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Prognostic Factors for Patients with Renal Cell Carcinoma and Tumour Thrombus: A Review.

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ABSTRACT

Background

There has been a large set of studies on potential prognostic factors in patients with renal cell carcinoma and venous tumor thrombus. However, the epidemiological evidence for the effect on survival of many of them has not been consistent. Therefore, we conducted a literature review of the studies on the prognostic factors in patients with renal cancer and tumor thrombus extending into the venous system to identify determinants with the strongest predicting potential.

Methods

We performed a literature review by searching the PubMed database for articles published from its inception until November 2015 based on clinical relevance.

Results

There have been several anatomical, histological, clinical and molecular prognostic factors identified in patients with the renal cell carcinoma and tumor thrombus. Anatomical factors of the highest prognostic potential include extent of tumor thrombus, venous wall cancer invasion,

and metastases to the regional lymph nodes or distant organs. Whereas the most important histological prognostic factors include renal cell carcinoma subtype, tumour grade and presence of tumor necrosis, sarcomatoid features, micro vascular, as well as the renal collecting system cancer invasion. Both clinical and molecular determinants have received a very limited amount of attention in terms of prognostic usefulness in renal cell carcinoma patients with tumor thrombus.

Conclusions

Although several anatomical, histological, clinical and molecular factors have been associated with the prognosis in patients with renal cell carcinoma and venous tumor thrombus, in majority of cases the evidence is based on retrospective and limited in size studies. Therefore, further multicentre and prospective studies are needed to better understand determinants negatively affecting outcome in patients with renal cell carcinoma and tumor thrombus.

Keywords: Renal cell carcinoma; Tumour thrombus; Prognostic factors.

Abbreviations: **BMI**=Body Mass Index; **CI**=Confidence Interval; **CSS**=Cancer Specific Survival, **HR**=Hazard Ratio; **IVC**=Inferior Vena Cava; **N**=Nodes; **NS**=Not Statistically Significant; **M**=Distant Metastases; **RCC**=Renal Cell Carcinoma; **cRCC**=Clear Cell Renal Cell Carcinoma; **pRCC**=Papillary Renal Cell Carcinoma; **chRCC**=Chromophobe Renal Cell Carcinoma; **RV**=Renal Vein; **TT**=Tumor Thrombus; **VS**=Versus.

INTRODUCTION

Renal Cancer Carcinoma **(RCC)** is one of the very few malignancies with an ability to extend into the venous system, and to form a Tumor Thrombus **(TT)** involving the Renal Vein **(RV)**, Inferior Vena Cava **(IVC)**, or even the heart [1,2]. An estimated TT prevalence ranges between 4% and 36% of all RCC patients, and it is most commonly located within the RV (50% of cases) [3,4]. The atrium is one the least affected sites with merely 1% of all RCC cases affected [5].

The natural course of RCC with concomitant TT within the venous system, without radical nephrectomy and thrombectomy, has very poor outcome. Epidemiological data from the Surveillance, Epidemiology and End Results **(SEER)** database from the USA revealed that the average survival among these individuals was 5 months shorter, whereas annual disease specific survival was only 29% [6]. Notably, radical nephrectomy extended by thrombectomy can improve the annual disease specific survival to as high as 90% in those individuals [7].

Individualized cancer treatment involves tailoring therapy to optimize the patient's care with a minimal risk of toxicity. This is particularly relevant with regard to renal cancer, which has the greatest mortality rate amongst all malignancies of the urinary tract [8]. Identification of factors determining the course of disease can inform the decision about treatment. Prognostic factors represent an example of these as they can predict the disease course regardless the treatment used.

In this section, we will summaries the literature in terms of prognostic factors significantly associated with the prognosis of RCC patients with venous tumor thrombus.

