Imaging predictors for assessment of inferior vena cava wall invasion in patients with renal cell carcinoma and inferior vena cava tumor thrombus: a retrospective study

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Abstract

Background: Renal cell carcinoma (RCC) has the propensity to lead to venous tumor thrombus (VTT). Nephrectomy with tumor thrombectomy is an effective treatment option but is a technically challenging surgical procedure that is accompanied by a high rate of complications. The aims of this study were to investigate pre-operative imaging parameters for the assessment of inferior vena cava (IVC) wall invasion due to a tumor thrombus in patients with RCC and to identify predictors from the intra-operative findings.

Methods: Clinical and imaging data were collected from 110 patients who underwent nephrectomy with IVC tumor thrombectomy (levels I–IV) for RCC and IVC tumor thrombus at the Peking University Third Hospital between May 2015 and March 2018. Univariable and multivariable logistic regression and receiver operating characteristic curves were used to assess the correlations between pre-operative imaging features and intra-operative macroscopic invasions of the IVC wall by tumor thrombus.

Results: Among the 110 patients, 41 underwent partial or segmental resection of IVC. There were univariate associations of pre-operative imaging parameters that could be used to predict the need for IVC resection, including those of the Mayo classification, maximum anterior-posterior (AP) diameter of the renal vein at the renal vein ostium (RVo), maximum AP diameter of the VTT at the RVo and IVC occlusion. For the multivariable analysis, the AP diameter of the VTT at the RVo and IVC occlusion were associated with a significantly increased risk of invasion of the IVC wall by tumor thrombus. The optimum imaging thresholds included an AP diameter of the VTT at the RVo larger than 17.0 mm and the presence of IVC occlusion, with which we predicted invasions of the IVC wall requiring IVC resection. The probabilities of intra-operative IVC resection for patients without both independent factors, with an AP diameter of the VTT at the RVo larger than 17.0 mm, with IVC occlusion, and with both concurrent factors were 5%, 23%, 56%, and 66%, respectively.

Conclusion: An increase in the AP VTT diameter at the RVo and the presence of complete occlusion of the IVC are independent risk factors for a high probability of IVC wall invasion by tumor thrombus.

Keywords: Renal cell carcinoma; Inferior vena cava; Thrombus; Imaging

Introduction

Renal cell carcinoma (RCC) accounts for 2% to 3% of all adult malignant neoplasms. In the United States, RCC accounts for 5% of new cancer cases and is the third most common cancer of the urinary system.[1] In China, RCC accounts for approximately 2% of all adult malignant tumors, making it the second most common urological malignancy, and the incidence is increasing.[2] One of the unique features of RCC is venous tumor thrombus (VTT) formation, which has been reported in 4% to 10% of all RCC cases.[4] VTTs can migrate through the renal vein to the inferior vena cava (IVC) and even to the right atrium in as many as 1% to 3% of all RCC patients.[3]

Nephrectomy with tumor thrombectomy is the most common treatment for patients with RCC and VTT,[4] with a survival rate significantly higher than that of those who only undergo radical nephrectomy.[5] In previous studies, the 1-year cancer-specific survival rate of untreated RCC patients with VTT was shown to be only 29%, whereas the overall 5-year survival rate of patients receiving surgical treatment was shown to be 40% to 65%.[5]

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During thrombectomy, partial or circumferential resection of the IVC is needed if there is evidence of tumor invasion into the IVC wall; however, the risk of surgery is generally high because the need for IVC resection is generally determined intra-operatively.[6] Therefore, accurate pre-operative predictions regarding the need for IVC resection are crucial. Previous studies have reported several imaging predictors of the need for IVC resection, albeit among small patient cohorts.[7,8] The results from the Mayo Clinic, which recently evaluated and internally validated the use of several radiologic features related to the need for IVC resection, were not corroborated outside the single institution.[9,10]

The objective of the present study, therefore, was to investigate pre-operative imaging parameters of IVC wall invasion that may be used to predict IVC resection at the time of tumor thrombectomy for patients with RCC with VTT, as well as to provide reference data for clinicians.

Methods

Ethical approval

As a retrospective study and data analysis were performed anonymously, this study was exempt from the ethical approval and informed consent from patients.

