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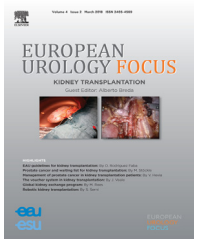

Review – Kidney Cancer

Predictive Value of Nephrometry Scores in Nephron-sparing Surgery: A Systematic Review and Meta-analysis

Alessandro Veccia [a,b], *Alessandro Antonelli* [b], *Robert G. Uzzo* [c], *Giacomo Novara* [d], *Alexander Kutikov* [c], *Vincenzo Ficarra* [e], *Claudio Simeone* [b], *Vincenzo Mirone* [f], *Lance J. Hampton* [a], *Ithaar Derweesh* [g], *Francesco Porpiglia* [h], *Riccardo Autorino* [a,*]

[a] *Division of Urology, VCU Health System, Richmond, VA, USA;* [b] *Urology Unit, ASST Spedali Civili Hospital, Brescia, Italy and Department of Medical and Surgical Specialties, Radiological Science, and Public Health, University of Brescia, Italy;* [c] *Division of Urology, Fox Chase Cancer Center, Philadelphia, PA, USA;* [d] *Department of Oncologic, Surgical and Gastrointestinal Sciences, Urologic Unit, University of Padua, Italy;* [e] *Department of Human and Pediatric Pathology "Gaetano Barresi", Urologic Section, University of Messina, Italy;* [f] *Department of Urology, Federico II University, Naples, Italy;* [g] *Department of Urology, UCSD Health System, La Jolla, CA, USA;* [h] *Division of Urology, San Luigi Hospital, University of Turin, Orbassano, Italy*

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Abstract

Context: Over the last decade, several nephrometry scores (NSs) have been introduced with the aim of facilitating preoperative decision making, planning, and counseling in the field of nephron-sparing surgery. However, their predictive role remains controversial.

Objective: To describe currently available nephrometry scores and to determine their predictive role for different outcomes by performing a systematic review and meta-analysis of the literature.

Evidence acquisition: PubMed, Embase®, and Web of Science were screened to identify eligible studies. Identification and selection of the reports were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). A pooled analysis of NS predictive role of intraoperative, postoperative, oncological, and functional outcomes was performed. Odds ratio was considered the effect size. All the analyses were performed using Stata 15.0, and statistical significance was set at $p \leq 0.05$.

Evidence synthesis: Overall, 51 studies meeting our inclusion criteria were identified and considered for the analysis. Except for one prospective randomized trial, all the studies were retrospective. All the studies were found to be of intermediate quality, except for one of high quality. Most studies assessed the predictive role of the Radius-Exophytic/Endophytic-Nearness-Anterior/Posterior-Location (RENAL) and Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) scores, mostly regarding complications after nephron-sparing surgery. RENAL was an independent predictor of an on-clamp procedure ($p < 0.001$). Mayo Adhesive Probability score was related to adhesive perinephric fat ($p = 0.005$). Continuous and high-complexity RENAL scores were predictors of warm ischemia time (WIT; $p = 0.006$ and $p < 0.001$, respectively). Continuous ($p < 0.001$) and high-complexity ($p < 0.001$) PADUA scores were related to WIT. Continuous and high-complexity RENAL scores were predictors of overall complications ($p = 0.002$ and $p < 0.001$, respectively). PADUA score was related to complications both as continuous ($p < 0.001$) and as a categorical value ($p < 0.002$). The RENAL scores $R = 3$ ($p = 0.008$), $E = 2$ ($p = 0.039$), and hilar location ($p = 0.006$) were predictors of histological malignancy. Continuous and categorical RENAL scores were independent

* Corresponding author. Division of Urology, VCU Health, PO Box 980118, Richmond, VA 23298-0118, USA. Tel. +1-804-828-5320, Fax: +1-804-828-2157.
E-mail address: ricautor@gmail.com (R. Autorino).

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predictors of an estimated glomerular filtration rate (eGFR) increase ($p = 0.006$ and $p < 0.001$, respectively). The Diameter-Axial-Polar score ($p = 0.018$) and Peritumoral Artery Scoring System (PASS; $p = 0.02$) were also independent predictors.
Conclusions: The literature regarding nephrometry scoring systems is sparse, and mostly focused on RENAL and PADUA, which are easy to calculate and have a good correlation with most outcomes. Renal Pelvic Score is the best predictor of pelvicalyceal entry/repair and urine leak, whereas Surgical Approach Renal Ranking and PASS strongly predict surgical approach and renal function variation, respectively. Other nephrometry scores based on mathematical models are limited by their complexity, and they lack evidence supporting their predictive value.
Patient summary: We reviewed the medical literature regarding the use and value of so-called "nephrometry scores," which are scoring systems based on radiological imaging and made to grade the complexity of a renal tumor. We analyzed whether these scoring systems can predict some of the outcomes of patients undergoing surgical removal of renal tumors.

1. Introduction

With the establishment of nephron-sparing surgery (NSS) as the preferred treatment option for the management of renal masses [1], the past decade has witnessed the development of "nephrometry scores." In 2009, the Radius-Exophytic/Endophytic-Nearness-Anterior/Posterior-Location (RENAL) [2] and the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) [3] systems were introduced with the common aim of objectifying the anatomical complexity of a renal mass, assisting in surgical decision making, and facilitating outcome assessment [4]. Since then, several other scoring systems have been conceptualized and reported in an effort to improve the predictive value and promote clinical applicability (Fig. 1) [2,3,5–20]. While comparisons among the different systems remain sparse, RENAL and PADUA remain the most known and used ones in the literature [21,22].

Notwithstanding this significant research effort, it remains unclear what is the uptake of these scoring systems in daily clinical practice and their predictive value. The aim of the present study is to assess, in a systematic fashion, the entire spectrum of currently available nephrometry scores and their performance in the prediction of clinical outcomes in patients undergoing NSS.

