PERIOPERATIVE KIDNEY ANATOMIC VASCULAR ASPECTS (KAVA) IN NEPHRON-SPARING SURGERY

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ABSTRACT

Objectives: For a consistent approach to NSS and easier interpretation of possible perioperative complications, we propose an original score = the kidney anatomic vascular aspects (KAVA) score = based on analysis of anatomic particularities of the renal vascular system and constants of possible complications (ischaemia, haemorrhage, and anaemia). When correlated with the PADUA score, the KAVA score provides information on prognosis and severity of postoperative complications. Design, setting, and participants: We retrospectively evaluated 272 patients who underwent NSS for clinical stage 1 renal tumours, in two surgical centres between May 2018 and September 2021.

Outcome Measurements and Statistical Analysis: The following anatomic features describe renal vascularisation: simplest vascular pedicle, supernumerary arteries and veins, early branching vessels, and precaval right renal artery. To predict the risk of complications, we generated an algorithm (KAVA score). All data were analysed with the STATA v.9.1 software, and a p-value < 0.05 was considered statistically significant.

Results and limitations: Constants of complications are statistically significant for the degradation of renal function in the context of surgical trauma. Using multivariate analysis, KAVA score indicates the severity of postoperative consequences depending on risk factors, and the degree of renal function deterioration. Limitations of this study include the number of patients, the lack of preoperative evaluation of potential renal vascular potential for some patients, and the lack of calculation of the volume of the resected specimen relative to the total volume of the kidney. Further external validation of the KAVA score is needed.

Conclusions: The current study is the first to assess the relationship of kidney vascular variants, tumour anatomy, and constants of possible complications in patients with elective indication for NSS. The KAVA score translates into details of the surgery and possible incidents that may occur perioperatively. It demonstrates that assessing the vascular capital of the renal unit is crucial for safe NSS, especially with a laparoscopic or robot-assisted approach.

KEYWORDS

Kidney vascular variants, Renal tumour, Anatomic classification, Complication.

1. INTRODUCTION

In-depth knowledge of the renal vasculature is essential for the safe practice of the nephron-sparing technique. The topic of renal vascular variants is both controversial and exciting because of its clinical significance [1]. The role of renal vascular variants is very important in conservative kidney surgery and in transplant surgery [2]. Partial nephrectomy may be a bleeding surgery, incurring alteration of haemodynamic status and impairment of the renal unit. In this context, preoperative assessment of the vascular capital of the pedicle renal unit is crucial. To ensure efficiency and safety of renal segmental excision, one must consider the anatomy of the possible vascular variants [3].

It is now widely accepted that open partial nephrectomy is the gold standard of treatment for patients with T1a tumours [4], but the minimally invasive approach has reached its maximum popularity with the progress of laparoscopic surgery. This procedure is standard in selected cases, and robot-assisted surgery is highly regarded [5,6]. An important element of nephron sparing is warm ischaemia time. This element is essential for the nephron's filtration viability and subsequent efficiency. Other factors, such as location and size of the tumour or vascular variations may adversely affect the duration of ischaemia [7]. The surgeon's preoperative knowledge of these factors can guide the therapeutic decision and how to implement it. To avoid unwanted events in NSS, the preoperative imaging protocol should include selective renal arteriography and/or three-dimensional (3D) computed tomography (CT)[8].

The objectives of our study are to describe and identify the correlations among renal variants of the vascular pedicle, tumour anatomy, and most frequent complications found in the operating context (bleeding, anaemia, and ischaemia time). Another goal of the present study is to propose an original classification system based on the renal capital of the vascular pedicle, the tumour anatomy, and the functionality of the renal unit. At the same time, we compare the results obtained when using this new system of assessing incidents that may arise in the context of the NSS with the PADUA score [9], to define the severity of potential perioperative complications, depending on the existence and complexity of renal variants of the vascular pedicle.

2. MATERIALS AND METHODS

2.1. Anatomical Aspects

We conducted a retrospective study that included 272 patients diagnosed with clinical stage T1N0M0 renal tumours who underwent NSS between May 2018 and September 2021. The surgical approach consisted of open surgery for 209 patients, and laparoscopic robot-assisted surgery for 63 of patients. The median age was 61 years (interquartile range: 33–80). A total of 147 patients included in the study were male and 125 were female.

