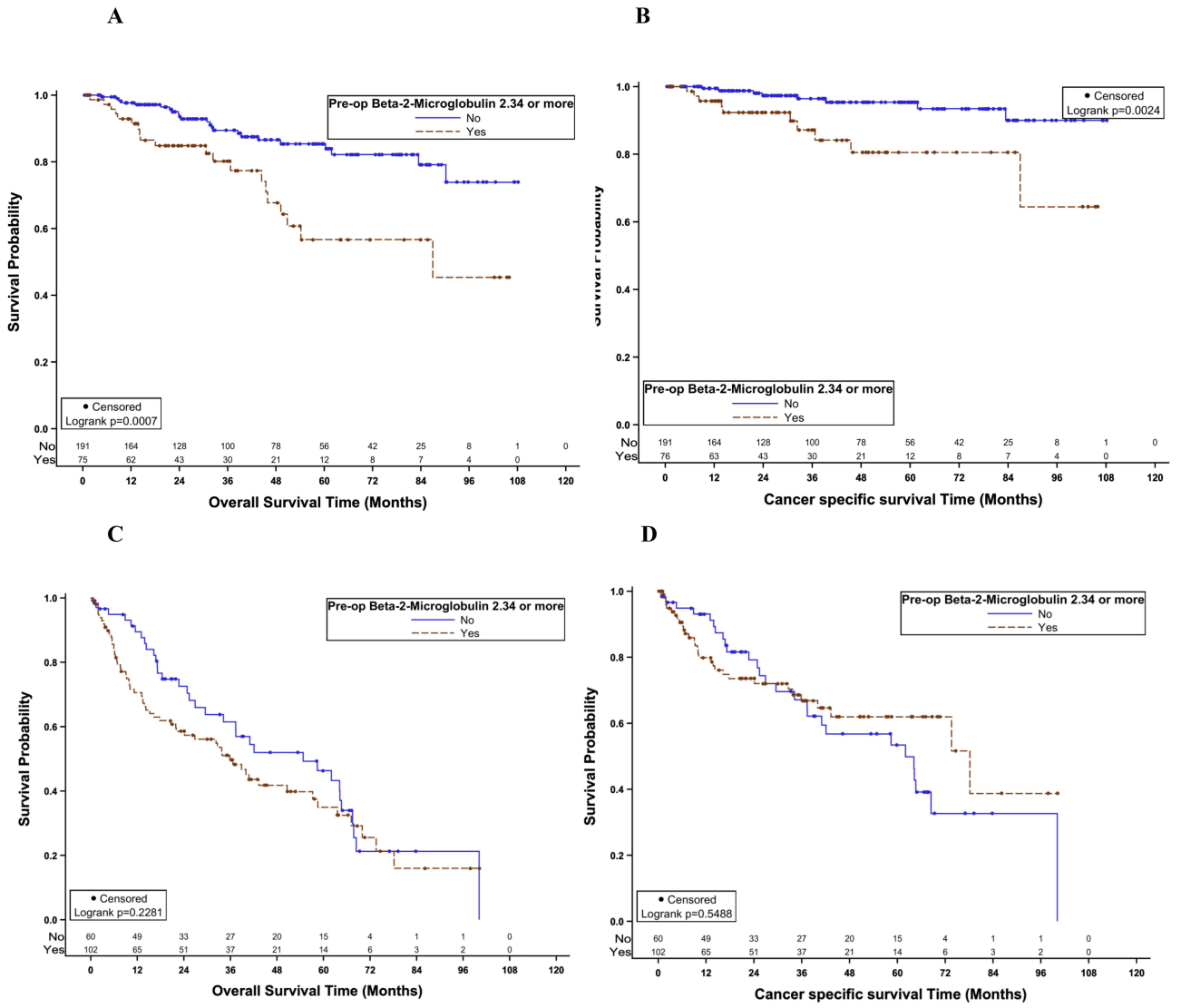

Figure 2 Kaplan-Meier curves illustrating the association between a β2 microglobulin ≥ 2.34 mg/L and overall survival (**A**) and cancer-specific survival (**B**) in patients with non-metastatic RCC and overall survival (**C**) and cancer-specific survival (**D**) in patients with metastatic RCC.

