ORIGINAL PAPER

A comparison of renal cell carcinoma with tumor thrombus across North America, Central/South America, and South Korea

Maxwell Sandberg [1], Rachel Vancavage [2], Claudia Marie-Costa [3], Emily Ye [3], Mitchell Hayes [4], Justin Miller [5], Reuben Ben David [6], Kartik Patel [7], Kimberly Waggener [1], Brejjette Aljabi [7], SeokSoon Byun [8], Patricio García Marchiñena [9], Thiago Mourao [10], Charles Peyton [7], Reza Mehrazin [6], Philippe Spiess [4], Rafael Zanotti [10], Steven Chang [11], Stenio de Casio Zequi [10], Diego Abreu [12], Alejandro Rodriguez [1]

[1] Atrium Health Wake Forest Baptist Medical Center, Winston Salem, NC, USA;
[2] Albany Medical College, Albany, NY, USA;
[3] Wake Forest University School of Medicine, Winston Salem, NC, USA;
[4] Moffitt Cancer Institute, Tampa Bay, FL, USA
[5] University of South Florida School of Medicine, Tampa Bay, FL, USA;
[6] Icahn School of Medicine at Mount Sinai, New York, NY, USA;
[7] University of Alabama Birmingham School of Medicine, Birmingham, AL, USA;
[8] Seoul Bundang University Hospital, Seoul, South Korea;
[9] Hospital Italiano, Buenos Aires, Argentina;
[10] AC Camargo Cancer Institute, Sao Paulo, Brazil;
[11] Harvard Medical School, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Division of Urology, Boston, USA;
[12] Paseur Hospital, Division of Urology, Montevideo, Uruguay.

Summary

***Purpose:** With multi-institutional collaboration, the purpose of this study was to analyze geographical differences of renal cell carcinoma with tumor thrombus between patients in North America, Central/South America, and South Korea.*
***Materials and methods:** Patients with renal cell carcinoma and a tumor thrombus who underwent nephrectomy plus thrombectomy were retrospectively analyzed. Patients were from North America, Central/South America, and South Korea. All comparisons were done based on the region where a patient had their surgery and follow-up. Chi-squared test, analysis of variance, Kaplan-Meier survival with log-rank test, and Cox regression analysis were used.*
***Results:** A total of 478 patients were included, 212 from North America, 209 from Central/South America, and 57 from South Korea. Of note, thrombus level was different using the Neves classification system between regions ($p < 0.001$), with a greater thrombus level in Central/South America. Surgical approach differed, with laparoscopic cases done most often in Central/South America and robotic in North America ($p < 0.001$). Tumor grade was lowest in South Korea ($p < 0.001$) and stage ($p < 0.001$) greatest in Central/South America. Overall survival was greater in South Korea compared to Central/South America ($p = 0.026$). Cancer-specific survival was greater in South Korea relative to North America and Central/South America ($p = 0.026$).*
***Conclusions:** Patients from North America, Central/South America, and South Korea diagnosed with renal cell carcinoma and tumor thrombus do not present the same and have different outcomes peri-/post-operatively. This includes important variables which have impacts on patient morbidity and mortality. Considering increased efforts on health equity in urology, the causes of these differences call for further investigation.*

KEY WORDS: *Renal cell carcinoma; Thrombus; Continental; Equity; Disparities.*

Submitted 13 March 2025; Accepted 5 April 2025

INTRODUCTION

Renal cell carcinoma (RCC) with a *tumor thrombus* (RCC-TT) carries a high morbidity and mortality. Incidence is estimated around 4-10%, and it is well-established that patients with a tumor thrombus tend to have poor prognosis (1, 2). Survival of these patients ranges at five years from 18%-57% depending on the study and patient characteristics being examined (3). There has recently been an important renewed focus on disparities in health access and survival outcomes in urology. Race has been studied for its association with inequities for RCC. Strong evidence exists that black race predisposes patients to worse treatment outcomes, and this research has highlighted the need for more equitable treatment in RCC to ensure the best outcomes for all patients (4, 5). While the impact of race is undoubtedly an area that necessitates further research for RCC, global disparities in presentation, management, and outcomes also exist and have lacked the appropriate attention in the literature currently.
It is estimated that there will be nearly 400,000 new cases of RCC worldwide and 175,000 deaths in the year 2024 (6). Current evidence shows that RCC incidence is higher in *North America* (NA) and Europe relative to other continents, and this has been theorized to be due to greater rates of abdominal imaging in these areas (7, 8). Nevertheless,

regions like Latin America and Asia, who historically have had a lower incidence of RCC, are expected to mirror that of NA and Europe in the coming years (9). Though there are few studies, survival from RCC has been examined across the world with results tending to point towards equivalent *overall survival* (OS) with worse *cancer-specific survival* (CSS), access to clinical trials, and/or guideline-based care in lower-income countries and regions of the world (6, 9). Perhaps most importantly, despite strong evidence that RCC is a cause for significant inequitable outcomes globally and is estimated to be responsible for approximately 2.5% of all cancer-related deaths across the world yearly, there is a paucity of research examining RCC-TT worldwide as most publications lack analysis on this important patient population (6, 7, 9, 10).

Over the last two years, a joint collaborative project was started to address global disparities in RCC-TT between institutions in NA, *Central/South America* (CSA) (via the Latin American Renal Cell Group), and South Korea known as the *Intercontinental Collaboration on Renal Cell Carcinoma* (ICORCC). The purpose of this study was to compare pre-, peri-, and post-operative management along with survival of patients with RCC-TT between NA, CSA, and South Korea using the ICORCC database. We hypothesized that no difference in presentation, operative management, or survival outcomes would exist by geography.