LITERATURE SEARCH

Potentially relevant studies were identified through searching the Medline electronic database from its inception until November 2015. We considered all human research articles published in English, not classified as review, editorial, comment, letter, guideline, or news. The search strategy included the following terms: renal cell carcinoma, renal carcinoma, renal cancer, clear cell renal carcinoma, clear cell renal cancer, tumor thrombus, venous thrombus, venous tumor thrombus, prognostic factor, prognostic factors, survival, survival factor, survival factors and determinants of outcomes, mortality, and recurrence.

STUDY SELECTIONS

A flow chart of the selection of eligible studies is given in Figure 1.

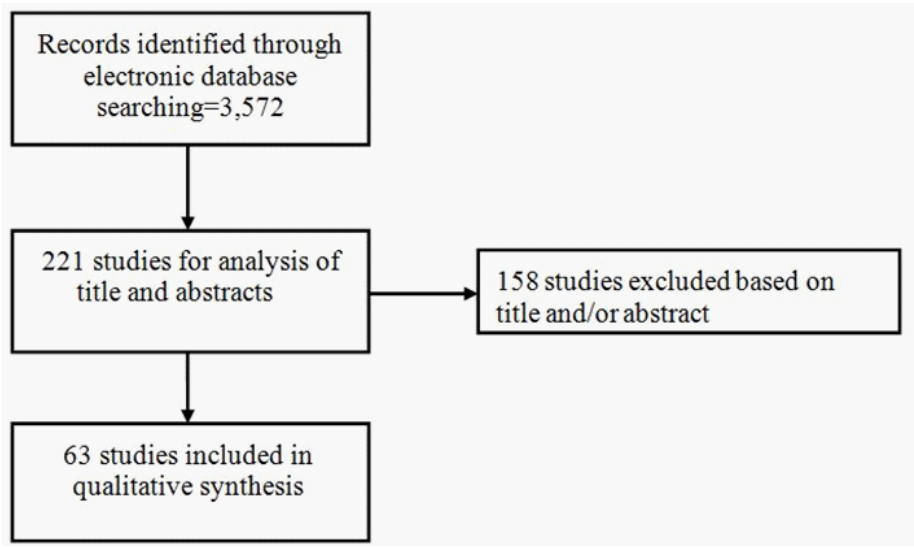

Figure 1: Flow diagram of studies identified.

Eligibility assessment was performed by 2 independent reviewers, in duplicate. The search strategy yielded 3,572 citations, of which 221 were considered potentially relevant. 158 of these were excluded after screening of titles and abstracts. The full texts of the remaining 63 studies were assessed and included in this review.

THE EVIDENCE

Anatomical Factors

Extent of tumor thrombus

Although the extent of tumor thrombus has been extensively investigated and is well recognized prognostic factor of RCC invading venous system, the way it affects the course of disease still

remains unclear and debatable [9-15]. Some available data suggest a negative prognostic value of vena caval involvement by TT, especially at the level above the diaphragm as compared to TT limited to renal vein only [9-11,16]. However, other study groups have failed to confirm this [12-15]. The reason of conflicting findings between studies reporting on the prognostic value of the TT extent could possibly be due to differences in terms of the inclusion criteria and number of study subjects, as well as, different operative techniques, duration of follow-up, but mainly due to study analyses adjusting for other clinico-pathological factors. A comparison between prognostic values in terms of mortality between the TT limited to the renal vein versus TT within the IVC based on all relevant studies has been shown in Table 1.

Table 1: A comparison between prognostic value in terms of mortality between the tumor thrombus limited to the renal vein versus tumour thrombus extending into the inferior vena cava.