Study Limitations

Our study builds upon previous β2 microglobulin research by analyzing the largest cohort to date and including patients with CKD; however, it has its limitations. This is a retrospective single-institution study, we were unable to control patient and surgical factors that could confound our results. In patients who received systemic therapy, we were unable to control for the type or duration of treatment. Despite these limitations, this represents the largest study to date assessing the prognostic utility of β2 microglobulin in patients with RCC. Future work establishing β2 microglobulin thresholds, with special consideration for if this biomarker can be used for patients with abnormal kidney function and metastatic disease is needed. Research examining whether return of preoperatively elevated β2 microglobulin to normal levels after surgery confers better overall or cancer-specific survival is also warranted. β2 microglobulin could support preoperative risk stratification and postoperative surveillance planning; however, this should be confirmed with validation studies. Finally, future studies should examine the prognostic utility of β2 microglobulin in patients receiving immunotherapy and explore how β2 microglobulin coincides with current understanding of tumor immunology.

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Table 4 Multivariable Cox Proportional Hazards Model for Overall Survival in Patients Undergoing Nephrectomy for Renal Cell Carcinoma with Number of Observations in the Original Data Set of 162

Covariates		Non-Metastatic RCC*			Metastatic RCC**		
		n (%)	Hazard Ratio (95% CI)	p-value	n (%)	Hazard Ratio (95% CI)	p-value
β2 microglobulin ≥ 2.34 mg/L		76 (28.5)	2.99 (1.37–6.54)	**0.006**	102 (63)	0.93 (0.56–1.55)	0.779
Male sex		173 (64.8)	1.39 (0.62–3.13)	0.421	113 (69.8)	1.78 (1.05–3.02)	**0.032**
Race							
	Black	68 (25.5)	1.37 (0.60–3.13)	0.448	29 (17.9)	1.25 (0.66–2.37)	0.502
	Other	19 (7.1)	1.21 (0.26–5.58)	0.811	13 (8)	1.33 (0.56–3.14)	0.519
	White	180 (67.4)	Ref		120 (74.1)	Ref	
eGFR ≤ 60***		79 (29.6)	0.82 (0.36–1.84)	0.627	70 (43.2)	0.96 (0.59–1.54)	0.853
BMI ≥ 30		127 (47.6)	0.55 (0.27–1.14)	0.107	57 (35.2)	1.36 (0.85–2.17)	0.205
Charlson Comorbidity Index							
	CCI 4 +	158 (59.2)	2.68 (0.94–7.69)	0.066	154 (95.1)	****	
	CCI 0–3	109 (40.8)	Ref		8 (4.9)	Ref	
pT stage							
	III–IV	112 (41.9)	1.90 (0.73–4.91)	0.188	154 (95.1)	****	
	I–II	155 (58.1)	Ref		8 (4.9)	Ref	
Clear cell histology		195 (73)	0.25 (0.11–0.57)	**0.001**	133 (82.1)	0.56 (0.31–1.03)	0.062
Furhman grade							
	G3-G4	165 (70.5)	0.68 (0.25–1.86)	0.45	149 (94.9)	1.04 (0.41–2.63)	0.934
	G1-G2	69 (29.5)	Ref		8 (5.1)	Ref	
IVC tumor thrombus		43 (16.1)	2.84 (1.16–6.95)	**0.022**	85 (52.5)	1.43 (0.91–2.26)	0.125
Any systemic treatment after surgery		26 (9.7)	1.26 (0.50–3.17)	0.629	94 (58)	0.54 (0.34–0.86)	**0.010**
IMDC Risk Score							0.203
		poor risk			114 (70.4)	1.40 (0.83–2.35)	
		High Intermediate risk			48 (29.6)	Ref	

Notes: Statistically significant parametric p-values (< 0.05) are bolded. *Number of observations in the original data set = 267. Number of observations used = 233. Harrell's Concordance statistic estimate = 0.7912. * Number of observations in the original data set = 162. **Number of observations used = 157. Harrell's Concordance statistic estimate = 0.6664. ***calculated using Chronic Kidney Disease Epidemiology Collaboration 2021 equation. ****Insufficient data for analysis.