MATERIALS AND METHODS

This was a multi-institutional study conducted under institutional review board number IRB00096722 across NA, CSA, and South Korea. Data was retrospectively collected from 1999-present and stored on a master database as part of the ICORCC project. Participating institutions were from the United States of America, Mexico, Peru, Uruguay, Bolivia, Chile, Argentina, Brazil, and South Korea. All patients required both a diagnosis of RCC-TT on *computerized tomography* (CT) and/or *magnetic resonance imaging* (MRI) and had to have undergone radical nephrectomy with tumor thrombectomy for inclusion. A variety of preoperative variables were collected including patient age, gender, race, *diabetes mellitus* (DM), *chronic kidney disease* (CKD), symptoms at presentation (local and metastatic), Karnofsky performance status, *Charlson Comorbidity Index* (CCI), preoperative CT chest scan, preoperative tumor size, and presence of preoperative metastasis. Perioperative variables were surgical approach, operative time, tumor grade, tumor stage, tumor pathologic characteristics (necrosis, sarcomatoid, rhabdoid), *lymph node* (LN) dissection, and soft tissue margin positivity. Postoperative variables were metastasis after surgery, *metastasis-free survival* (MFS), follow-up time, OS, and CSS.

Local symptoms were defined as flank pain and/or palpable abdominal or flank mass. Metastatic symptoms were shortness of breath, chest pain, hemoptysis, bone pain/swelling, jaundice, seizures, fever, weight loss, or dizziness. For patients with preoperative metastatic location information available, locations were defined as the lungs, bone, liver, brain, retroperitoneum, regional lymph nodes, adrenal gland, and "*other regions*". Thrombus level was classified according to the Neves classification system (11). Preoperative tumor size was taken as the greatest dimension of tumor size on CT or MRI imaging as closest to the date of surgery. Systemic therapy was defined as any use/combination of chemotherapy (chemo), immunotherapy (immuno), or targeted therapy (targeted) for treating RCC-TT either before or after surgery. A minority of patients did not have complete data on the specific systemic therapeutic used and were defined as "*unknown*". Surgical approach was classified as either open, laparoscopic (pure or hand-assist), or robotic. Tumors were staged according to the TNM classification system and graded according to the International Society of Urological Pathology grading system (12, 13).

Patients were classified according to geographic location where they underwent primary surgery for their RCC-TT and received most of their postoperative care (*NA, CSA, or South Korea*). *Analysis of variance* (ANOVA) was run to compare continuous variables by geographic location. Chi-squared test was used to compare categorical variables by geographic location. Kaplan-Meier survival curves with log-rank test were used to compare OS, MFS, and CSS by geographic location. Additionally, a cox-regression analysis model for OS and CSS was also performed using variables with $p < 0.05$ and/or clinical relevance. Patients with missing values for a particular variable were excluded from that analysis. Significance was set to $p < 0.05$ and conducted using SPSS Statistics Version 28 (*Armonk, NY*).

RESULTS

A total of 478 patients were included in the study, 212 from NA, 209 from CSA, and 57 from South Korea (Table 1;

Variable		NA	CSA	South Korea	P-value
N		212	209	57	-
Age (years)		63.1 (10.9)	61.3 (12.4)	61.1 (10.9)	0.282
BMI		29.3 (6.6)	27.3 (4.7)	23.4 (3.4)	< 0.001
Female		64 (30.2)	52 (24.9)	12 (21.1)	0.273
Race	Caucasian	163/208 (78.4)	70/169 (41.4)	0	< 0.001
	Black	24/208 (11.5)	7/169 (4.1)	0	
	Hispanic	0	84/169 (49.7)	0	
	Asian	12/208 (5.8)	8/169 (4.7)	57 (100)	
	Other	9/208 (4.3)	0	0	
Active smoker		32 (15.1)	24 (11.5)	6 (10.5)	0.612
Former smoker		97/205 (47.3)	75 /172 (43.6)	12 (21.1)	0.002

Table 1.
Geographical comparisons for Renal Cell Carcinoma with Tumor Thrombus.
The following table compares pre-, peri-, and postoperative outcomes between each geographical region in the study.
Continuous variables are reported as means with standard deviations in parentheses aside from