Author, year	Nr of patients with TT in RV	Nr of patients with TT in IVC	Multivariate analysis of prognostic value of TT extent (p value)
Tang et al. 2015 [16]	93	76	0.036*
Antonelli et al., 2015[17]	99	48	0.001*
Nakayama et al., 2014[18]	7	21	0.028*
Tilki et al., 2013[19]	400	638	<0.001*
Cho et al., 2013[20]	88	36	NS
Pirola et al 2013[21]	40	27	NS
Ali i wsp., 2013[22]	12	38	<0.05*
Hirono et al., 2013[23]	152	132	0.0241*
Vergho et al., 2012[15]	5	45	0.31
Miyake et al., 2012[24]	65	70	NS
Spiess et al., 2012[25]	23	76	0.059
Sidana et al., 2012[26]	64	68	0.069
Martínez-Salamanca et al., 2011[27]	537	355	<0.005*
Wagner et al., 2009[13]	933	196	<0.001*
Klaver et al., 2008[28]	50	51	0.003*
Ficarra et al., 2007[29]	276	60	0.11
Klatte et al., 2007[14]	166	137	0.28
Leibovich et al., 2005[30]	283	139	<0.0001*
Moinzadeh et al., 2004[12]	46	68	0.0001*
Kim et al., 2004[31]	41	28	0.575
Blute et al., 2004[32]	191	171	0.002*
Gettman et al., 2003[33]	127	160	0.048*
Staehler et al., 2000[34]	19	51	NS
Ljungberg et al., 1995[35]	47	19	0.95

Key: TT=Tumour Thrombus; **RV**=Renal Vein; **IVC**=Inferior Vena Cava; **NS**=Not Statistically Significant; *=Statistically Significant.

Venous wall cancer invasion

As opposed to the extent of TT, there is no doubt about the poor prognostic value of direct venous wall cancer invasion, which worse than the sole presence of TT within the vessel lumen (Table 2) [13,20,23,35-37].

Table 2: The effect of venous wall cancer invasion on survival in renal cell carcinoma patients with tumor thrombus within the venous system.

Author, year	N	Follow-up (months)	Multivariate analysis HR (95%CI)	5-year survival without invasion vs. with invasion (%)	Mean survival without invasion vs. with invasion (months)
Cho et al., 2013[20]	124	29.0 (m)	4.4 (1.2-15.6)	---	---
Hirono et al., 2013[23]	280	40.4 (m)	---(---)	59 vs. 33	---
Manassero et al., 2011[36]	22	32.2 (a)	---(---)	---	24 vs. 8
Hatcher et al., 1991[37]	44	48(m)	---(---)	69 vs 57	115 vs. 64

Key: **N**=Number of RCC patients with TT; **a**=Mean; **m**=Median; **HR**=Hazard Ratio; **CI**=Confidence Interval; **vs**.=Versus; ---=no data.

Tumor size

Tumor size has been recognized as a negative prognostic factor in patients with RCC and TT extending into the venous system [13,23,24,26,28]. Table 3 presents studies which have identified tumour size as an important parameter in terms of survival. So far, no positive correlation between the tumour size and the RCC disease course has been shown, whereas the lack of prognostic value has been reported by Lambert et al. in their study on 118 RCC patients with TT extending into the venous system. In their report tumour size negatively correlated with overall survival in univariate analysis. However, a multivariate analysis failed to confirm this [39].

Table 3: The effect of tumor size on survival in renal cell carcinoma patients with tumour thrombus within the venous system.

Author, year	N	Tumour size cut-off (cm)	Follow-up (months)	Multivariate analysis HR (95%CI)	5-year survival tumour size cut-off ≤ vs > tumour size cut-off (%)
Whitson et al. 2013[38]	1875	Per each 5cm tumour growth	12 (m)	1.2 (1.0-1.4)	---
Hirono et al., 2013[23]	280	>8.3	40.4 (m)	--- (---)	59 vs 36
Miyake et al., 2012[24]	135	>10.0	32.7 (a)	2.80 (---)	60 vs 35
Sidana et al., 2012[26]	132	>7.5	30.3 (a)	1.16 (1.07-1.27)	---
Wagner et al., 2009[13]	1192	>7.0	61.4 (m)	---(---)	---

Key: N=Number of RCC patients with TT within the venous system; **a**=Mean; **m**=Median; **HR**=Hazard Ratio; **CI**=Confidence Interval; **vs.**=Versus; ---=no data.