2. Evidence acquisition

2.1. Literature search

After establishing a study protocol, two authors (A.V. and A.A.) performed an independent literature research on PubMed, Embase®, and Web of Science to identify relevant studies up to April 2019 (Supplementary material). It was filtered to include original articles only, while conference abstract, conference paper, reviews, letters, notes, editorials, and book chapters were excluded. Identification and selection of the studies was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (www.prisma-statement.org; Supplementary Fig. 1) [23,24]. Title and abstracts were first reviewed to ascertain whether they would potentially follow the inclusion criteria (studies on nephrometry score reporting multivariate logistic regression analyses expressed by odds ratio [OR]). A full-text analysis was performed to confirm inclusion. References of collected reports were manually reviewed to find additional studies of interest. The study protocol was registered on PROSPERO (CRD42019133331).

2.2. Assessment of study quality

We classified each study according to the level of evidence [25]. The quality of the studies was determined using the Newcastle-Ottawa Scale for nonrandomized controlled trials [26]. A total score of $\leq$5 was considered low quality, 6–7 intermediate quality, and 8–9 high quality. Jadad scale was deemed suitable for evaluating the quality of the randomized studies [27].

2.3. Data extraction and analysis

OR and confidence interval (CI) were collected to assess the predictive value of nephrometry scores to predict surgical strategy (minimally invasive surgery [MIS] vs open, partial nephrectomy [PN] vs radical nephrectomy [RN], or on-clamp resection), prolonged warm ischemia time (WIT; defined as >20 min), adhesive perinephric fat, overall and major complications, conversion to RN, pelvicalyceal system entry/repair, urine leak, malignancy, high-grade tumor, new-onset chronic kidney disease (CKD), renal function variation, and trifecta achievement.

Nephrometry scores were considered continuous and/or categorical (high complexity). OR and CI lower and upper limit logarithms were calculated. The results allowed us to obtain the standard error. LogOR and logCI were pooled to obtain the effect size of the variables. Heterogeneity among the studies was weighted according to random effect [28]. If pooled analysis included <25 studies, a small sample size bias was established according to Egger's regression test [29]. A nonstatistically significant p value was indicative of the absence of a small sample size bias. All the analyses have been performed using Stata 15.0 (StataCorp 2017, Stata Statistical Software: release 15; StataCorp LLC, College Station, TX, USA), and statistical significance was set at

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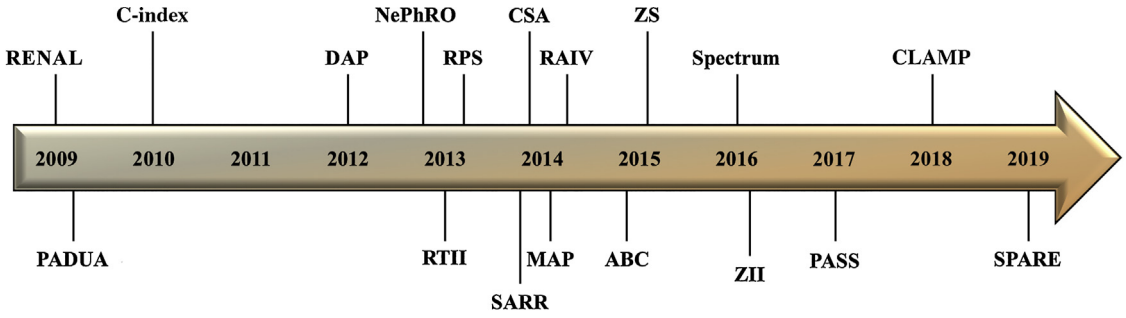

RENAL [2]	Radius-Exophytic/Endophytic-Nearness-Anterior/Posterior-Location	RTII [8]	Renal Tumor Invasion Index	RAIV [13]	Renal And Ischemic Volume	CLAMP [19]	Coefficient -Location - Anterior boundary, Multi-boundary and Posterior boundary
PADUA [3]	Preoperative Aspects and Dimensions Used for an Anatomical	RPS [9]	Renal Pelvic Score	ABC [14]	Arterial Based Complexity	SPARE [20]	Simplified PAdua REnal
C-index [5]	Centrality Index	SARR [10]	Surgical Approach Renal Ranking	ZS [15]	Zhongshan Score		
DAP [6]	Diameter-Axial-Polar	CSA [11]	Contact Surface Area	ZII [17]	Zero Ischemia Index		
NePhRO [7]	Zonal-Nearness-Physical-Radius-Organization	MAP [12]	Mayo Adhesive Probability	PASS [18]	Peritumoral Artery Scoring System		

Fig. 1 – Nephrometry scores.