DM		65 (30.7)	39 (18.7)	15 (26.3)	0.021
Hypertension		153 (72.2)	82 (39.2)	33 (57.9)	< 0.001
CKD		39 (18.4)	13 (6.2)	3 (5.3)	< 0.001
Karnofsky		90 (80-90)	90 (80-97.5)	90 (90-90)	0.692
CCI		6 (4-8)	5 (3-6)	1 (0-6)	< 0.001
Local symptoms at diagnosis		147 (69.3)	98 (46.9)	30 (52.6)	0.020
Metastatic symptoms at diagnosis		19 (9)	25 (12)	0	0.007
Preoperative chest CT		167 (78.8)	81 (38.8)	34 (59.6)	< 0.001
Preoperative tumor size (cm)		9.1 (3.3)	9.8 (3.6)	8.4 (3)	0.021
Thrombus level	I	109/204 (53.4)	29/93 (31.2)	32 (56.1)	< 0.001
	II	45/204 (22.1)	25/93 (26.9)	7 (12.3)	
	III	24/204 (11.8)	26/93 (28)	16 (28.1)	
	IV	26/204 (12.7)	13/93 (14)	2 (3.5)	
Metastatic before surgery		80/122 (65.6)	36/94 (38.3)	20/39 (51.3)	0.002
Multiple metastatic sites at presentation		27/80 (33.4)	24/36 (66.7)	8/20 (40)	0.128
Preoperative metastatic locale	Lung	15	13	0	-
	Bone	10	5	1	
	Liver	8	12	0	
	Brain	3	0	0	
	Retroperitoneum	16	16	3	
	Nodal	1	5	4	
	Adrenal	9	3	2	
	Other	10	1	7	
Approach	Open	107/211 (50.7)	107/185 (57.8)	50 (87.7)	< 0.001
	Laparoscopic	13/211 (6.2)	65/185 (35.1)	5 (8.8)	
	Robotic	91/211 (43.1)	13/185 (7)	2 (3.5)	
Operative time (minutes)		290.8 (122.7)	285.6 (138.3)	265 (121.1)	0.422
Length of stay (days)		6.6 (6)	15.5 (76.3)	12.3 (7.1)	0.199
Stage	T3a	63/182 (34.6)	40/153 (26.1)	0	< 0.001
	T3b	80/182 (44)	74/153 (48.4)	49 (86)	
	T3c	25/182 (13.7)	23/153 (15)	8 (14)	
	T4	14/182 (7.7)	16/153 (10.5)	0	
Grade	1	7/202 (3.5)	2/155 (1.3)	0	< 0.001
	2	36/202 (17.8)	17/155 (11)	2 (3.5)	
	3	101/202 (50)	54/155 (34.8)	33 (57.9)	
	4	58/202 (28.7)	82/155 (53)	22 (38.6)	
Sarcomatoid		28 (13.9)	82 (39.2)	9 (15.8)	< 0.001
Rhabdoid		24 (11.3)	9 (4.3)	0	0.371
Necrosis		119/201 (59.2)	112/166 (67.5)	43 (75.4)	0.048
Subtype	Clear cell	162/205 (79)	166/188 (88.3)	50 (87.7)	0.071
	Papillary	17/205 (8.3)	12/188 (6.4)	4 (7)	
	Other	26/205 (12.7)	10/188 (5.3)	3 (5.3)	
Lymph node dissection		100 (47.2)	67 (32.1)	25 (43.9)	0.004
Lymph nodes positive		0 (0-1)	0 (0-1)	0 (0-1)	0.123
Lymph nodes negative		2 (0-4)	2 (0-5)	5 (2-14.5)	0.003
Soft tissue margin positive		58 (27.4)	34 (16.3)	1 (1.8)	< 0.001
Systemic therapy		92 (43.3)	56 (26.8)	30 (52.6)	< 0.001
Systemic therapy type	Chemo	6	7	0	-
	Immuno	16	10	0	
	Targeted	26	34	12	
	Chemo and immuno	6	1	2	
	Chemo and targeted	3	0	0	
	Immuno and targeted	21	4	0	
	Chemo, immuno, targeted	1	0	3	
	Unknown	13	0	13	
Postoperative tumor size (cm)		9.6 (3.7)	9.7 (3.5)	9.3 (3.2)	0.768
Metastatic after surgery		42/122 (34.4)	58/94 (61.7)	19/39 (48.7)	< 0.001
Metastatic ever		122/211 (57.8)	94/181 (51.9)	39 (68.4)	0.075
Initial number of metastatic sites		1.5 (1.1)	2.2 (1.2)	1.1 (0.6)	< 0.001
Metastasis-free survival (months)		15.5 (25.8)	15.4 (21.9)	17.8 (23.7)	0.938
Overall survival (years)		1.9 (2.1)	1.3 (2)	3 (2.9)	0.012
Cancer-specific survival (years)		1.5 (1.5)	1.5 (1.3)	2.9 (2.9)	0.014
Dead		70 (33)	67 (32.1)	26 (45.6)	0.207
Cancer-specific death		46/53 (86.8)	28/54 (51.9)	21/26 (80.8)	< 0.001
Follow-up (years)		3.9 (6.4)	2.7 (3.5)	3.4 (5.4)	0.023

Karnofsky performance status, Charlson Comorbidity Index, and the number of positive and negative lymph nodes which are medians with interquartile ranges in parentheses.
Categorical variables are reported as total numbers with percentage of the cohort in parentheses.
Associated p-values for each comparison are also provided.

Figure 1.
Geographical Differences.
The following figure shows each geographical region in the study: North America, Central/South America, and South Korea. Patients from the United States of America were labeled as "North America" in red, patients from South Korea were labeled as "South Korea" in blue, and all other regions were labeled as "Central/South America" in green.
Relevant demographic, peri-, and post-operative differences are shown. The most common thrombus level, tumor stage, and tumor grade are provided for each region. The total number of metastatic patients pre- and post-operatively are also shown. Means for overall survival and cancer specific survival are represented with standard deviation in parentheses.