Patient selection

We identified 168 patients who underwent surgical treatment for RCC with VTT between May 2015 and March 2018. The VTT severity was categorized using the Mayo Clinic classification system.[11] Patients with level 0 VTT ($n = 51$) who did not undergo IVC resection and seven patients whose data were not available were excluded from the study. Therefore, 110 patients with histologically proven RCC and level I–IV VTT, all of whom received radical nephrectomy and vena cava thrombectomy, were included in the analysis. Whether the IVC wall was actually invaded was assessed and determined intra-operatively.

Clinical and imaging features

We recorded clinical characteristics of the patients pre-operatively, including their age and sex. The pre-operative magnetic resonance imaging (MRI) or computed tomography (CT) scans were then re-reviewed by one of two radiologists who were blinded to the surgical management plans selected for patients. The imaging data were analyzed to determine the following pre-determined features: the VTT level based on the Mayo Clinic classification system, the maximum diameter of the renal tumor, whether the tumor was on the right or left side, the maximum diameter of the bilateral renal vein at the renal vein ostium (RVo) in the anterior-posterior (AP) dimension, the maximum AP diameter of the VTT at the RVo, the presence of complete occlusion of the IVC by thrombus (defined as the absence of contrast flow alongside the tumor thrombus), and whether the proximal part of the VTT was smooth (defined as the absence of irregularity on the surface of the proximal part of VTT on CT or MRI).

Operation technique

The technique used for IVC tumor thrombectomy is as follows: in simple terms, through laparotomy and/or laparoscopy, the renal hilar vessels are exposed, and the renal artery is ligated; the ureter is ligated; the ipsilateral adrenal gland is explored; the contralateral renal vein is dissociated; the IVC behind the liver is exposed; and an infusion tube is used to block the IVC. In addition, the blood vessels are blocked in the following order: first, the IVC below the renal vein and the contralateral renal vein are blocked, the hepatic artery and portal vein are then blocked for level III–IV thrombus cases, and finally, the retrohepatic IVC is blocked. The IVC wall is incised, and the tumor thrombus is removed. The management strategy for vena cava tumor thrombus cases and the IVC depends on the level of the thrombus extension and whether the IVC wall is macroscopically invaded. A 4-0 prolene suture is used to stitch the IVC incision in a continuous way. If the VTT shows any megascopic adherence to the IVC wall, partial or circumferential vein resection is performed. Reconstruction of the vena cava is performed as follows: segmental resection of the IVC can be performed directly in patients with right RCC and VTT, and reconstruction of the IVC is not necessary because the left renal vein compensates sufficiently for collateral circulation. In patients with left RCC and VTT, the branches of the right renal vein are small and scarce, and sufficient collateral circulation cannot be established. Therefore, the right renal vein outflow tract should be reserved, lengthened or repaired with a vena cava patch.

Intra-operative evaluation, procedure, and observation parameters

Intra-operatively, wall invasion is recorded if the IVC thrombus shows any adherence to the IVC wall. The absence of IVC wall invasion was confirmed if the vena cava thrombus could be easily removed. If there are no signs of IVC invasion or resection injuries to the IVC lumen intra-operatively, the standard operative procedure for our institution is performed, involving a combination of tumor thrombectomy with subsequent rrhaphy using continuous polypropylene sutures. If tumor invasion is evident, IVC resection, either segmental or circumferential, is necessary. We observed whether pre-operative imaging parameters can be used to predict the need for IVC resection, as determined by the intra-operative macroscopic findings. To establish the predictive model, IVC resection was defined as any type of partial or segmental resection of the IVC.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (minimum-maximum); categorical variables are presented as frequency counts and percentages. Student's t test was used to compare the differences in the means, and the Chi-square test was used to assess the differences in the proportions. Univariate and multivariate associations of variables with the need for IVC resection were evaluated using logistic regression models and