All patients included in the study were preoperatively investigated with computed CT with contrast substance or magnetic resonance imaging (MRI). Preoperative renal scintigraphy with technetium Tc99m diethylene-triamine-penta-acetic acid was performed for eight patients with a single functioning kidney or altered renal function (creatinine value $\geq$ 1.4 mg /dl and glomerular filtration rate < 50 ml/min per1.73 m^2).

Patients were divided into three groups: Group A included patients with simple vascular pedicle (an artery and a vein, without early branches), group B included patients with vascular variants, and group C included patients who went from robot-assisted surgery to open surgery or those who underwent new surgery for immediate or delayed intraoperative bleeding complications.

Renal tumours were classified according to tumour anatomy described by the PADUA score. Surgeries were performed by three surgeons at the European Institute of Oncology in Milan, Italy, and the Centre for Robotic Surgery at the Municipal Hospital of Cluj-Napoca, Romania.

2.2. Constants of Complications (Ischemia, Haemorrhage and Anaemia)

Warm ischaemia time was compared to the average threshold of 22.6 min., and we excluded cases in which tumour resection was performed for zero-time ischaemia.

In assessing blood loss, we considered the average amount lost intraoperatively, bleeding that can obtain a clinical and paraclinical response, and we set it to at least 300 ml.

The severity of anaemia was divided into four levels according to the haemoglobin in grams per decilitre, according to the World Health Organisation classification [10].

2.3. Statistical Analysis

Statistical analyses use the ordinary least-squares multiple regression model and the ordered logit model. For all statistical analyses, a p-value < 0.05 was considered statistically significant. All data were analysed with the STATA v.9.1 software (StataCorp, College Station, TX, USA). The final sample included 105 patients from group B for whom all variables necessary for the study were available (Table 1).

Table 1. Explanations of the variables and some descriptive statistics

	Details	**Mean or proportion**	**St.dev.**
Endogenous variables			
Ischemia	Time of ischemia (minutes)	22.6	5.95
Haemorrhage	Intraoperatory blood loss	414	310
Haemoglobin difference	The difference between the haemoglobin levels recorded at 2 days after surgery minus the baseline before surgery	-2.59	1.47
Difference in creatinine values	The difference between the creatinine levels recorded at 2 days after surgery minus the baseline before surgery	0.454	0.262
KAVA score	From 0 to 6. Severity score, indicating the likelihood of intra / post-operative complications from the standpoint of ischemia, haemorrhage, anaemia and renal function deterioration.	3.24	1.79
Exogenous variables			
Age	Age of the patient	61.6	10.1
Gender	0 (male) 1 (female)	1.67	0.47
Tumour location	1 (polar location) 2 (middle location)	1.31	0.47
PADUA score	From 6 to 10	7.05	0.91
Ischemia score	0 (time of ischemia < 20 minutes) 1 (time of ischemia between 20 and 24 min.) 2 (time of ischemia > 24 min.)	1.08	0.80
Haemorrhage score	0 (blood loss < 300 ml) 1 (blood loss between 300 and 600 ml) 2 (blood loss > 600 ml)	1.02	0.81

Anaemia score	0 (haemoglobin difference > -1.5g/dl) 1 (haemoglobin difference between - 3.0 and -1.5g/dl) 2 (haemoglobin difference < -3.0 g/dl)	1.14	0.73
Pedicle Ramification	0 (normal renal pedicle) 1 (multiple arteries) 2 (multiple veins and multiple arteries) 3 (multiple veins, multiple arteries and early ramifications)	0.51	0.77
Precaval	0 (normal anatomical position) 1 (associate precaval position with other content variants of renal pedicle)	0.06	0.23

3. RESULTS

Group B included 109 patients (40.1%), for whom preoperative and intraoperative vascular variants were revealed. An open surgical approach was used for 72 patients, and robot-assisted laparoscopy was used for 37 patients. Group C included 11 patients, 6 of whom required conversion to open surgery and ligation of multiple arterial branches, which showed active bleeding through irrigation on the resection edges of the residual renal segment. The other five patients in group C required another open surgery or selective embolization of arterial branches in the first 12 h before initial surgery.