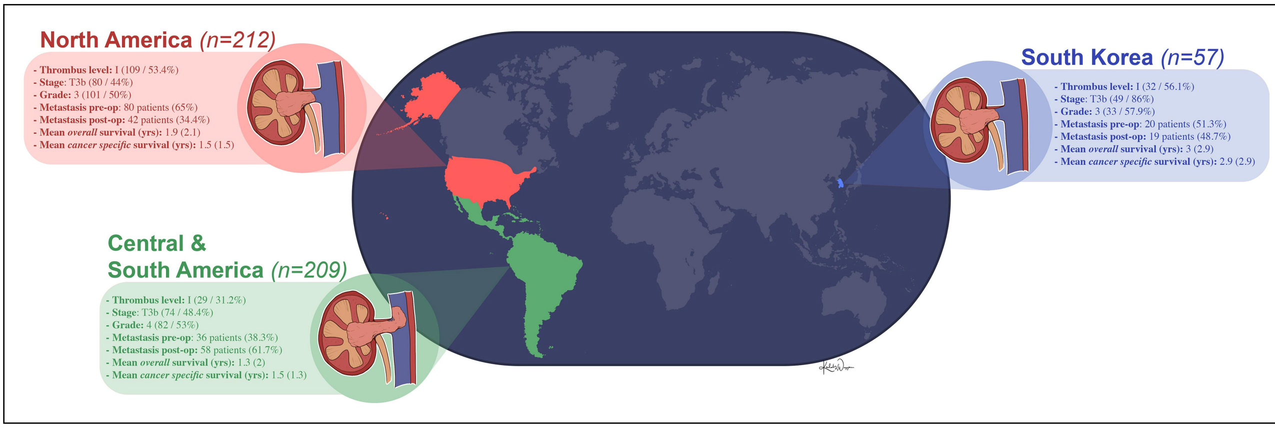


Figure 1). Mean age at surgery, gender, active smoking status, and Karnofsky performance status were not significantly different between the geographical regions ($p > 0.05$). CCI was greatest in NA patients (median-6) compared to both CSA (median-5) and South Korea (median-1; $p < 0.001$). BMI was significantly greater in NA patients compared to CSA and South Korean patients (29.3 versus 27.3 *versus* 23.4; $p < 0.001$). Race of the patients from each geographical region also was significantly different ($p < 0.001$). A greater percentage of patients were former smokers in NA (47.3%) and CSA (43.6%) in comparison to South Korea (21.1%; $p = 0.002$). DM was less prevalent in CSA patients (18.7%) relative to NA (30.7%) and South Korea (26.3%; $p = 0.021$). Hypertension was more prevalent in NA patients (72.2%) compared to CSA and South Korea ($p < 0.001$). CKD was also more likely in NA patients (18.4%) compared to CSA and South Korea ($p < 0.001$).

At diagnosis local symptoms were more likely in NA (69.3%) in comparison to CSA (46.9%) and South Korea (52.6%; $p = 0.020$). Metastatic symptoms were more common in NA (9%) and CSA (12%) relative to South Korea (0%; $p = 0.007$). Patients from NA (78.8%) and South Korea (59.6%) were more likely to undergo a preoperative chest CT scan compared to CSA (38.8%; $p < 0.001$). Preoperative tumor size was significantly smaller in South Korea (8.4 cm) relative to NA (9.1 cm) and CSA (9.8 cm; $p = 0.021$). Thrombus level also differed by region, with a greater average thrombus level in CSA ($p < 0.001$). NA had the greatest percentage of patients metastatic at diagnosis (65.6%; $p = 0.002$). The most common location of metastases seen preoperatively was the retroperitoneum for NA (N = 16) and CSA (N = 16), and "other regions" for South Korea (N = 7). No difference existed in the number of patients with multiple metastatic sites at presentation ($p > 0.05$). Operative approach also differed, with a significantly greater proportion of robotic cases in NA (43.1%) and a greater proportion of laparoscopic cases in CSA (35.1%) (Figure 2;

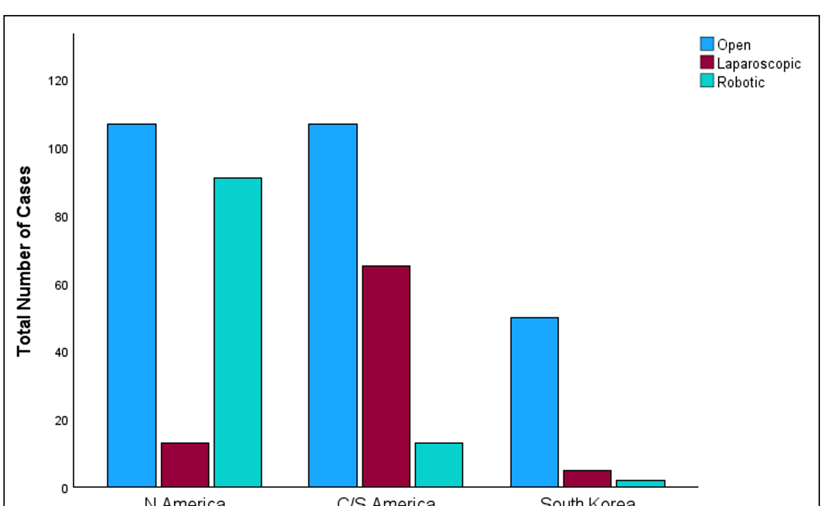
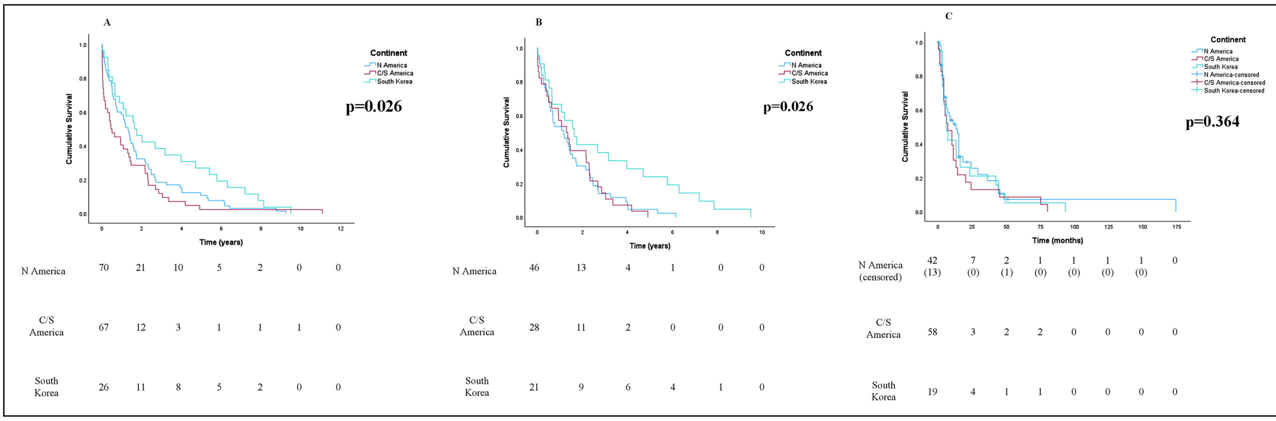


Figure 2.
Operative Approach by Geographical Region.
The following figure shows all operations performed in each of the three geographical regions: North America, Central/South America, and South Korea. Each bar represents a specific operative approach, which was either open, laparoscopic, or robotic.
Number of operations is on the y-axis and geographical region is on the x-axis.