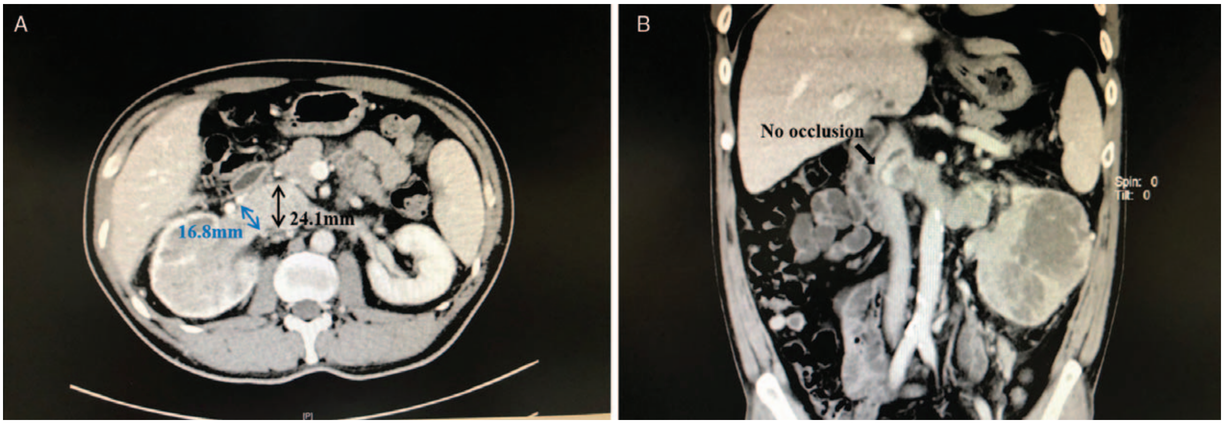

Figure 1: The Axial contrast-enhanced CT image (A) from a RCC patient with a level II thrombus. Renal ostial (blue arrow) and AP VTT (black arrow) are measured. The coronal image (B) from another RCC patient with a level I thrombus shows no occlusion on the condition that the contrast agent can pass through the IVC (black arrow). AP: Anterior-posterior; CT: Computed tomography; IVC: Inferior vena cava; RCC: Renal cell carcinoma; VTT: Venous tumor thrombus.

summarized with odds ratios (ORs) and 95% confidence intervals (CIs). All variables that met a significance level of less than 0.05 in the univariate model were included in the multivariate models. All tests were two-sided, and $P < 0.05$ was considered statistically significant. The statistical analyses were performed using SPSS 20.0 (IBM Inc., Chicago, IL, USA).

Results

Baseline data

Among the 110 patients, 87 (79%) patients were scanned pre-operatively by CT, and 23 (21%) underwent pre-operative MRI scans. They were divided into two groups: the no vascular resection group and the IVC resection group. The number of patients who did not undergo IVC resection was 69, including 29 (42%) patients with Mayo I tumor thrombus, 28 (41%) patients with Mayo II tumor thrombus, seven (10%) patients with Mayo III tumor thrombus, and five (7%) patients with Mayo IV tumor thrombus. The other group comprised five (12%) patients with Mayo I tumor thrombus, 17 (42%) patients with Mayo II tumor thrombus, 13 (32%) patients with Mayo III tumor thrombus, and six (15%) patients with Mayo IV tumor thrombus.

Comparison of clinical and imaging features

A total of 41 (37%) of these patients underwent IVC resection, including 20 (49%) who were treated with partial IVC resection and 21 (51%) who underwent segmental IVC resection. There were no significant differences in the age and sex distributions between the patients who underwent IVC resection and those who did not undergo IVC resection. Based on the radiographic imaging results [Figure 1], the patients who required IVC resection had a significantly larger maximum median AP VTT diameter at the RVo (24.6 *vs*. 19.3 mm; $P = 0.001$), a significantly larger AP diameter of the RV at the RVo (17.4 *vs*. 15.5 mm; $P = 0.005$), significantly more cases of complete occlusion of the IVC due to the thrombus (61% *vs*. 22%; $P = 0.001$) and were significantly less likely to have a level I thrombus (12% *vs*. 42%, $P = 0.001$) [Table 1].

Univariate and multivariate associations

The univariate associations of the pre-operative imaging features with the need for IVC resection are summarized in Table 2. The statistically significant risk indicators were the Mayo classification (95% CI: 1.39–3.47, $P = 0.001$), AP diameter of the RV at the RVo (95% CI: 1.01–1.20, $P = 0.037$), AP VTT diameter at the RVo (95% CI: 1.05–1.18, $P = 0.001$), and the presence/absence of complete occlusion of the IVC due to a tumor thrombus (95% CI: 2.41–13.15, $P < 0.001$).

The multivariable logistic regression model that was created to predict whether IVC resection is necessary is summarized in Table 2. As there were eight variables in the univariate regression model, only four significant variables were included in the multivariable analysis. On the basis of the multivariable model, we suppose that there are two risk indicators that are independently correlated with the need for IVC resection: the AP diameter of the VTT at the RVo (OR 1.10; $P = 0.031$) and the presence of radiographically identified complete occlusion of the IVC (OR 3.06, $P = 0.029$) [Table 2].