Compared with the number of patients in study group B, major arterial variants including supernumerary and early branching arteries outside the renal sinus were found in 87 patients (79.4%; 37.2% in left kidneys, and 62.7% in right kidneys, respectively). Venous variants were detected in 42.5%, with 17.3% in left kidneys and 25.1% in right kidneys. Precaval right renal artery was detected in 4.2%, and duplicate abdominal vena cava was identified in 3,6% (Fig. 1).

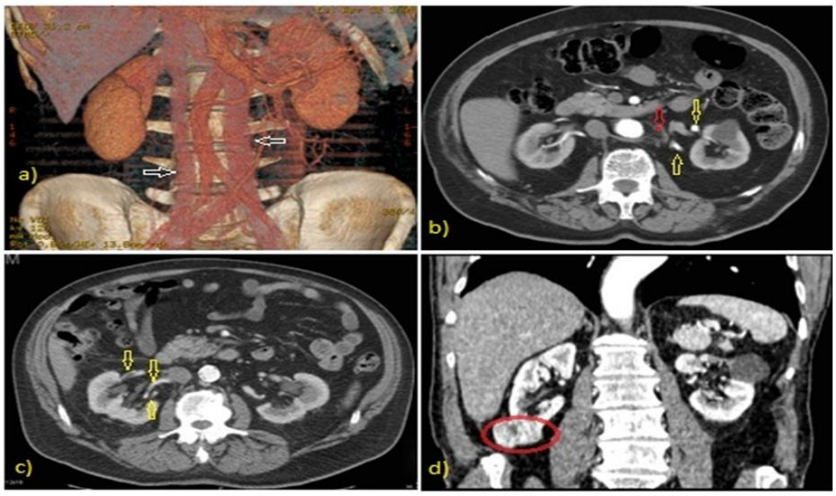

Fig.1 Vascular variants: a) duplicate abdominal vena cava (arrows); b) left renal two arteries (yellow arrows) and early left renal vein bifurcation; c) three arteries right kidney (arrows); d) polar inferior right kidney tumour (ellipse)

Notably, for the constants of complications (ischaemia, haemorrhage, and anaemia), the same risk factors are significant: PADUA score ($p < 0.002$), pedicle ramification ($p < 0.045$), and precaval renal artery and arteries plus veins ($p < 0.002$) (Table 2).

Age, sex, and tumour location were not significant in any of the cases, and placing them in the regression does not generate a consistent growth of R^2. We investigated the relationship between the renal pedicle and the location of the tumour, but this proved statistically insignificant. It is a matter of study and interpretation whether this is due to the PADUA score (a purely statistic problem of multicollinearity). According to study data, the PADUA score is more effective than isolated interpretation of tumour location, because it takes into account factors such as exophytic /endophytic rate, renal rim, relationship with renal sinus/collector system, and tumour size.

Table 2. The impact of variables (risk factors) over ischemia, haemorrhage and anaemia - OLS multiple regression results (coefficients and *p*-values)

	Ischemia		**Haemorrhage**		**Anaemia**	
	Eq. 1	Eq. 2	Eq. 3	Eq. 4	Eq. 5	Eq. 6
Age	0.030 (0.560)	-	4.074 (0.138)	-	-0.009 (0.534)	-
Gender	0.151 (0.887)	-	-29.89 (0.598)	-	- 0.111 (0.713)	-
Tumour location	-1.198 (0.328)	-	-29.39 (0.647)	-	-0.249 (0.468)	-
PADUA score	2.100 (0.001)	1.778 (0.002)	104.4 (0.002)	92.54 (0.002)	0.047 (0.794)	0.001 (0.993)
Ramification	2.153 (0.003)	2.169 (0.002)	79.32 (0.035)	90.13 (0.015)	-0.360 (0.072)	-0.390 (0.045)
Precaval	8.127 (0.000)	7.995 (0.000)	317.9 (0.006)	315.3 (0.006)	-1.354 (0.028)	-1.332 (0.028)
Arteries + veins	0.022 (0.002)	2.049 (0.002)	118.9 (0.001)	119.6 (0.001)	-0.432 (0.019)	-0.415 (0.022)
Constant	-1.186 (0.841	1.489 (0.716)	-977.5 (0.003)	-714.9 (0.002)	-0.132 (0.937)	-0.889 (0.445)
	R^2 = 0.339 N = 105	R^2 = 0.330 N = 105	R^2 = 0.330 N = 105	R^2 = 0.307 N = 105	R^2 = 0.123 N = 105	R^2 = 0.114 N = 105