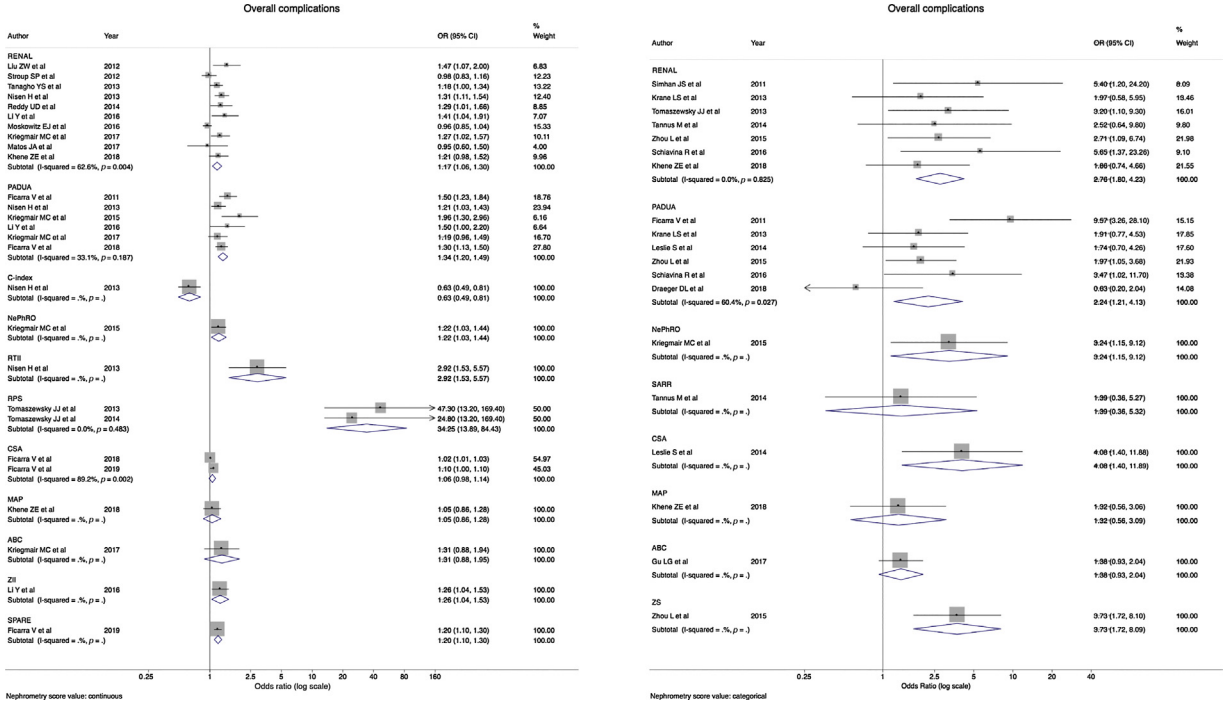

Fig. 2 – Predictive value of nephrometry score for overall complications. ABC = Arterial Based Complexity; CI = confidence interval; C-index = Central Index; CSA = Contact Surface Area; MAP = Mayo Adhesive Probability; NePhRO = Nearness-Physical-Radius-Organization; OR = odds ratio; PADUA = Preoperative Aspects and Dimensions Used for an Anatomical; RENAL = Radius-Exophytic/Endophytic-Nearness-Anterior/Posterior-Location; RPS = Renal Pelvic Score; RTII = Renal Tumor Invasion Index; SARR = Surgical Approach Renal Ranking; SPARE = Simplified PAdua REnal-; ZII = Zero Ischemia Index; ZS = Zhongshan Score.

$p \leq 0.05$. A detailed description of statistical codes is reported in the Supplementary material.

3. Evidence synthesis

3.1. Nephrometry scores

Currently available nephrometry scores can arbitrarily be grouped into those based on a visual anatomical assessment of a renal mass and those based on a mathematical assessment.

3.1.1. Visual anatomical assessment-based scores

Most of the scores fall into this group as they are based on an immediate visual assessment. The RENAL [2] and PADUA [3] scores evaluate the tumor location, its degree of penetration within the kidney, and its relationship with the pelvicalyceal system. The Diameter-Axial-Polar (DAP) score establishes the

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renal mass dimension and distance from two referring lines: axial and polar lines [6]. The Zonal Nearness-Physical-Radius-Organization (NePhRO) score presents five parameters that mirror those of the RENAL and PADUA scores. Differently, it divides the kidney into three zones (zone 1: kidney parenchyma; zone 2: medullary and sinus; and zone 3: collecting system and hilum) and adopts another dimensional scale to establish renal mass dimension [7]. Differently, the Renal Pelvic Score (RPS) departs from the abovementioned scores. Indeed, it assesses the presence of an intra- or extrarenal pelvis referring to a sagittal line that crosses the kidney hilum [9]. Another score, the Surgical Approach Renal Ranking (SARR), presents the same features as those of the RENAL, PADUA, and Zonal NePhRO scores, but it provides a scoring system from 0 to 4, which allows obtaining more granular stratification of renal masses [10]. Most of the scores consider the longitudinal position of the tumor, while the Zhongshan score takes into account the transversal tumor position: lateral, central, and medial [15]. Recently, the Simplified PAdua REnal (SPARE) nephrometry system merged the main features of both the nephrometry scores to create a tumor rim location, renal sinus involvement, exophytic rate, and maximum tumor size–based score [20]. The Arterial Based Complexity (ABC) scoring system considers the vascular involvement by the tumor. The four categories assessed (1, 2, 3S, and 3 H) are linked to the neoplasm contact with interlobular or arcuate, interlobar, segmental, or hilum arteries, respectively [14]. Another vasculature-based score is the Peritumoral Artery Scoring System (PASS) [18]. It is a three-dimension–based score that ranks tumor dissection difficulty according to the number and diameter of peritumoral arteries. Differently from the aforementioned scores, the Mayo Adhesive Probability (MAP) score evaluates the perinephric fat thickness as a mean to predict its adhesion to the kidney, which could translate into a more challenging resection [12].

3.1.2. Mathematical assessment–based scores

This category is based either on a visual or a mathematical assessment of the tumor, requiring detailed imaging analysis. The first one, the Centrality Index (C-index) classifies the tumor complexity according to its mathematical distance from the center of the kidney: $\sqrt{x^2+y^2}=c$; ${}^{d}/_{2}=r$; ${}^{c}/_{r}C-\text{index}$ [5]. Less complex is the Renal Tumor Invasion Index (RTII), which is the ratio of the maximal invasion of the tumor from the surface of the kidney into the parenchyma and the parenchymal thickness of the kidney just beside the tumor (${}^{I}/_{P}$) [8]. Other two scores calculate matematically the tumor Contact Surface Area (CSA) and the Renal And Ischemia Volume (RAIV), with both using the mass radius and diameter measurements. In addition, the RAIV requires the measurement of the resected and ischemized renal parenchyma cross section [11–13]. Similarly, the Zero Ischemia Index (ZII) represents the result of the product of the tumor diameter and its depth within the kidney parenchyma [17]. The only score assessing the vascular complexity is the Coefficient, Location, Anterior boundary, Multi-boundary, and Posterior boundary (CLAMP) score. This three-dimensional (3D) imaging-based score evaluates the anatomy of the arteries that feed the renal mass. This tool could predict the effectiveness of segmental artery clamping through the following mathematical formula: $(X+Y)_1\times 1+(X+Y)_2\times\frac{1}{2}+\ldots(X+Y)_x\times\frac{1}{2}$, where $(X+Y)_x$ = ranking number of the target artery feeding the tumor [19]. Finally, the Spectrum score is a pure mathematic score that allows evaluation of the acute ipsilateral renal dysfunction based on renal scintigraphy measurements and serum creatinine levels [16].