The threshold (17.0 mm) of the AP diameter of the VTT at the RVo was calculated based on the receiver operating characteristic curve [Figure 2]. The predicted probabilities of IVC resection according to the two statistically significant imaging features are shown in Figure 3. There were a total of 75 patients with an AP diameter of the VTT at the RVo larger than 17.0 mm, among whom 17 (23%) patients underwent IVC resection; there were a total of 45 patients with complete occlusion of the IVC, among whom 25 (56%) patients underwent IVC resection. Furthermore, a total of 35 patients had an AP diameter of the VTT at the RVo larger than 17.0 mm as well as complete occlusion of the IVC, among whom 23 (66%) underwent IVC resection.

Table 1: Comparison of clinical and imaging features of patients who underwent surgical treatment for RCC with VTT by need for resection of IVC ($N = 110$).

Features	No IVC resection ($n = 69$)	IVC resection ($n = 41$)	Statistics	*P*
Age (years)	55.8 ± 15.9	60.1 ± 11.5	1.525*	0.130
Diameter of renal tumor (cm)	9.2 ± 3.3	8.7 ± 3.7	1.138*	0.250
AP diameter of the renal vein at the RVo (mm)	15.5 (6.7–26.2)	17.4 (6.7–28.1)	–2.787†	0.005
AP diameter of the tumor in IVC at the RVo (mm)	19.3 (7.4–40.7)	24.6 (8.1–37.1)	–3.421†	0.001
AP diameter of the Contralateral renal vein at the RVo (mm)	10.1 (3.9–25.4)	10.2 (3.1–16.3)	–0.652†	0.510
Gender			0.64‡	0.330
Female	21 (30)	9 (22)		
Male	48 (70)	32 (78)		
Side			1.53‡	0.330
Left	16 (21)	13 (32)		
Right	53 (79)	28 (68)		
Smoothness of distal VTT			1.95‡	0.110
Yes	52 (75)	25 (61)		
No	17 (25)	16 (39)		
Occlusion			5.63‡	0.001
Yes	15 (22)	25 (61)		
No	54 (79)	16 (39)		
Mayo classification			2.19‡	0.001
I	29 (42)	5 (12)		
II	28 (41)	17 (42)		
III	7 (10)	13 (32)		
IV	5 (7)	6 (15)		

Values were shown as mean ± standard deviation, median (minimum–maximum), or *n* (%). * *t* values; † Z values; ‡ Chi-square values. IVC: Inferior vena cava; AP: Anterior-posterior; RCC: Renal cell carcinoma; RVo: Renal vein ostium; VTT: Venous tumor thrombus.

Table 2: Univariate and multivariate associations of imaging features with the need for IVC resection at the time of tumor thrombectomy ($N = 110$).

Features	OR	95% CI	*P*
Univariable			
Mayo classification	2.19	1.39–3.47	0.001
Maximum diameter of renal tumor	0.96	0.85–1.07	0.449
Left *vs*. right	1.54	0.64–3.65	0.328
AP diameter of the RV at the RVo	1.10	1.01–1.20	0.037
AP diameter of the contralateral RV at the RVo	0.72	0.91–1.15	0.719
AP VTT diameter at the RVo	1.11	1.05–1.18	0.001
Smoothness of proximal part of VTT	1.96	0.85–4.50	0.114
Contrast flow within IVC	5.63	2.41–13.15	<0.001
Multivariable			
Mayo classification	2.17	0.65–7.25	0.210
AP diameter of the RV at the RVo	0.93	0.82–1.06	0.309
AP VTT diameter at the RVo	1.10	1.01–1.20	0.031
Complete IVC occlusion	3.06	1.12–8.34	0.029

OR: Odds ratio; CI: Confidence interval; AP: Anterior-posterior; RVo: Renal vein ostium; VTT: Venous tumor thrombus; IVC: Inferior vena cava.