Table 3. The impact of ischemia, haemorrhage and anaemia on renal function deterioration – OLS multiple regression results (coefficients and *p*-values)

	Renal function eq. 7	**Renal function eq. 8**	**Renal function eq. 9**	**Renal function eq. 10**
Ischemia	0.020 (0.000)	-	-	0.015 (0.001)
Haemorrhage	-	0.0004 (0.000)	-	0.0002 (0.017)
Haemoglobin difference	-	-	-0.044 (0.011)	0.0008 (0.964)
Constant	0.027 (0.761)	-		-
	R^2 = 0.215 N = 105	R^2 = 0.183 N = 105	R^2 = 0.061 N = 105	R^2 = 0.269 N = 105

Ischaemia, haemorrhage, and anaemia have a significant impact on the deterioration of renal function, in relation to their presence and severity (Table 3).

Ischaemia ($p < 0.001$), haemorrhage ($p < 0.001$), and anaemia ($p < 0.011$) are statistically significant to the deterioration of renal function due to their direct, indirect, and systemic effect

on it. In multiple regression, the p-value is not significant for anaemia ($p < 0.964$), but this is a purely statistical effect of multicollinearity with other factors. Consequently, we can create a score to indicate the severity of perioperative consequences (ischaemia, haemorrhage, and anaemia) depending on risk factors. Moreover, this score indicates the severity of deterioration of renal function through relationships shown in equations 7 to 10.

Based on data obtained during the study, we propose the KAVA (kidney vascular anatomical aspects) score to assess the severity of intra- and post-operative complications.

The KAVA score aims to add to the PADUA score by also taking into account the vascular arsenal of the renal pedicle, in addition to tumour anatomy, as this is an important factor for kidney resection surgery.

The importance of each element of the KAVA score will be assessed based on the estimated likelihood of severe complications. For this purpose, we used an ordered logit model (Table 5), in which the endogenous variable (with possible values from 0 to 6) is the severity of the complication (Table 4) and is the sum of the severity of ischemia, haemorrhage and anaemia.

Table 4. The severity of post-operative complications
t.i. = time of ischemia (min)
b.l. = blood loss (ml)
d.a. = variation of haemoglobin - after surgery and before surgery (mg/dl).

Severity of complication	**Ischemia**	**Haemorrhage**	**Anaemia (Hb mg/dl)**
Minor (0)	t.i. < 20	b.l. < 200	d.a. > -1.5
Medium (1)	20 ≤ t.i. ≤ 24	200 ≤ b.l. ≤ 500	-3.0 ≤ d.a. ≤ -1.5
Major (2)	24 < t.i.	600 < b.l.	d.a. < -3.0

These values have been statistically determined based on empirical distributions, so that about 30% of the patients score 0, 40% of the patients score 1, and 30% of the patients score 2. Thus, we try to maintain a distribution of patients as close to normal.

Table 5. The impact of risk factors on the gravity of complications – Ordered Logit Model results (coefficients, odds ratios, and *p*-values)

	Coefficient	**Odds Ratio**	***p* - value**
PADUA score	0.407	1.503	0.055
Ramification	0.702	2.019	0.004
Arteries + veins	0.924	2.519	0.000
Precaval	1.412	4.105	0.041

In creating the KAVA score, we took into account the estimates in Table 5. For the score to increase proportionally to the likelihood of serious complications, we used the Odds Ratio values. We note that the Odds Ratios are around 2 for the PADUA score, pedicle ramification, and artery / vein arsenal and about 4 for the precaval renal artery. Therefore, in the KAVA score, we assign a double weight to the precaval renal artery score compared to other risk factors. The calculation of the KAVA score is described in Table 6. The KAVA score has a minimum possible value equal to 6, if all other risk factors are null. There isn't a maximum possible value, but the probability of values greater than 13 is very small.