3.2. Description of included studies, and quality and bias assessment

Overall, 51 studies meeting our inclusion criteria were identified and considered for the analysis [8–11,15,17,18,20,30–72]. Except for one prospective randomized trial [71], all the studies were retrospective. All the studies were found to be of intermediate quality, except for one of high quality [59] (Table 1). The majority of the studies assessed the predictive role of the RENAL and PADUA scores, mostly regarding complications after NSS (Supplementary Fig. 2 and 3).

A small sample bias was found in studies assessing WIT, overall and major complications, and pelvicalyceal system entry/repair. No obvious biases were marked regarding the other outcomes assessed (Supplementary Table 2).

3.3. Prediction of outcomes

3.3.1. Surgical strategy

Prediction of the use of an MIS approach was evaluated in only two studies [36,52]. Their pooled analysis failed to show RENAL as a predictor (Table 2 and the Supplementary material). The MAP score was assessed in only one study [52], and it also failed to demonstrate a predictive role.

Regarding the decision to perform PN versus RN, this was assessed in two studies, one for RENAL and SARR [10], and the other for PADUA and RTII [62]. No pooled analysis could be done. Only RENAL (OR 30.45; 95% CI: 8.73, 106.1; $p<0.001$) and SARR (OR 39.53; 95% CI: 10.55, 148; $p<0.001$) showed predictive values (Table 2 and the Supplementary material).

A cumulative analysis of three available studies [59,71,72] showed RENAL as an independent predictor of on-clamp resection (OR: 1.55; 95% CI: 1.23, 1.95; $p<0.001$). Each of the PADUA, ABC [59], and MAP [72] scores was assessed in only one study and associated with on-clamp technique (all $p<0.001$; Table 2 and the Supplementary material).

3.3.2. Adhesive perinephric fat

Cumulative analysis of the two studies [46,58] reporting on this outcome demonstrated the MAP score to be an independent predictor of adhesive perinephric fat (OR: 1.98; 95% CI: 1.23, 3.18; $p=0.005$; Table 2 and the Supplementary material).

3.3.3. Warm ischemia time

A pooled analysis of five studies demonstrated that the RENAL score as continuous (OR: 1.53; 95% CI: 1.13, 2.06; $p=0.006$) [35–38,59] or categorical (high complexity; OR: 9.29; 95% CI: 5.37, 16.06; $p<0.001$) [35,53] is an

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Table 1 – Characteristics of the studies included.

Author	Nephrometry score	Year	Journal	Institution	Study design	Patients	Surgical procedure	Surgical technique	Nephrometry score correlations assessed	LE	SQ
Mottrie et al [30]	PADUA	2011	*World J Urol*	Single	Retrospective analysis	62	PN	Robotic	Warm ischemia time ≥20 min	3	*******
									Perioperative complications		
									Overall complications		
									Pelvicalyceal repair		
Kutikov et al [31]	RENAL	2011	*Eur Urol*	Single	Retrospective analysis	525	PN	NA	Malignant histology	3	*******
									High-grade histology		
Simhan et al [32]	RENAL	2011	*Eur Urol*	Single	Retrospective analysis	390	PN	Open	Major complications	3	*******
								Laparoscopic			
								Robotic			
Ficarra et al [33]	PADUA	2011	*Eur Urol*	Multiple	Retrospective analysis	349	PN	Robotic	Warm ischemia time ≥20 min	3	*******
									Overall complications		
Liu et al [34]	RENAL	2012	*World J Urol*	Single	Retrospective analysis	179	PN	Laparoscopic	Overall complications	3	*******
								Robotic			
Mayer et al [35]	RENAL	2012	*Urology*	Single	Retrospective analysis	67	PN	Laparoscopic	Warm ischemia time	3	*******
								Robotic	Collecting system entry		
Stroup et al [36]	RENAL	2012	*Urology*	Multiple	Retrospective analysis	284	PN	Open	Undergoing MIS vs OPN	3	*******
								Laparoscopic	Overall complications		
								Robotic	Major complications		
									Urine leak		
Long et al [37]	RENAL	2012	*BJU Int*	Single	Retrospective analysis	177	PN	Open	Conversion to RN	3	*******
								Laparoscopic			
Kopp et al [38]	RENAL	2012	*Urology*	Single	Retrospective analysis	228	PN	Open	Warm ischemia time ≥20 min	3	*******
									De novo CKD development		
Mullins et al [39]	RENAL	2012	*J Urol*	Single	Retrospective analysis	671	PN	Robotic	Malignant histology	3	*******
									High-grade histology		
Tanagho et al [40]	RENAL	2013	*Urology*	Multiple	Retrospective analysis	886	PN	Robotic	Perioperative complications	3	*******
Mehrazin et al [41]	RENAL	2013	*BJU Int*	Multiple	Retrospective analysis	322	PN	Open	eGFR <60 ml/min/1.73 m^2 in the last follow-up	3	******
								Laparoscopic			
								Robotic			
Nisen et al [8]	RENAL	2013	*Scand J Urol*	Single	Retrospective analysis	285	PN	Open	Any-grade complications	3	*******
	PADUA							Laparoscopic			
	C-index							Robotic			
	RTII										
Krane et al [42]	RENAL	2013	*BJU Int*	Single	Retrospective analysis	233	PN	Robotic	Any complication	3	*******
	PADUA								Major complication		
Tomaszewski et al [9]	RENAL	2013	*Eur Urol*	Single	Retrospective analysis	255	PN	Open	Urine leak	3	*******
	RPS							Robotic			
Tannus et al [10]	RENAL	2014	*J Endourol*	Single	Prospective analysis	80	PN	Open	Surgical approach selection	2	*******
	SARR						RN	Laparoscopic	General complications		
								Robotic			
Antonelli et al [43]	RENAL	2014	*Clin Genitourin Cancer*	Multiple	Retrospective analysis	506	PN	Open	Malignancy	3	*******
								Laparoscopic	High-grade features		
								Robotic			
Leslie et al [11]	PADUA	2014	*Eur Urol*	Single	Retrospective analysis	200	PN	Laparoscopic	Operative time ≥4 h	3	********
	CSA							Robotic	Estimated blood loss >500 ml		
									Overall complications		
									Length of stay ≥4 d		
									Warm ischemia time		