Regional lymph nodes and distant metastases

Presence of metastases to regional lymph nodes at the time of diagnosis with RCC is an independent negative prognostic factor in terms of survival in patients with or without TT [9,12,30-32,40-42]. An association between the extent of TT within the IVC and the regional lymph nodes involvement, hence a more advanced disease, has been reported by Gettman et al. [33], Bissad et al. [43], Glazer et al. [40], as well as the Martinez-Salamanca team [27]. The latter study was a multicentre retrospective analysis of 1,215 patients, who underwent combined radical nephrectomy and thrombectomy in 11 urology centers in Europe and the USA. Higher level TT correlated more often with the regional lymph node involvement (TT within the RV: 20%, TT within the IVC below the diaphragm: 32%, TT within the IVC above the diaphragm: 36%).

However, these observations have not been confirmed by other researchers [12,44], hence bringing argument favouring radical treatment in all patients with confirmed TT (regardless TT extent), who are in good general condition, and have no metastases.

Cancer spread to the regional lymph nodes is considered an unfavorable prognostic sign significantly lowering survival in RCC patients [45,46]. These patients have 5-30% 5-year survival rate [47,48], whereas 5-year survival of those who undergo additional extended lymphadenectomy is: 52% (N1) vs 72%(N0), and 5-year cancer specific survival: 22% (N1) vs 78% (N0), proving lymphadenectomy very advantageous in terms of survival [45,46].

Similar to RCC without TT, further cancer spread to the lymph nodes significantly lowers survival in subjects with RCC and concomitant TT. Their 5-year cancer specific survival is 0-27%, as compared to those of N0: 17-63% [27,28,33,49].

Distant metastases carry a very grim prognosis whether or not TT is present [50-52]. The 5-year survival rates of N0M0 vs. N1M1 patients with TT confined to the RV are 55% vs. 35%, respectively; whereas in patients with TT confined to the infra diaphragmatic IVC the 5-year survival rates are: 55% vs. 24%, and in patients with TT confined to the supra diaphragmatic IVC the 5-year survival rates are: 36% vs. 23%, respectively for the N0M0 and N1M1disease stages [27]. Table 4 shows negative impact of distant metastases on overall survival in the RCC patients with confirmed TT within the venous system.

Table 4: Negative impact of distant metastases on overall survival in renal cancer patients with tumor thrombus extending into the venous system.

Author, year	N	Follow-up (months)	Multivariate analysis cM1 vs. cM0 HR (95%CI)	Overall survival cM0 vs. cM1 (%)
Tang et al. 2015 [16]	143	45 (m)	4.14 (2.17–7.93)	---
Antonelli et al., 2015 [17]	147	40.3	4.97 (2.62-9.43)	---
Nakayama et al., 2014[18]	61	33.7 (m)	6.0 (2.2-16.6)	50 months: 78 vs.35
Haddad et al., 2014[53]	166 of TT above the diaphragm	27.8 (m)	2.3 (1.2-4.6)	5-year:42 vs 7
Tilki et al., 2013[19]	1774	63.3 (ś)	cM1 vs.cM0: 0.4 (0.3-0.5)	---
Cho et al., 2013[20]	124	29.0 (m)	3.8 (1.8-8.0)	5-year: 64 vs. 18
Ali et al.. 2013[22]	50	38.0 (a)	---(---)	5-year: 62 vs. 0
Whitson et al.. 2013[38]	1875	12.0 (m)	3.3 (2.6-4.8)	12 months: 90 vs. 60
Hirono et al.. 2013[23]	280	40.4 (m)	---(---)	5-year: 51 vs. 31
Vergho et al.. 2012[15]	50	26.0 (m)	---(---)	5-year:50 vs. 7
Miyake et al.. 2012[24]	135	32.7 (a)	5.3 (---)	---
Spiess et al.. 2012[25]	56	42.0 (m)	2.9 (1.6-5.3)	---
Sidana et al.. 2012[26]	132	30.3 (a)	2.2 (1.1-4.4)	5-year: 43 vs. 22
Wagner et al. 2009[13]	1192	61.4 (m)	---(---)	---
Lambert et al. 2007[39]	118	17.8 (m)	---(---)	5-year: 60 vs.---
Gettman et al.. 2003[33]	303	90 (m)	---(---)	5-year: 42 vs. 7

Key: N= Number of RCC patients with TT within the venous system; **cM0**= No metastases clinically present; **cM1**- Metastases clinically present; **a**=Mean; **m**=Median; **HR**=Hazard ratio; **CI**=confidence interval; **vs**.=versus; ---=no data.