Abbreviations: RCC, renal cell carcinoma; CI, confidence interval; eGFR, estimated glomerular filtration rate; BMI, body mass index; pT stage, pathologic tumor; IVC, inferior vena cava; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

Table 5 Multivariable Cox Proportional Hazards Model for Cancer-Specific Survival in Patients Undergoing Nephrectomy for Renal Cell Carcinoma

Covariates		Non-Metastatic RCC			Metastatic RCC		
		n (%)	Hazard Ratio (95% CI)	p-value	n (%)	Hazard Ratio (95% CI)	p-value
β2 microglobulin ≥ 2.34 mg/L		76 (28.5)	4.55 (1.24–16.77)	**0.023**	102 (63)	0.95 (0.51–1.76)	0.872
Age 60+		162 (60.7)	4.85 (0.59–39.65)	0.141	100 (61.7)	0.82 (0.46–1.47)	0.51
Male sex		173 (64.8)	1.69 (0.44–6.59)	0.447	113 (69.8)	1.53 (0.80–2.93)	0.193
Race							
	Black	68 (25.5)	1.21 (0.34–4.30)	0.764	29 (17.9)	1.08 (0.52–2.24)	0.832
	Other	19 (7.1)	0.88 (0.10–7.58)	0.905	13 (8)	0.95 (0.28–3.19)	0.932
	White	180 (67.4)	Ref		120 (74.1)	Ref	
eGFR ≤ 60*		79 (29.6)	0.37 (0.09–1.47)	0.157	70 (43.2)	0.73 (0.39–1.36)	0.327
Furhman grade							
	G3-G4	165 (70.5)	1.84 (0.21–15.90)	0.581	149 (94.9)	1.22 (0.33–4.51)	0.765
	G1-G2	69 (29.5)	Ref		8 (5.1)	Ref	
Clear cell histology		195 (73)	0.36 (0.11–1.15)	0.086	133 (82.1)	0.31 (0.16–0.62)	**< 0.001**
Any systemic treatment after surgery		26 (9.7)	4.32 (1.29–14.47)	**0.018**	94 (58)	0.68 (0.37–1.24)	0.212
IMDC Score							
	Poor risk				114 (70.4)	1.62 (0.82–3.19)	0.164
	Favorable Intermediate risk				48 (29.6)	Ref	

Notes: Statistically significant parametric p-values (< 0.05) are bolded. *Number of observations in the original data set = 267. Number of observations used = 234. Harrell's Concordance statistic estimate = 0.8397. **Number of observations in the original data set = 162. Number of observations used = 157. Harrell's Concordance statistic estimate = 0.6436. ***Calculated using Chronic Kidney Disease Epidemiology Collaboration 2021 equation.

Abbreviations: RCC, renal cell carcinoma; CI, confidence interval; eGFR, estimated glomerular filtration rate; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

Conclusions

Preoperative β2 microglobulin ≥ 2.34 mg/L is independently associated with worse OS and CSS in patients with RCC undergoing nephrectomy. This association is limited to patients with normal kidney function and non-metastatic disease. Given the current lack of reliable biomarkers in RCC, β2 microglobulin may offer clinical utility; however, future validation studies are needed to confirm.

Data Sharing Statement

Individual participant data that underlie the results reported in this article, after deidentification, can be made available upon reasonable request by investigators who provide a methodological sound proposal following publication. Proposals should be directed to the corresponding author. To gain access, data requestors will need to sign a data access agreement.

Ethics Approval and Informed Consent

Complete waiver of HIPAA authorization and informed consent was granted by the Emory University Institutional Review Board (study ID 00002846). The study described herein complies with the Declaration of Helsinki.

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