Figure 3.
Kaplan-Meier Survival Analysis by Geographical Region.
The following figure represents a Kaplan-Meier survival analysis comparison between North American patients, Central/South American patients, and South Korean patients in the study for (A) - overall survival and (B) - cancer-specific survival, and (C) - metastasis-free survival. The proportion of patients surviving at each time interval is shown on the y-axis and time is represented on the x-axis in years or months. Log-rank significance p-values are shown below the figure legends.
Number at risk tables of all patients experiencing the event of interest during the study are also provided below the graphs with censored patients in parentheses.

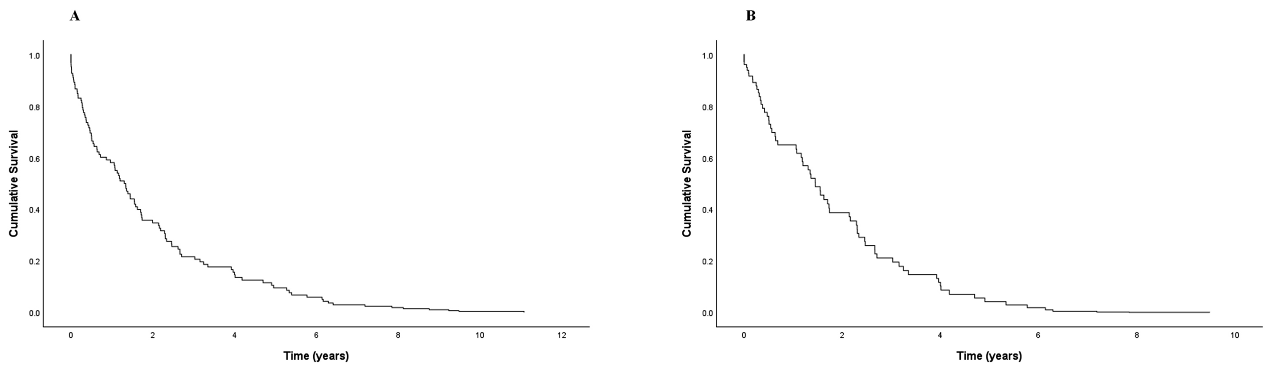


p < 0.001). Operative time and length of stay were similar (p > 0.05). Tumor stage was different by geographic region, with a greater percentage of T3b patients (86%) in South Korea (p < 0.001). Tumor grade was also different by region, with a greater proportion of grade 4 RCC in CSA (p < 0.001). On pathology, sarcomatoid variants were significantly more prevalent in CSA (39.2%), compared to NA and South Korea (p < 0.001). Tumor necrosis was most prevalent in NA patients (59.2%; p = 0.048). Tumor subtype was not different (p > 0.05). CSA had the lowest percentage of LN dissections performed (23.1%; p = 0.004). The median number of LNs positive for cancer were similar (p > 0.05), and the median number of negative LNs was greatest in South Korea (median-5; p = 0.003). Soft tissue margin positivity was least likely in South Korean patients (1.8%; p < 0.001).
CSA patients were significantly less likely to receive systemic therapy (26.8%) in comparison to NA (43.3%) and South Korean patients (52.6%; p < 0.001). The most common regimen was targeted therapy in NA (N = 24), CSA (N = 34), and South Korea (N = 12). Postoperative tumor size on gross specimen was similar by geographical region (p > 0.05). The percentage of patients metastatic at any time in the study window and MFS was not different (p > 0.05). The percentage of patients who went on to develop metastasis after surgery was highest in CSA (61.7%; p < 0.001). CSA patients had a greater number of initial metastatic sites (2.1) compared to the NA (1.5) and South Korea (1.1; p < 0.001). OS favored South Korean patients (3 years) in comparison to CSA (1.9 years) and on log-rank test this was significantly different (Figure 3; p = 0.026).
No OS survival difference existed between South Korea and NA, nor NA and CSA (p > 0.05). CSS favored South Korean patients (2.9 years) compared to both NA (1.5 years) and CSA (1.5 years) and on log-rank test this was significantly different (Figure 3; p = 0.026). On Cox regression analysis for OS no significant differences were seen (Table 2 and Figure 4; p > 0.05) and for CSS, CSA patients had a significantly greater hazard (HR) of cancer-specific death (Table 3 and Figure 4; HR = 0.44; p = 0.015).

Variable	B	S.E	P-value	Exp(B)	Confidence interval Upper	Lower
Geographical region			0.14			
North America	0.16	0.42	0.7	1.2	0.52	2.64
Central/South America	-0.45	0.27	0.1	0.64	0.38	1.1
Thrombus level	0.29	0.11	0.008	1.3	1.08	1.67
Approach			0.83			
Open	0.08	0.42	0.85	1.1	0.48	2.44
Laparoscopic	0.18	0.3	0.55	1.2	0.67	2.17
Tumor stage	-0.01	0.16	0.95	1	0.73	1.34
Tumor grade	0.22	0.19	0.25	1.2	0.86	1.8
Sarcomatoid pathology	0.37	0.32	0.26	1.4	0.77	2.71
Metastatic anytime	0.37	0.31	0.23	1.4	0.79	2.66
Systemic therapy	-0.8	0.27	0.003	0.45	0.27	0.77

Table 2.
Cox Regression Analysis for Overall Survival.
The following table is a cox regression analysis with death as the outcome of interest. S.E. is standard error, B represents the predicted hazard of the terminal event (death) and Exp(B) is the hazard ratio for each variable in the model. For geographical region, South Korea is the reference category and for approach, robotic surgery is the reference category. Associated p-values for each variable are also provided.