Table 6. Calculation of the KAVA score

Risk factors	Calculation
PADUA score	Values from 6 to 10
Ramification	0 normal pedicle 1 early ramification 2 two ramifications 3 three or more ramifications
Arteries + veins	0 anatomically normal pedicle (an artery and a vein) 1 an additional artery or vein 2 two arteries and two veins or two arteries and one vein 3 three or more arteries + / - multiple veins
Precaval	0 retrocaval 2 precaval
KAVA score	∑

4. DISCUSSION

In the case of NSS, vascular variants of the renal pedicle do not receive the same attention as those for renal transplantation, although in many cases these variants are of vital importance. Due to the small number of studies on this topic, implementation of imaging procedures, such as angio-MRI, angio-CT, multi-detector CT, and 3D ultrasound with contrast agent is often neglected and is not treated as an essential part of protocols supplementing the preoperative diagnosis of bilateral kidney tumours suitable for NSS.

According to anatomic terminology, the renal pedicle consists of an artery and a vein, although the artery divides into one anterior branch and one posterior branch [11], in approximately 70-75% of cases [12, 13]. Renal vein variants are more rare than artery variants, and their incidence is approximately 15- 30% [14].

The classification we recommend takes into account the importance of vascular variations of renal pedicle in renal resection surgery, and correlates with PADUA score and with factors of the most common complications found in NSS. By correlating these elements, we obtained a score describing the severity of intra- and postoperative possible complications, providing the surgeon with a more reliable approach to the renal unit. The description of vascular variants was performed preoperatively based on standard CT with contrast agent evaluation. Vascular variants have not been described with imaging and have been intraoperatively identified for approximately 57% of patients.

Our study evaluated 272 patients who underwent NSS, and 109 patients (40.1%) had vascular variants. Accessory renal arteries were the most common renal pedicle malformations, found in 31% of patients. In two cases, we found five distinct renal arteries with different starting points: aorta, lumbar artery, superior mesenteric, and diaphragmatic. In our study group, the incidence of arterial and venous vascular variants is more common on the right side, with a ratio of 2:1, although from the theoretical perspective of vascular embryogenesis, the ratio should be reversed, especially in the case of the renal vein.

Warm ischaemia time is one of the most important factors influencing the viability of the remaining kidney, and every minute should be taken into account. Studies have shown that the optimal warm ischaemia time for minimal nephron lesions must not exceed 20 min [15- 17]. Normal renal artery lumen diameter is 5- 5.6 mm [18]. In the case of vascular variants, the calibre of arteries is smaller, and we must keep in mind that dissecting and preparing them generates microtraumas, which release proinflammatory and vasospastic substances that induce and

maintain ischaemia of irrigated areas. The same pathophysiologic phenomenon occurs in repeated clamping of the renal pedicle. This is carried out for late- detected arterial variants, which produce unexpected bleeding in the renal resection stump and urge the surgeon to intermittently clamp the pedicle until the location has been identified and the bleeding has been stopped. Clamping produces lesions of the vascular endothelium, and the effect is described as ischaemia.

When calculating the final ischaemia time, we believe that aspects that cannot be mathematically quantified should be considered. Reperfusion phenomenon produced by oxygen free radicals should be included in the same array of ischaemia [19, 20].

Their impact on nephron units is lower if, during the process of isolating the renal pedicle, clamping is only arterial and the venous lumen is free. In our study group, we noticed that using bulldog clamps produces micro haemorrhages on the resection edges. This demonstrates the existence of minimal blood flow that is insufficient for efficient tissue irrigation, but is enough to mobilise free radicals produced by ischaemia through the permeable renal vein. We have not performed intraoperative measurement of intravascular pressure in the renal pedicle. Pressure has been macroscopically ascertained, by viewing micro-haemorrhages or by comparing tissue staining in the case of clamping or arterial ligature with Hem-o-Lok clips. Ischaemia time is longer due to vascular variants involving thorough isolation and, in some cases, unexpected haemorrhage. Due to time needed to obtain surgical comfort, ischemic lesions grow and the KAVA score increases proportionally.