Cytoreductive nephrectomy

The advantage of thrombus extraction in patients with metastatic disease has not been clearly explained yet. This is mainly due to the fact that postoperative patient's survival does not justify such an extensive surgery, which in itself carries a very high perioperative risk of death. Staehler et al. have reported a significantly worse survival of patients with metastatic disease and concurent tumour thrombus (TT) (mean postoperative survival: 13months, 2-year survival rate was 26%) compared to those with TT but no metastases (34% 5-year postoperative survival rate) [34]. However, other authors reported much better results. Zisman et al. observed the 2-year survival rate as high as 76% in patients with non-metastatic disease and TT within the IVC, and 43% in those with metastatic disease and concurrent TT [49]. In the study by Parekh et al. the reported 3-year postoperative survival rates were 64% and 74%, respectively in subjects with metastatic disease and concurrent TT, and those without metastases but a TT present (p=0.16) [54].

Considering a high risk of complications and perioperative mortality, particularly in those individuals with level IV TT (tumour thrombus extending into the right atrium), as well as the fact that a metastatic disease does not necessarily mean a much shorter survival, the authors of

this book chapter have opted to carry on performing cytoreductive nephrectomy combined with thrombectomy in all patients with levels 0-III TT, and only in those with level IV TT whose ECOG performance status is 0 or 1. The remainder of patients is treated palliatively.

Perirenal fat invasion

There is large body of evidence supporting the poor prognostic value of perirenal fat cancer invasion on survival [13,17,19,29,30,33]. However, it is still unknown whether perirenal fat invasion is an independent prognostic factor only in patients with TT confined to the RV regardless lymph node and/or distant metastases, and not in subjects with non-metastatic disease (N0M0) who have TT confined to the IVC, as shown by Glazer [40], Gettman et al [33], and Wagner et al [13]. Contrasting findings have been reported by Leibovich et al [30], Bertini et al [55], and Tilki et al [19] who proved that perirenal fat invasion in patients with RCC and TT is a universal prognostic factor regardless the extent of TT.

Histological Factors

Histological subtype of Renal Cell Carcinoma (RCC)

Few studies have reported on possible relationship between the RCC histological subtype and survival [56,57]. The chromophobe RCC **(chRCC)** has more favourable prognosis than the papillary type, whereas the clear Cell RCC **(cRCC)** bears the worst prognosis. Of note, this correlation was only present in univariate analyses and disappeared after regression analyses, which took into account stage of the disease [56,57]. Despite there is no consensus regarding prognosis of different histological RCC subtypes, a locally advanced pRCC is generally considered to carry a better prognosis than if metastatic [58].

Several groups of researchers have recently examined the prognostic value of major histological RCC subtypes in subjects with established TT within the venous system [13,58-60]. Cianco et al analysed histological data of 87 RCC patients with TT (including 25 subjects with cRCC), who underwent radical nephrectomy [59]. In multivariate analysis the presence of non-clear cell RCC was associated with worse outcome in terms of prognosis and survival (Hazard Ratio **(HR)** =2.4, p=0.03). However, this observation was not confirmed by either Wagner et al [13] or Kaushik et al. [58].