Figure 4.
Cox Regression Analysis for Overall Survival and Cancer-Specific Survival.
The following figure represents the survival curve from the cox regression model for (A) - overall survival and (B) - cancer-specific survival. The proportion of patients surviving at each time interval based on the mean of covariates in the model is shown on the y-axis and time is represented on the x-axis in years.



Variable	B	S.E	P-value	Exp(B)	Confidence interval	
					Upper	Lower
Geographical region			0.053			
North America	-0.29	0.47	0.54	0.75	0.3	1.9
Central/South America	-0.82	0.34	0.015	0.44	0.23	0.86
Thrombus level	0.003	0.13	0.98	1	0.77	1.3
Approach			0.98			
Open	-0.08	0.49	0.86	0.92	0.35	2.4
Laparoscopic	0.01	0.36	0.98	1	0.5	2.03
Tumor stage	0.19	0.18	0.3	1.2	0.84	1.73
Tumor grade	0.38	0.23	0.1	1.5	0.92	2.23
Sarcomatoid pathology	-0.01	0.39	0.97	0.99	0.46	2.13
Metastatic anytime	-0.81	0.42	0.06	0.45	0.2	1.02
Systemic therapy	-0.95	0.31	0.002	0.39	0.21	0.71

Table 2.
Cox Regression Analysis for Cancer-specific Survival.
The following table is a cox regression analysis with cancer-specific death as the outcome of interest.
B represents the predicted hazard of the terminal event (death) and Exp(B) is the adjusted hazard ratio for each variable in the model.
For geographical region, South Korea is the reference category and for approach, robotic surgery is the reference group.
Associated p-values for each variable are also provided.

Discussion

Several important differences were identified in how patients presented prior to surgery with RCC-TT. BMI was greater in the NA cohort, which has been linked to an increased likelihood of RCC, but results are mixed with respect to survival, as some studies show a protective effect (14). Unsurprisingly, race differed by geographical region, and as stated it is also known to impact patient outcomes for RCC and RCC-TT (4, 15). Patients from NA and CSA were more likely to be former smokers, which is a well-established factor predisposing to poor survival in RCC (16). Despite a variety of comorbidities differing by region, Karnofsky performance status was equivalent, and is known to correlate with poor outcomes for RCC-TT (17). Interestingly, CSA patients had the lowest prevalence of local symptoms at diagnosis but the highest rate of metastatic symptoms. This may indicate that these patients are more likely to present later in their disease course and fits with some publications showing a high rate of metastatic presentation for RCC in CSA countries (18). Nevertheless, NA patients had the highest percentage of metastasis at presentation. CSA patients had a significantly lower likelihood of undergoing a chest CT preoperatively, which should be done prior to surgery and is well-supported in the literature (19). This is of concern and the disparity is difficult to ascertain by current access to care alone. CT chest omission could be due in part to the large time span of the study including cases from 1999 onward where CT scan access and care guidelines were not as ubiquitous. Additionally, patients without a CT chest did have a chest x-ray in most instances. Nevertheless, this is one of the most significant discrepancies we identify in our study and requires additional investigation as to its causes. While the prognostic significance of thrombus level remains controversial, NA and South Korea had the most patients with a level I thrombus, and it has been shown that rates of abdominal imaging differ worldwide, potentially catching the thrombus before further spread to a higher level (7, 8).

Peri-operative management/outcomes also differed by region. NA had the greatest percentage of robotic surgery and CSA had the greatest percentage of laparoscopic. While the open approach has traditionally been employed for RCC-TT, a robotic approach has been described with equivalent to superior postoperative outcomes (20). With the ubiquitous use of robotic access across academic centers in NA, it is unsurprising this region had the greatest rate of robotic surgery. Pure/hand-assist laparoscopy has also been reported on for RCC-TT, but its use may be greater and success better than what is currently accepted, especially in CSA countries (21). A lower tumor stage was more prevalent in South Korea relative to both NA and CSA. It is worth noting that CSS was greatest in South Korean patients and tumor stage is associated with poor survival for RCC and RCC-TT (22). Tumor grade was highest in CSA, a poor prognostic factor for RCC-TT (23). Similarly, sarcomatoid variants were most common in CSA, which is linked to poor outcomes in patients treated surgically for RCC-TT (24). Rates of LN dissection were lowest in CSA, but the number of positive nodes on pathology was similar by region. This is relevant as research shows the number of positive LNs after radical nephrectomy and tumor thrombectomy is independently associated with worse CSS (25).

Multiple postoperative and survival outcomes differed by geography. The overall number of patients metastatic in the study window was similar, but there was a greater number of patients metastatic at presentation in NA and a greater number of metastatic sites at presentation in CSA. Further, CSA had the highest proportion of patients who developed metastasis after surgery. Despite these differences, MFS was similar amongst each region. This is particularly relevant as MFS has been shown to predict OS for RCC (26). In our population though, OS was not equivalent on primary analysis, and patients from South Korea had a significantly greater OS relative to CSA. CSS was also greatest in South Korean patients but whereas OS was greater only compared to CSA, CSS was greater than both CSA and NA. *Tian et al.* published on prognostic indicators for OS and CSS in RCC-TT patients, noting that lower tumor grade, lower tumor stage, lower thrombus level, and the use of systemic therapy predicted better outcomes (23). South Korean patients had lower tumor stages in the study, and CSA patients had greater tumor grades and thrombus level, which appears to fall in line with *Tian et al.*'s findings. Moreover, systemic therapy utilization was not equivalent across each region, with CSA patients having the lowest usage. Importantly, access to systemic therapy clinical trials in RCC differs across the world, and patients with higher risk RCC are not as well represented in these trials in CSA (6, 9, 10). On Cox regression analysis, when controlling for variables like tumor stage, grade, and metastasis, most survival differences disappeared, unsurprisingly showing that survival is multifactorial and additional factors besides geography are clearly at play. However, CSS was still worse in CSA, which is concerning and calls for further investigation.