The risk of definitive ischaemic lesions increases 3 times for a KAVA score above 9 and 5 times for a score above 11. (Fig.2)

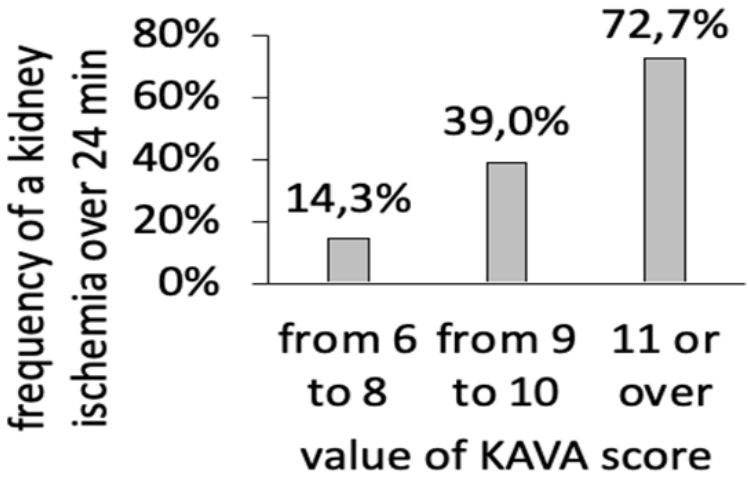

Fig 2. The relation between KAVA score and kidney ischemia

The correlation to the PADUA score increases the likelihood of ischemic and haemorrhagic lesions because, along with the vascular arsenal of the renal unit, tumour anatomy and topography play an important role in the decision to maintain a balance between physiological status and complications.

We established that an increased number of renal arteries and veins of the renal pedicle, as well as early ramifications, if unknown, could produce unexpected complications. Intraoperative incidents have a significant impact on ischemic and haemorrhagic phenomena that were

encountered in cases of the precaval- route ($p < 0.041$) right renal artery associated with early branches.

We identified duplicity of the abdominal vena cava in four patients (3,6%). Isolating the renal pedicle incurred a higher degree of difficulty, especially on the left, but because of this isolated effect and low incidence relative to the total number of patients, it is statistically irrelevant. For practical implications, increased attention in these cases is perfectly justified. The severity of the haemorrhage depends on debit, duration, and amount of blood loss but especially on the body's ability to respond to haemorrhage. In these cases, our attention is focused on elderly patients with multiple associated diseases. In ≥75% of cases, intraoperative and immediate postoperative haemorrhage is triggered more by technical factors and less by coagulopathy [21]. The impact of intraoperative haemorrhage was statistically set to a cut-off of at least 600 ml of fluid aspirated in a short intraoperative time plus blood- soaked fields in the case of open surgery, which can result in a high degree of anaemia and severe pathologic consequences. Systemic effects in a traumatic context are secondary to blood loss in a short period of time. For healthy blood donors, a standard amount of 450 ml is extracted, in which case plasma recovers quantitatively within 2- 3 d and cells recover between 20- 59 d [22]. This occurs without involvement of anaesthetic, teratogenic, oncogenic, or drug factors, which prolong recovery time and thus increase the risk of complications. A KAVA score ≥11 means that there is a risk of blood loss (more than 600 ml) with systemic implications, especially for elderly patients with associated pathology (over 63%) (Fig.3).

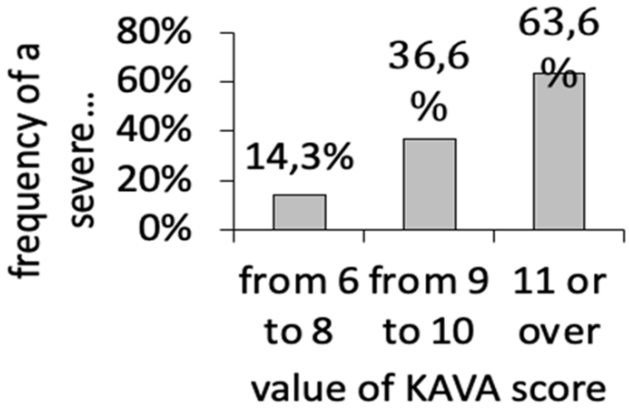

Fig 3. The relation between KAVA score and the amount of blood lost perioperatively

The impact of ischaemia, haemorrhage, and anaemia on renal function is statistically significant for each factor taken separately but particularly in combination. Renal function is compromised by the factors noted, to which pneumoperitoneum effects of minimally invasive surgery are added [23, 24]. For the group of patients included in the study, we conducted pre- and postoperative renal scintigraphy for only eight patients with absolute indication for NSS or with impaired renal function. We showed impaired renal function by calculating the difference between pre- and postoperative serum creatinine at 24, 48, and 72 h and on the day of discharge. Total renal function was monitored during subsequent visits, and 17% of patients did not return to preoperative values. For these patients, ischaemia time exceeded 20 min, and the amount of intraoperative blood loss was ≥600 ml. Adverse change in renal function may later alter quality of life. An increasing KAVA score implies a direct alteration of renal function and requires a more detailed practical perioperative approach of vascular capital (Fig. 4).