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Table 1 (*Continued*)

Author	Nephrometry score	Year	Journal	Institution	Study design	Patients	Surgical procedure	Surgical technique	Nephrometry score correlations assessed	LE	SQ
Tomaszewski et al [44]	RENAL	2014	*Urology*	Single	Retrospective analysis	831	PN	Open	Urine leak	3	*******
	RPS							Robotic			
Reddy et al [45]	RENAL	2014	*Ann R Coll Surg Engl*	Single	Retrospective analysis	128	PN	Open	Postoperative complications	3	*******
								Laparoscopic			
Kocher et al [46]	RENAL	2014	*BJU Int*	Single	Retrospective analysis	245	PN	Laparoscopic	Adherent perinephric fat	3	*******
	MAP							Robotic			
Ball et al [47]	RENAL	2014	*Urol Oncol*	Multiple	Retrospective analysis	1009	PN	NA	Malignancy	3	*******
									Unfavorable pathology		
Zhou et al [15]	RENAL	2015	*Medicine (Baltimore)*	Single	Prospective study	1231	PN	NA	Overall complications	2	*******
	PADUA						RN				
	ZS										
Kwon et al [48]	RENAL	2015	*Ann Surg Oncol*	Single	Retrospective analysis	266	PN	NA	GFR reduction	3	******
	PADUA								New-onset CKD		
	C-index										
Li et al [49]	DAP	2015	*Medicine (Baltimore)*	Single	Retrospective analysis	237	PN	Open	Warm ischemia time ≥20 min	3	******
								Laparoscopic	eGFR decline >10%		
								Robotic			
Kriegmair et al [50]	NePhRO	2015	*World J Urol*	Single	Retrospective analysis	200	PN	Open	Perioperative complications	3	******
Kriegmair et al [51]	PADUA	2015	*Biomed Res Int*	Single	Retrospective analysis	233	PN	Open	Major complications	3	*******
Sharma et al [52]	RENAL	2016	*Indian J Urol*	Single	Retrospective analysis	119	PN	Open	Predictors OPN	3	******
	MAP							Robotic			
Raheem et al [53]	PADUA	2016	*BJU Int*	Single	Retrospective analysis	295	PN	Open	Trifecta achievement	3	*******
								Laparoscopic			
								Robotic			
Schiavina et al [54]	RENAL	2016	*BJU Int*	Multiple	Retrospective analysis	277	PN	Robotic	Warm ischemia time ≥20 min	3	*******
	PADUA								Need for UCS repair		
									Overall complications		
									Major complications		
Ricciardulli et al [55]	PADUA	2016	*Urologia*	Single	Retrospective analysis	402	PN	Laparoscopic	Warm ischemia time ≥20 min	3	*******
Li et al [17]	RENAL	2016	*World J Urol*	Single	Retrospective analysis	149	PN	Open	Estimated blood loss ≥500 ml	3	*******
	PADUA							Laparoscopic	Operative time >2 h		
	ZII							Robotic	Overall complications		
									eGFR decrease >10%		
Moskowitz et al [56]	RENAL	2016	*J Endourol*	Multiple	Retrospective analysis	1139	PN	Robotic	Overall complications	3	*******
									Major complications		
Kara et al [57]	RENAL	2017	*J Urol*	Single	Retrospective analysis	1023	PN	Robotic	Conversion to RN	3	*******
							RN				
Martin et al [58]	MAP	2017	*Urology*	Single	Retrospective analysis	86	PN	NA	Adherent perinephric fat	3	*******
Kriegmair et al [59]	RENAL	2017	*J Surg Oncol*	Single	Retrospective analysis	300	PN	Open	Complications	3	********
	PADUA							Robotic	On-clamp excision		
	ABC								Ischemia time		
									Opening of the CS		
Matos et al [60]	RENAL	2017	*Int Braz J Urol*	Single	Retrospective analysis	71	PN	Open	Major complications	3	*******
							RN	Laparoscopic			
Gu et al [61]	ABC	2017	*J Surg Oncol*	Single	Retrospective analysis	350	PN	Laparoscopic	Overall complications	3	*******
								Robotic	Minor complications		
Zhang et al [18]	RENAL	2017	*Sci Rep*	Single	Retrospective analysis	220	PN	NA	GFR percent decline ≥10%	3	*******
	PADUA								GFR percent decline ≥20%		
	RAIV										
	ABC										

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Table 1 (*Continued*)