Margulis et al. analysed the relationship between the histological RCC subtypes and survival in 2,157 RCC patients (245 cases of pRCC), of which 20 had a confirmed TT [60]. An unpaired comparison revealed that the 5-year cancer specific survival was worse in the pRCC subtype group as compared to the cRCC subtype group (35% vs. 66%, p=0.01). Similar results came from a multicentre study of 1,774 RCC patients with TT [18]. The histological subtypes within the study cohort were as follows: cRCC (89.9%), pRCC (8.5%), and chRCC (1.6%), and the estimated Cancer Specific Survival **(CSS)** rates were 54%, 36%, and 59%, respectively. In univariate analysis pRCC had statistically significantly worse survival rate than cRCC. The difference was still apparent despite limiting the analysis to N0M0 subjects. Multivariate analysis showed, however, that

the presence of pRCC was an independent prognostic factor for CSS. A multicentre study led by Tilki et al, which analysed data of 2,017 patients who underwent radical nephrectomy and thrombectomy, revealed that pRCC was indeed an independent poor prognostic factor (HR=1.61; CI=1.09-2.37), when compared with the cRCC subtype [42].

Interesting data in terms of relationship between the RCC histological subtype and survival have been reported by Kim et al. from their study on 74 RCC patients with concomitant TT (66 x cRCC, 12 x pRCC (4 x pRCC type 1, 8 x pRCC type 2) [61]. Type 2 pRCC was shown to harbour worse 5-year survival rates when compared with cRCC (0% vs. 53%). These results need to be interpreted with caution since this was a retrospective analysis on a small group of patients, plus the targeted treatment offered to those with a metastatic disease was not taken into consideration.

Moreover, some rarer histological subtypes of RCC i.e. Bellini duct carcinoma, renal medullary carcinoma, as well as sarcomatoid foci have been recognised as independent negative prognostic factors [38,62]. In the largest published study reporting mortality data of 1,875 RCC patients with TT from the SEER database led by the National Cancer Institute in the USA, the presence of Bellini duct carcinoma or sarcomatoid cancer foci proved independently unfavourable in terms of prognosis following multivariate regression analysis (HR=2.2 (CI=3.3)) [38].

Tumour grade

Tumour grade is typically assessed according to the Fuhrman classification system [63]. Several studies on RCC patients with or without TT have proven that tumour grade is an independent prognostic factor in terms of long-term survival [8,15,20,256,27,38,53,69]. Survival falls with worsening tumour grade. Hirono et al. [23] have reported a total 5-year survival rate of 53% in RCC patients with TT (for G1 and G2 tumours), and 37% 5-year survival rate for G3 tumours according to the Hermanek classification [65].

Tumour thrombus consistency

Association between the Tumour Thrombus **(TT)** consistency and survival in RCC patients was for the first time reported by Bertini et al. in 2011 [55]. In both N0M0 and metastatic disease stage, the friable TT consistency carried worse prognosis that the solid TT variant. Weiss et al. have indeed confirmed these observations, however, in their analysis TT consistency was not an independent prognostic marker of survival among patients with RCC [66]. In a retrospective study by Antonelli et al. the univariate analysis showed that the presence of friable TT correlated with some poor prognostic markers of survival (symptoms, distant metastases and lymph node involvement, greater tumour size, higher TT extent, necrosis and microvascular invasion), as well as worse the cancer specific and the overall survival. However, the predictive value of TT consistency on survival could not be replicated in multivariate analysis [16]. Table 5 shows the effect of TT consistency on overall survival in patients with RCC and TT within the venous system.

Table 5: Effect of tumor thrombus consistency on overall and cancer specific survival in patients with RCC and venous tumor thrombus.

Author, year	Solid TT	Friable TT	5-year CSS; Solid TT vs. Friable TT (%)	5-year OS; Solid TT vs. Friable TT (%)	Multivariate analysis Solid TT vs. Friable TT HR (p value)
Antonelli et al. 2015 [17]	79	68	61 vs. 60	59 vs. 57	1.03 (0.54-1.97)
Weiss et al. 2013[66]	130	70	---	89 vs. 29	1.3 (0.227)
Bertini et al. 2011[55]	107	67	47 vs. 21	---	0.6 (0.021)

Key: TT=Tumour Thrombus. **CSS**=Cancer Specific Survival; **OS**=Overall Survival; **HR**=Hazard Ratio.