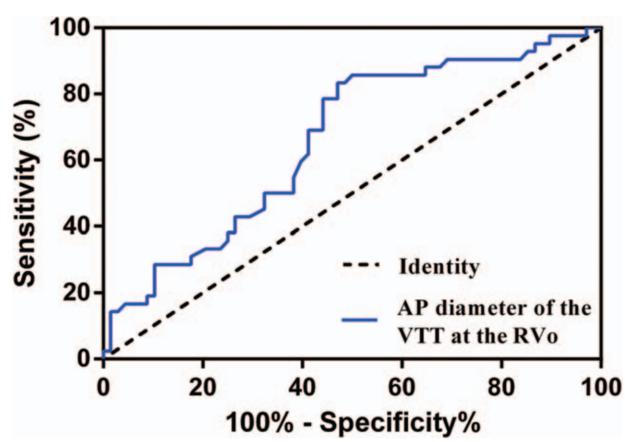

Figure 2: The ROC curve of the AP diameter of the VTT at the RVo which the threshold was 17.0 mm. AP: Anterior-posterior; ROC: Receiver operating characteristic; RVo: Renal vein ostium; VTT: Venous tumor thrombus.

Discussion

Approximately 4% to 10% of cases of RCC are associated with venous thrombus, of which 22% to 70% show involvement of the IVC.[11] IVC wall invasion due to a tumor thrombus was found to be a significant independent factor for survival and capable of predicting a poor prognosis.[12-15] When vena cava wall invasion is found intra-operatively, performing complete resection of the invaded cava vein wall significantly prolonged the survival time.[15] Therefore, IVC resection was performed in all patients in our institution in whom the IVC wall was found to be macroscopically invaded by a tumor thrombus. IVC

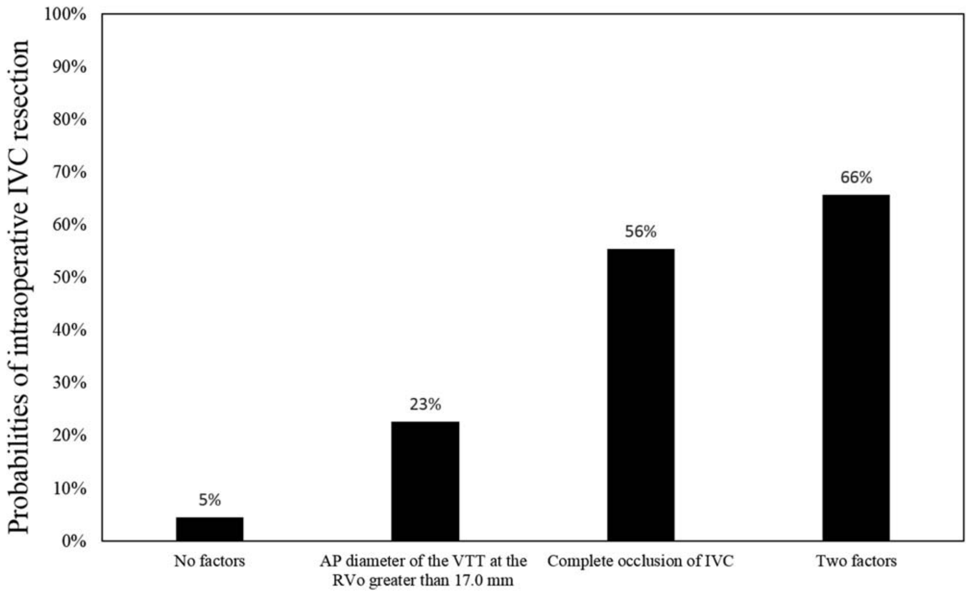

Figure 3: Histogram for predicting probabilities of intra-operative IVC resection based on the two statistically significant imaging features. IVC: Inferior vena cava; AP: Anterior-posterior; VTT: Venous tumor thrombus; RVo: Renal vein ostium.

tumor thrombectomy is one of the most challenging open surgeries to perform, with a major complication rate of as high as 38% and a peri-operative mortality rate of 4% to 10%.[16] In light of the potential for major intra-operative complications, it is essential that more accurate pre-operative predictive models for megascopic invasion of the IVC wall requiring IVC resection are established to help surgeons overcome the challenges and select the best treatment strategies.[17] In this context, in the present study, imaging features of the VTT at the RVo and IVC were identified and measured by pre-operative imaging, and the features were used to predict whether IVC needed to be performed at the time of tumor thrombectomy for patients with a level I–IV thrombus. Specifically, an AP diameter of the VTT at the RVo of >17.0 mm and the presence of complete occlusion of the IVC were independently associated with a higher probability of IVC resection. For patients who have both risk factors, the model predicts the probability for IVC resection to be 66%. For patients with neither of the two features, however, there is a 95% chance that IVC sutures alone are required.