Several limitations are worth acknowledging in our analysis. While the multi-continental and diverse nature of our cohort is a strength, we rely on the fact that the medical records at each participating institution are correct and up to date with patient information. Further, our findings are subject to the inherent biases of any retrospective review, and every patient in the study did not necessarily have a complete set of data to include in statistical analysis. While the Cox regression attempted to control for confounding variables, we cannot fully control for the fact that each geographical regions' demographic characteristics were not equivalent at baseline. In addition, NA, CSA, and South Korea are not homogeneous regions and there is variability in patient management within regions which we did not assess in this study. Despite using the same staging and grading systems for RCC, pathologist evaluation could have varied by both institution and geographical region and may account for some of the differences seen in sarcomatoid, rhabdoid, and necrotic tumor features. We also recognize that the external validity of our results is limited by the institutions that submitted data to participate in this study, all of which are tertiary academic centers. Nevertheless, we feel most cases of RCC-TT end up being referred to high-volume academic centers for definitive management and thus still see utility in our results.

Conclusions

This is one of the largest series of patients with RCC-TT in the literature, and one of the only publications to focus on geographical differences in presentation, management, and outcomes using collaboration via the ICORCC database. Given the need for stronger emphasis on health equity worldwide, our findings are particularly timely. While multiple studies have examined demographics such as race, gender, and functional status in RCC-TT, few have recognized how patient geography plays into this. A multifaceted approach should be taken to address the disparities we identify. There is no single fix to this complex patient population. However, what we do feel is that a global health emphasis on funding and investment in CSA is required to improve access to optimal patient care like systemic therapy, surgical robots, and the like. Moreover, new clinical trials need to be better about inclusion of patients and healthcare centers around the globe, rather than just the United States. We hope this study sheds light on important regional differences in the interest of narrowing worldwide gaps in healthcare and achieving more equitable outcomes in RCC-TT for all.

Declarations

Ethical approval: *The following study was approved by an institutional review board on 5/16/2023 under IRB00096722.*

Availability of data and material: *The data sets generated during and/or analyzed during the current study are not publicly available due patient privacy, but are available from the corresponding author on reasonable request.*

Competing interests: *None.*

Funding: *None.*

Authors' contributions: *Project design: MS, RV, CMC, EY, MH, JM, RBD, KP, KW, BA, SB, PM, TM, CP, RM, PS, RZ, SC, SZ, DA, AR. Data collection: MS, RV, CMC, EY, MH, JM, RBD, KP, KW, BA, SB, PM, TM, RM, RZ, SC. Visualization: MS, RV, CMC, EY, MH, SB, PM, TM, CP, RM, PS, RZ, SC, SZ, DA, AR. Statistical analysis: MS, RV, CP, PS, RZ, SC, SZ, DA, AR. Validation: MS, CP, PS, SC, AR. Drafting manuscript original draft: MS, RV, CMC, EY, CP, PS, SZ, AR. Drafting manuscript editing draft: MS, RV, CMC, EY, MH, JM, RBD, KP, KW, BA, SB, PM, TM, CP, RM, PS, RZ, SC, SZ, DA, AR.*

Acknowledgments: *None.*

References

1. Almatari AL, Sathe A, Wideman L, et al. Renal cell carcinoma with tumor thrombus: A review of relevant anatomy and surgical techniques for the general urologist. Urol Oncol 2023; 41:153-165.

2. Tilki D, Hu B, Nguyen HG, et al. Impact of synchronous metastasis distribution on cancer specific survival in renal cell carcinoma after radical nephrectomy with tumor thrombectomy. J Urol. 2015; 193:436-42.

3. Tang Q, Song Y, Li X, et al. Prognostic outcomes and risk factors for patients with renal cell carcinoma and venous tumor thrombus after radical nephrectomy and thrombectomy: The prognostic significance of venous tumor thrombus level. Biomed Res Int. 2015; 2015:163423.

4. Anastos H, Martini A, Waingankar N, et al. Black race may be associated with worse overall survival in renal cell carcinoma patients. Urol. Oncol. 2020; 38:938.e9-938.e17.

5. Gupta A, Roy AM. Racial and Ethnic Disparities in Survival Outcomes of Metastatic Renal Cell Carcinoma Patients Receiving Immunotherapy. Clin Genitourin Cancer. 2024; 22:102104.

6. Cirillo L, Innocenti S, Becherucci F. Global epidemiology of kidney cancer. Nephrol Dial Transplant. 2024; 39:920-928.

7. Bukavina L, Bensalah K, Bray F, et al. Epidemiology of Renal Cell Carcinoma: 2022 Update. Eur Urol. 2022; 82:529-542.

8. Capitanio U, Bensalah K, Bex A, et al. Epidemiology of Renal Cell Carcinoma. Eur Urol. 2019; 75:74-84.

9. Padala SA, Barsouk A, Thandra KC, et al. Epidemiology of renal cell carcinoma. World J Oncol. 2020; 11:79-87.

10. Fay AP, McKay RR, Lin X, et al. Impact of geographic regions on overall survival in patients with metastatic renal cell carcinoma: Results from an international clinical trials database. J Glob Oncol. 2018; 2018:1-14.

11. Neves RJ, Zincke H. Surgical Treatment of Renal Cancer with Vena Cava Extension. Br J Urol. 1987; 59:390-5.

12. Brierley J.D., Gospodarowicz M.K., Wittekind C. TNM Classification of Malignant Tumours, 8th edition. Union for International Cancer Control. Published online 2017. https://www.uicc.org/resources/tnm-classification-malignant-tumours-8th-edition.