Author	Nephrometry score	Year	Journal	Institution	Study design	Patients	Surgical procedure	Surgical technique	Nephrometry score correlations assessed	LE	SQ
	PASS										
Tornberg et al [62]	PADUA	2017	*Scand J Surg*	Single	Retrospective analysis	915	PN	NA	Performing PN	3	*******
	RTII						RN				
Takagi et al [63]	RENAL	2017	*J Endourol*	Single	Matched-pair analysis	227	PN	Robotic	eGFR decrease 10%	3	******
Correa et al [64]	RENAL	2018	*Clin Genitourin Cancer*	Single	Retrospective analysis	334	PN	NA	Malignancy	3	*******
									High-grade features		
Draeger et al [65]	PADUA	2018	*Turk J Urol*	Single	Retrospective analysis	213	PN	NA	Symptoms	3	*******
									CT stage T1b, T2		
									Complications		
Petros et al [66]	RENAL	2018	*Urology*	Single	Retrospective analysis	90	PN	Open	Conversion to RN	3	*******
							RN	Laparoscopic			
								Robotic			
Khene et al [67]	RENAL	2018	*Urol Oncol*	Single	Retrospective analysis	500	PN	NA	Conversion to RN	3	*******
	MAP								Overall complications		
									Major complications		
									Trifecta achievement		
Wang et al [68]	RENAL	2018	*Urol Oncol*	Single	Retrospective analysis	337	PN	NA	eGFR stabilization or variation	3	******
Ficarra et al [69]	PADUA	2018	*BJU Int*	Multiple	Retrospective analysis	531	PN	Open	Postoperative complications	3	*******
	CSA							Laparoscopic			
								Robotic			
Yu et al [70]	RENAL	2018	*Int J Urol*	Single	Matched-pair analysis	375	PN	Open	AKI or CKD progression	3	******
								Laparoscopic			
Antonelli et al [71]	RENAL	2019	*J Urol*	Multiple	Randomized controlled trial	149	PN	Robotic	On-clamp excision	1	3[a]
Qian et al [72]	RENAL	2019	*Urology*	Single	Retrospective analysis	225	PN	Laparoscopic	Segmental artery clamp	3	*******
	MAP										
Ficarra et al [20]	CSA	2019	*BJU Int*	Multiple	Retrospective analysis	531	PN	Open	Overall complications	3	*******
	SPARE							Laparoscopic			
								Robotic			

ABC = Arterial Based Complexity; AKI = acute kidney injury; C-index = Centrality Index; CKD = chronic kidney disease; CS = collecting system; CSA = Contact Surface Area; DAP = Diameter-Axial-Polar; eGFR = estimated GFR; GFR = glomerular filtration rate; LE = level of evidence; MAP = Mayo Adhesive Probability; MIS = minimally invasive surgery; NePhRO = Nearness-Physical-Radius-Organization; OPN = open partial nephrectomy; PADUA = Preoperative Aspects and Dimensions Used for an Anatomical; PASS = Peritumoral Artery Scoring System; PN = partial nephrectomy; RAIV = Renal and Ischemia Volume; RENAL = Radius-Exophytic/Endophytic-Nearness-Anterior/Posterior-Location; RN = radical nephrectomy; RPS = Renal Pelvic Score; RTII = Renal Tumor Invasion Index; SARR = Surgical Approach Renal Ranking; SPARE = Simplified PAdua REnal; SQ = study quality; UCS = urinary collecting system; ZII = Zero Ischemia Index; ZS = Zhongshan Score.

[a] LE according to the Jadad scale for randomized controlled trials.

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Table 2 – Predictive values of nephrometry scores.