Previous studies have demonstrated an association between IVC diameters and the presence of wall invasion. Gohji *et al*[18] suggested that an IVC diameter larger than 40 mm probably indicates extensive tumor invasion, but from the study involved only small number of patients. Psutka *et al*[9] considered an AP diameter of the IVC at the level of the RVo of ≥24.0 mm to be a probable indicator of IVC invasion. In the present study, the probability of megascopic IVC wall invasion requiring IVC resection was also higher with an increasing AP diameter of the VTT at the level of the RVo, which is logical and coincides with the results in previous reports, as a larger thrombus shows a higher proclivity for IVC wall invasion.

The American Joint Committee on Cancer incorporated the presence of IVC wall invasion into the cancer staging criteria for RCC by changing stage T3b to stage T3c.[19] The results from the present study indicate that complete occlusion of the IVC (the absence of contrast flow alongside the IVC) due to a tumor thrombus is associated with an increased likelihood of IVC resection, which was consistent with the research results presented by Adams *et al*,[20] who collected data on 81 patients with RCC and IVC thrombus undergoing nephrectomy and vena cava thrombectomy and found that complete occlusion of the IVC lumen is reliable in predicting IVC wall invasion, with a sensitivity of 92.3% (95% CI: 0.75–0.99) and a specificity of 86.4% (95% CI: 0.65–0.97). Psutka *et al*[21] found that complete occlusion of the IVC at the RVo (OR 4.9; $P < 0.001$) was also associated with a significantly increased risk of IVC resection. This result was thought to be related to an increased risk of venous wall invasion when tumor are poorly differentiated[22] or a large tumor burden; hence, segmental IVC resection is necessary to obtain a clear vein margin.[9]

Although intra-operative exploration could not be replaced by the assessment of pre-operative features, the a priori assessment of wall invasion can be a helpful adjunct to other examinations, such as duplex ultrasound or transesophageal echocardiography, which can be used to further characterize the mobility, consistency, and exact extension of the thrombus. As suggested in a previous study,[23] multidetector CT and MRI are comparable and more effective than abdominal ultrasound in diagnosing an IVC tumor thrombus in RCC patients, but none of these methods can be used to detect IVC wall invasion. Therefore, it is important to develop a pre-operative prediction model through which the probability of IVC resection can be assessed. When surgeons decide whether to resect IVC or to remove a VTT, the probability of the need for venous wall resection and reconstruction can serve as a reference and be applied to optimize the use of resources in clinical practice; for example, it may be used in consultations with vascular surgeons for the arrangement of cardiopulmonary bypass surgery or scheduling of the surgeons with the most experience and considerable expertise. The derived information is especially important for patients in whom reconstruction of the IVC beyond rrhaphy is needed to determine the need for specific operative resources (eg, cardiopulmonary bypass) in advance and to augment the patient information available pre-operatively.[21] To the best of our knowledge, using pre-operative imaging features to predict megascopic invasion of the IVC wall requiring resection of the IVC has not been specifically addressed as an endpoint in previous studies in Chinese populations. We found that an AP diameter of the IVC at the level of the RVo of >17.0 mm to be a predictor of megascopic IVC invasion among Chinese patients.

There are also some limitations of this study. First, different MRI or CT scanners were used, leading to potential variability across scanners and imaging sessions. Second, the study was a single-center analysis conducted in the mainland of China, so the threshold of the AP diameter (>17.0 mm) of the IVC at the level of the RVo may be specific to the Chinese population. External validation of the applied MRI or CT features is warranted. Finally, frozen section diagnoses of these cases were not performed during the operations, and no elaborate pathology reports on microscopic invasion into the vein cava wall were available in our institution, limiting us from studying potential pre-operative imaging predictors of the presence of histological invasion of the IVC wall.

In conclusion, an AP diameter of the VTT at the RVo of >17.0 mm and the presence of radiographically identified complete occlusion of the IVC were significantly associated with and independently predictive of megascopic IVC wall invasion among Chinese people. In the future, the imaging model might be helpful, as an adjunct tool, in optimizing pre-operative plans using quantifiable features that predict the probability of intra-operative IVC wall invasion.

Conflicts of interest

None.

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