13. Delahunt B, Cheville JC, Martignoni G, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J Surg Pathol. 2013; 37:1490-504.

14. Goebell PJ, Müller L, Hübner A, et al. Body mass index as independent predictor of overall survival in patients with advanced renal cell carcinoma at start of systemic treatment—Analyses from the German clinical RCC-Registry. Urol Oncol 2018; 36:433-472.

15. Dursun F, Patel R, Hui D, et al. The Latinx Disparity in Surgery for Kidney Cancer: Data from The South Texas Region. Kidney Cancer J. 2022; 20:6-13.

16. Xu Y, Qi Y, Zhang J, et al. The impact of smoking on survival in renal cell carcinoma: A systematic review and meta-analysis. Tumor Biol. 2014; 35:6633-40.

17. Kaptein FHJ, van der Hulle T, Braken SJE, et al. Prevalence, Treatment, and Prognosis of Tumor Thrombi in Renal Cell Carcinoma. JACC CardioOncol. 2022; 4:522-531.

18. Soares A, Monteiro FSM, da Trindade KM, et al. Advanced renal cell carcinoma management: the Latin American Cooperative Oncology Group (LACOG) and the Latin American Renal Cancer Group (LARCG) consensus update. J Cancer Res Clin Oncol. 2024; 150:183.

19. Woodruff DY, Van Veldhuizen P, Muehlebach G, et al. The perioperative management of an inferior vena caval tumor thrombus in patients with renal cell carcinoma. Urol. Oncol. 2013; 31:517-21.

20. Garg H, Psutka SP, Hakimi AA, et al. A Decade of Robotic-Assisted Radical Nephrectomy with Inferior Vena Cava Thrombectomy: A Systematic Review and Meta-Analysis of Perioperative Outcomes. J Urol. 2022; 208:542-560.

21. Sun Y, De Castro Abreu AL, Gill IS. Robotic inferior vena cava thrombus surgery: Novel strategies. Curr Opin Urol. 2014; 24:140-7.

22. Pandey J, Syed W. Renal Cancer. Treasure Island, FL:StatPearls Publishing; 2024. https://www.ncbi.nlm.nih.gov/books/NBK558975/. Accessed September 14, 2024

23. Tian J, Zeng X, Guan W, et al. Prognostic indicators for survival in renal cell carcinoma with venous thrombus and development of predictive nomograms. Transl Androl Urol. 2022; 11:1374-1388.

24. Yang B, Xia H, Xu C, et al. Impact of sarcomatoid differentiation and rhabdoid differentiation on prognosis for renal cell carcinoma with vena caval tumour thrombus treated surgically. BMC Urol. 2020; 20:14.

25. Tilki D, Chandrasekar T, Capitanio U, et al. Impact of lymph node dissection at the time of radical nephrectomy with tumor thrombectomy on oncological outcomes: Results from the International Renal Cell Carcinoma-Venous Thrombus Consortium (IRCC-VTC). Urol Oncol. 2018; 36:79.e11-79.e17.

26. Smith MR, Mehra M, Nair S, et al. Relationship Between Metastasis-free Survival and Overall Survival in Patients With Nonmetastatic Castration-resistant Prostate Cancer. Clin Genitourin Cancer. 2020; 18:e180-e189.

Correspondence

Maxwell Sandberg (Corresponding Author)
maxwellsandberg@msn.com
950 N Trade Street, Winston Salem, NC, 27101, USA

Rachel Vancavage
vancavr@amc.edu
Albany Medical College, Albany, NY, USA

Claudia Marie-Costa
cmcosta@wakehealth.edu
Emily Ye
ewye@wakehealth.edu
Alejandro Rodriguez
alrrodri@wakehealth.edu
Wake Forest Baptist Medical Center, Winston Salem, NC, USA, 27157

Mitchell Hayes
Mitchell.Hayes@moffitt.org
Moffitt Cancer Institute, Tampa Bay, FL, USA

Justin Miller
justinmiller1@usf.edu
University of South Florida School of Medicine, Tampa Bay, FL, USA

Reuben Ben David
Reuben.BenDavis@mountsinai.org
Reza Mehrazin
reza.mehrazin@mountsinai.org
Icahn School of Medicine at Mount Sinai, New York, NY, USA

Kartik Patel
kartikp@uab.edu
Brejjette Aljabi
bnaljabi@uab.edu

Charles Peyton
cpeyton@uabmc.edu
University of Alabama Birmingham School of Medicine, Birmingham, AL, USA

Kimberly Waggener
kwaggene@wakehealth.edu
Atrium Health Wake Forest Baptist Medical Center, Winston Salem, NC, USA, 27157

SeokSoon Byun
seoksoo.byeon@gmail.com
Seoul Bundang University Hospital, Seoul, South Korea

Patricio García Marchiñena
patricio.garcia@hospitalitaliano.org.ar
Hospital Italiano, Buenos Aires, Argentina

Thiago Mourao
thiago.mourao@accamargo.org.br
Rafael Zanotti
rafael.zannotti@accamargo.org.br
Stenio de Casio Zequi
stenio.zequi@accamargo.org.br
AC Camargo Cancer Institute, Sao Paulo, Brazil

Philippe Spiess
Philippe.Spiess@moffitt.org
Moffitt Cancer Institute, Tampa Bay, FL, USA

Steven Chang
slchang@bwh.harvard.edu
Harvard Medical School, Dana-Farber Cancer Institute, Brigham and Women's Hospital,
Division of Urology, 45 Francis Street, Boston, MA 02115, USA.

Diego Abreu
die.abreu@gmail.com
Paseur Hospital, Division of Urology, Montevideo, Uruguay