Tumour necrosis

The presence of coagulative tumour necrosis is considered a negative prognostic marker of survival in all RCC patients with or without TT. In a multivariate regression analysis Haddad et al. have studied the presence of tumour necrosis as a poor prognostic marker of survival in patients with RCC and TT, HR=3.1 (1.4-6.7) [53]. Additionally, Blute et al. have reported 5-year CSS rates as 25% and 61% respectively for subjects with and without tumour necrosis within the TT [32].

Molecular Factors

The usefulness of molecular factors in predicting the disease course in patients with RCC and TT has not been so far examined on a large scale. Laird et al. have analyzed the proteomic markers expression such as: Ki67, p53, VEGF1, SLUG and SNAIL in RCC patients without TT and distant metastases, RCC patients with TT, and RCC patients with distant metastases. They have found that the expression was statistically greater in those with metastatic disease compared to patients with or without TT [67]. There were no differences in biomarker expression, however, between subjects with TT and those with distant metastases.

The expression analysis of eight different onco-micro RNAs in RCC patients with or without TT was first performed by Vergho et al. They have proven that the expression of three microRNAs: miR-21, miR-126 and miR-221 were significantly greater in patients with TT compared to those without TT [68]. Moreover, by determinig the level of miR-21, miR-221, and let-7b expression they were able to identify with 94% accuracy those individuals with TT either within the RV or IVC, and hence confirmed the utility of microRNA expression analysis as prognostic factors in patients with RCC and TT regardless the clinico-pathological features. However, due to limited number of patients participating in this study, the results should be interpreted with caution.

Laboratory Studies and Other Prognostic Factors

Laboratory studies have not been so far subject to the great amount of attention in terms of prognostic usefulness in RCC patients with TT. Multivariate analysis by Nakayama et al. showed that elevated levels of lactic dehydrogenase and C reactive protein significantly correlated with poor prognosis in this group of patients [17]. Haddad et al. reported that preoperatively raised

levels of alkaline phosphatase correlated with poor prognosis in patients with RCC and TT within the IVC extending beyond the level of hepatic veins [53]. Additionally Abel et al. reported that low preoperative levels of albumin in the serum were independently correlated with 90-day postoperative mortality in patients with RCC and TT within the IVC extending beyond the level of hepatic veins [69].

An interesting relationship between patient's Body Mass Index **(BMI)** and survival, as well as disease recurrence in patients with RCC and TT was reported by Cho et al. [20]. A BMI lower that 23 kg/m2 negatively correlated with cancer specific survival, as well as cancer recurrence. Whereas, obesity was independently associated with better outcomes in terms of survival and the risk of future recurrence. Similar observations were reported by Spiess et al. who showed that BMI>30 kg/m2 was associated with greater survival [25]. The mechanisms responsibe for these observations remain unclear. Several proteins and other mediators such as leptin and/or adiponectin have been proposed to possibly play a role as substances produced by the adipose tissue and slowing the RCC progression. Another explanation could be that low BMI is a marker of cachexia in those patients with advanced disease.

CONCLUSIONS

Recent years have brought a better understanding of the prognostic factors influencing the course of RCC associated with TT. Similar to RCC with no venous involvement, TT associated with RCC also heralds three major categories of prognostic factors, which can help predict its course. Anatomical factors of the highest prognostic potential include extent of tumor thrombus, venous wall cancer invasion, and metastases to the regional lymph nodes or distant organs. Whereas the most important histological prognostic factors include RCC subtype, tumor grade and presence of tumor necrosis, sarcomatoid features, micro vascular, as well as the renal collecting system cancer invasion. Some molecular factors seem also promising. However, in majority of cases the evidence is based on retrospective and limited in size studies. Therefore, further research preferably multicenter and prospective is needed to better understand the factors negatively affecting outcome in patients with RCC and TT.

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