Outcomes	τ^2	χ^2	df	*p* value	I^2 (%)	OR	95% CI	*p* value
RENAL								
Minimally invasive surgery	0.28	28.29	1	0.000	96.5	0.95	0.44, 2.03	0.896[a]
PN vs RN[b]	–	–	–	–	–	30.45	8.73, 106.10	<**0.001**[a]
On-clamp resection	0.02	4.13	2	0.127	51.6	1.55	1.23, 1.95	<**0.001**[a]
Warm ischemia time	0.04	5.04	2	0.082	60.3	1.53	1.13, 2.06	**0.006**[a]
	0.05	1.32	1	0.251	24.1	9.29	5.37, 16.06	<**0.001**[c]
Overall complications	0.01	24.05	9	0.004	62.6	1.17	1.05, 1.30	**0.002**[a]
	0.00	2.87	6	0.825	0.0	2.75	1.80, 4.23	<**0.001**[c]
Major complications	0.00	1.70	3	0.638	0.0	1.07	0.96, 1.21	0.212[a]
	0.00	3.03	4	0.553	0.0	3.55	2.00, 6.28	<**0.001**[c]
Conversion to RN	0.00	0.01	1	0.940	0.0	1.40	1.14, 1.73	**0.001**[a]
	1.07	7.30	2	0.026	72.6	1.52	0.38, 6.03	0.551[c]
Pelvicalyceal system entry/repair	0.02	2.02	1	0.155	50.5	1.53	1.15, 2.04	**0.003** [a]
	1.72	4.63	1	0.031	78.4	6.42	0.83, 49.78	0.075[c]
Urine leak[b]	–	–	–	–	–	1.56	1.17, 2.06	**0.002**[a]
Malignancy	1.44	4.09	1	0.043	75.6	3.49	0.54, 22.63	0.190[c]
New-onset CKD	0.04	8.10	2	0.017	75.3	1.28	0.96, 1.70	0.086[a]
Renal function variation	0.00	0.56	1	0.455	0.0	1.28	1.07, 1.53	**0.006**[a]
	0.14	1.46	1	0.228	31.3	5.64	2.22, 14.32	<**0.001**[c]
Trifecta achievement[b]	–	–	–	–	–	0.77	0.34, 1.70	0.518[c]
PADUA								
PN vs RN[b]	–	–	–	–	–	0.72	0.60, 0.86	<**0.001**[a]
On-clamp resection[b]	–	–	–	–	–	1.53	1.23, 1.90	<**0.001**[a]
Warm ischemia time	0.00	2.55	2	0.280	21.5	1.28	1.12, 1.45	<**0.001**[a]
	0.00	2.63	4	0.621	0.0	2.93	2.05, 4.20	<**0.001**[c]
Overall complications	0.00	7.48	5	0.187	33.1	1.34	1.20, 1.49	<**0.001**[a]
	0.34	12.62	5	0.027	60.4	2.23	1.21, 4.13	**0.010**[c]
Major complications	–	–	–	–	–	1.95	1.29, 2.94	**0.001**[a,b]
	0.00	0.60	2	0.742	0.0	2.39	1.36, 4.20	**0.002**[c]
Pelvicalyceal system entry/repair[b]	–	–	–	–	–	1.41	1.18, 1.67	<**0.001**[a]
	0.00	0.13	1	0.722	0.0	3.27	1.96, 5.46	<**0.001**[c]
Renal function variation[b]	–	–	–	–	–	0.60	0.36, 1.00	**0.050**[a]
Trifecta achievement[b]	–	–	–	–	–	0.88	0.14, 5.18	0.888[c]
C-index								
Overall complications[b]	–	–	–	–	–	0.63	0.49, 0.81	<**0.001**[a]
DAP								
Warm ischemia time[b]	–	–	–	–	–	1.74	1.37, 2.20	<**0.001**[a]
Renal function variation[b]	–	–	–	–	–	1.29	1.04, 1.59	**0.018**[a]
NePhRO								
Overall complications[b]	–	–	–	–	–	1.20	1.03, 1.44	**0.020**[a]
	–	–	–	–	–	3.24	1.15, 9.12	**0.026**[c]
RTII								
PN vs RN[b]	–	–	–	–	–	0.55	0.19, 1.58	0.267[a]
Overall complications[b]	–	–	–	–	–	2.91	1.52, 5.52	**0.001**[a]
RPS								
Overall complications	0.00	0.48	1	0.002	0.0	34.25	13.89, 84.43	<**0.001**[a]
Major complications	0.00	0.49	1	0.483	0.0	34.25	13.89, 84.43	<**0.001**[a]
						1.11	0.30, 4.10	0.876[c]
Urine leak	0.00	0.49	1	0.483	0.0	34.12	13.87, 83.93	<**0.001**[a]
SARR								
PN vs RN[b]	–	–	–	–	–	39.53	10.55, 148.13	<**0.001** [a]
Overall complications[b]	–	–	–	–	–	1.39	0.36, 5.31	0.631[c]
CSA								
Warm ischemia time[b]	–	–	–	–	–	3.51	1.24, 9.94	**0.018**[c]
Overall complications	0.00	9.25	1	0.002	89.2	1.05	0.98, 1.13	0.152[a]
	–	–	–	–	–	4.08	1.40, 11.88	**0.010**[c,b]
MAP								
Minimally invasive surgery[b]	–	–	–	–	–	1.04	0.81, 1.33	0.760[a]
Adhesive perinephric fat	0.07	2.73	1	0.098	63.4	1.98	1.23, 3.18	**0.005**[a]
On-clamp resection[b]	–	–	–	–	–	3.91	2.18, 6.99	<**0.001**[a]
Overall complications[b]	–	–	–	–	–	1.05	0.86, 1.28	0.631[a]
	–	–	–	–	–	1.32	0.56, 3.08	0.522[c]
Major complications[b]	–	–	–	–	–	1.11	0.81, 1.52	0.516[a]
	–	–	–	–	–	1.10	0.30, 4.09	0.876 [c]
Conversion to RN[b]	–	–	–	–	–	7.66	3.10, 18.94	<**0.001**[a]
	–	–	–	–	–	3.29	1.39, 7.77	**0.007**[c]
Trifecta achievement[b]	–	–	–	–	–	0.79	0.38, 1.60	0.515[c]
RAIV								
Renal function variation[b]	–	–	–	–	–	1.11	1.00, 1.23	0.052[a]

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Table 2 (*Continued*)

Outcomes	τ^2	χ^2	df	*p* value	I^2 (%)	OR	95% CI	*p* value
ABC								
On-clamp resection[b]	–	–	–	–	–	1.84	1.31, 2.57	<**0.001**[a]
Warm ischemia time[b]	–	–	–	–	–	1.25	0.95, 1.62	0.098[a]
Overall complications[b]	–	–	–	–	–	1.31	0.88, 1.94	0.181[a]
	–	–	–	–	–	1.38	0.93, 2.04	0.108[c]
Pelvicalyceal system entry/repair[b]	–	–	–	–	–	1.85	1.37, 2.49	<**0.001**[a]
Renal function variation[b]	–	–	–	–	–	3.98	0.09, 164.91	0.467[c]
ZS								
Overall complications[b]	–	–	–	–	–	3.70	1.71, 8.08	**0.001**[c]
ZII								
Overall complications[b]	–	–	–	–	–	1.26	1.04, 1.52	**0.019**[a]
PASS								
Renal function variation[b]								
SPARE								
Overall complications[b]	–	–	–	–	–	1.20	1.10, 1.30	<**0.001**[a]

ABC = Arterial Based Complexity; CI = confidence interval; C-index = Centrality Index; CKD = chronic kidney disease; CSA = Contact Surface Area; DAP = Diameter-Axial-Polar; df = degrees of freedom; MAP = Mayo Adhesive Probability; NePhRO = Nearness-Physical-Radius-Organization; OR = odds ratio; PADUA = Preoperative Aspects and Dimensions Used for an Anatomical; PASS = Peritumoral Artery Scoring System; PN = partial nephrectomy; RAIV = Renal and Ischemia Volume; RENAL = Radius-Exophytic/Endophytic-Nearness-Anterior/Posterior-Location; RN = radical nephrectomy; RPS = Renal Pelvic Score; RTII = Renal Tumor Invasion Index; SARR = Surgical Approach Renal Ranking; SPARE = Simplified PAdua REnal; ZII = Zero Ischemia Index; ZS = Zhongshan Score. Bold *p* values indicate statistical significance.

[a] Nephrometry score value: continuous.

[b] Pooled analysis not possible.

[c] Nephrometry score value: categorical.

independent predictor of prolonged WIT. Similarly, the pooled analysis showed the PADUA score to predict prolonged WIT as a continuous variable (OR: 1.28; 95% CI: 1.12, 1.45; $p < 0.001$) [33,54,58] and a categorical (high complexity) variable (OR: 2.93; 95% CI: 2.05, 4.20; $p < 0.001$) [11,30,33,54,55]. Only one study was reported as continuous on DAP [49] and ABC [59] and as categorical on CSA [11], with DAP and CSA found to be independent predictors of WIT ($p < 0.01$; Table 2 and the Supplementary material).