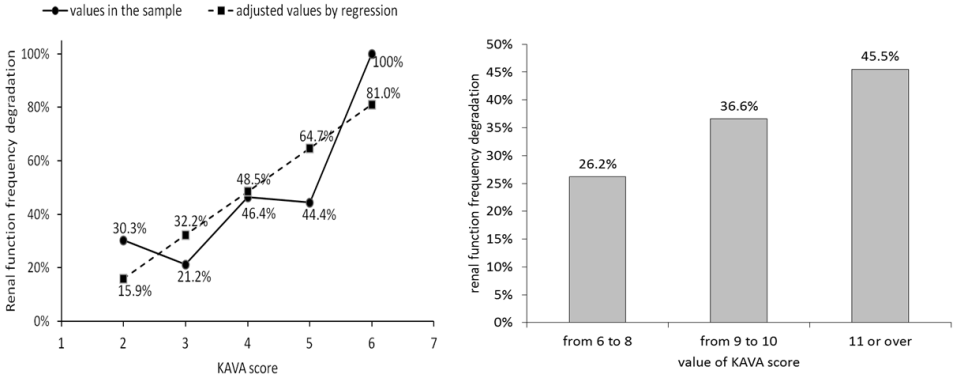

Fig 4. The relation between KAVA score and renal function

The PADUA score proved effective for our study group and, together with the KAVA score, can highlight the probability of the risk of complications and their severity.

Our experience with NSS began with a classical approach, and current cases are handled with robot-assisted surgery. We believe that the approach to T1 and T2 renal tumours depends greatly on the experience of the surgeon, but in most situations, comorbidities associated with open surgery, including rib resection or subcostal nerve injury, direct us to the minimally invasive, robot-assisted approach. Isolation and careful dissection of the renal pedicle are performed much more easily thanks to the degrees of freedom and the 3D picture offered by the da Vinci device and provide a faster learning curve, so robotic surgery tends to be more commonly used [25].

5. CONCLUSIONS

The KAVA score quantifies the details of surgery and the possible incidents that may occur perioperatively and demonstrates that assessing the vascular capital of the renal unit is crucial for safe NSS, open surgery, and especially minimally invasive laparoscopic or robot-assisted surgery. Because of comorbidities generated by open surgery, the minimally invasive approach tends to be the “gold standard” for treatment of T1 renal tumours and even carefully selected T2 cases.

Not knowing the vascular capital of the renal pedicle during thorough dissection in an attempt to selectively isolate vascular elements generates intraoperative bleeding incidents or active bleeding from an aberrant vessel with inadvertently neglected, impaired renal function, especially in patients with one functional kidney or systemic complications due to anaemia.

The incidence of vascular variants is increasing, probably influenced by the large number of teratogenic environmental and food factors. Implementing imaging procedures to monitor vascular details will certainly show a higher incidence of these variants and will provide useful information for safe NSS.

Using these prognostic diagrams of possible complications and their severity provides surgeons with an increased degree of safety and guides stricter and more effective selection of candidates for NSS, both functionally and oncologically.

AUTHOR CONTRIBUTIONS

Cristian Nicolae Manea had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Cristian Nicolae Manea, Deliu Victor Matei Data acquisition:

Cristian Nicolae Manea, Feciche Bogdan Data analysis and interpretation: Cristian Nicolae Manea, Cristian Mihai Dragos, Deliu Victor Matei Drafting of the manuscript: Cristian Nicolae Manea Critical revision of the manuscript for important intellectual content: Nicolae Crisan, Ioan Coman, Ottavio de Cobelli Statistical analysis: Cristian Mihai Dragos Fund raising: None. Administrative, technical, or material support: Nicolae Crisan, Feciche Bogdan, Ioan Coman, Deliu Victor Matei, Ottavio de Cobelli. Supervision: Ioan Coman, Ottavio de Cobelli Other (specify): None. Financial disclosures: None. Funding/Support and role of the sponsor: None Acknowledgment statement: None

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