3.3.4. *Overall complications*

Continuous (OR: 1.17; 95% CI: 1.05, 1.30; $p = 0.002$) and high-complexity (OR: 2.75; 95% CI: 1.80, 4.23; $p < 0.001$) RENAL scores were found to be independent predictors of overall complications. In addition, the PADUA score was related to complications as continuous (OR: 1.34; 95% CI: 1.20, 1.49; $p < 0.001$) and categorical (OR: 2.23; 95% CI: 1.21, 4.13; $p < 0.002$) value. A cumulative analysis was not possible for the NePhRO score [49], Zhongshan score [15], ZII [17], and SPARE [20], which was shown to be related to overall complications. CSA was correlated to overall complications as a categorical variable ($p = 0.010$) [11] but not as a continuous one [20,69]. C-index was not a predictor of overall complications (OR: 0.63; 95% CI: 0.49, 0.81; $p < 0.001$; Table 2 and the Supplementary material) (Fig. 2).

3.3.5. *Major complications*

Both RENAL high complexity (OR: 3.55; 95% CI: 2.00, 6.28; $p < 0.001$) [9,37,42,53,66] and PADUA categorical (OR: 2.39; 95% CI: 1.36, 4.20; $p = 0.002$) [42,54,65] were independent predictors of major complications. RPS was strongly related to the incidence of major complications (OR: 34.25; 95% CI: 13.89, 84.43; $p < 0.001$) [9,43]. A pooled analysis was not feasible for PADUA as well as for MAP as continuous variables because only one study reported these data for each nephrometry score [50,65]. Only PADUA was found to be a predictor of major complications (Table 2 and the Supplementary material).

3.3.6. *Conversion to RN*

Continuous RENAL score was an independent predictor of conversion to RN (OR: 1.40; 95% CI: 1.14, 1.73; $p = 0.001$) [65,66], but this was not the case for high-complexity RENAL score ($p = 0.551$). Only one study reported about MAP as a predictor of conversion to RN both as continuous ($p < 0.001$) and as categorical ($p = 0.007$; Table 2 and the Supplementary material).

3.3.7. *Pelvicalyceal system entry/repair*

Only two studies per nephrometry score were available regarding this outcome [30,35,54,59]. RENAL as a continuous variable was directly related to pelvicalyceal system entry/repair (OR: 1.53; 95% CI: 1.15, 2.04; $p = 0.003$) [35,59]. This was not the case for high-complexity RENAL score, whereas high-complexity PADUA score was shown to be an independent predictor of pelvicalyceal effraction (OR: 3.27; 95% CI: 1.96, 5.46; $p < 0.001$) [30,54]. Only one study assessed ABC, which was a strong predictor of pelvicalyceal system entry/repair ($p < 0.001$; Table 2 and the Supplementary material).

3.3.8. *Urine leak*

RPS as a continuous value was demonstrated to predict the risk of urine leak strongly (OR: 34.12; 95% CI: 13.87, 83.93; $p < 0.001$) [9,44]. The only other nephrometry score evaluated regarding this outcome was the RENAL score, which

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was shown to predict urine leak too ($p = 0.002$; Table 2 and the Supplementary material) [36].

3.3.9. Malignant histology

The categorical RENAL score was the only score to be assessed as a predictor of malignancy, but it was not found to be predictive ($p = 0.190$; Table 2 and the Supplementary material) [39,47]. A subanalysis of its single components showed that $N = 3$ (OR: 1.98; 95% CI: 1.18, 3.34; $p = 0.010$) was an independent predictor of histological malignancy [31,43,64]. In only one study $R = 3$ was assessed, which was shown to be a predictor of malignant histology and high-grade tumor (OR: 4.05; 95% CI: 1.43, 11.39; $p = 0.008$ and OR: 3.89; 95% CI: 2.12, 7.11; $p < 0.001$, respectively) [31]. RENAL $E = 2$ was an independent predictor of high-grade tumor (OR: 1.67; 95% CI: 1.07, 2.62; $p = 0.024$; Fig. 3) [31,43,64].

3.3.10. Postoperative renal function

Meta-analysis of new-onset CKD was feasible for the RENAL score only, but it did not predict it ($p = 0.086$; Table 2 and the Supplementary material) [38,41,70]. In terms of renal function variation, continuous [18,70] and categorical RENAL scores [19,63] were independent predictors of an estimated glomerular filtration rate (eGFR) increase (OR: 1.28; 95% CI: 1.07, 1.53; $p = 0.006$, and OR: 5.64; 95% CI: 2.22, 14.32; $p < 0.001$, respectively). A pooled analysis was not feasible for the other nephrometry scores because only one study per nephrometry score was available. The DAP score ($p = 0.018$) [49] and PASS ($p = 0.02$) [18] were independent predictors of renal function variation. PADUA ($p = 0.05$) [52] and RAIV ($p = 0.052$) [18] demonstrated a sort of correlation with renal function variation but they did not achieved the usual levels of statistical significance. (Table 2 and Fig. 4).

3.3.11. Trifecta achievement

None of the nephrometry scores included was demonstrated to be an effective predictor of trifecta achievement (Table 2 and the Supplementary material).

3.4. Discussion

Herein, we present the first systematic review and meta-analysis assessing the predictive role of nephrometry scores in NSS. Our findings raise some interesting points of discussion.

Since their introduction in 2009 [2,3], the aim of these tools was to facilitate preoperative planning, surgical decision making, and counseling. Our analysis found nephrometry scores to be a predictor of surgical strategy. Nevertheless, this was not the case regarding the decision to perform a MIS. Previous literature had suggested that patients with more complex renal masses were more likely to have an open PN [36]. Sharma et al [52] found that patients with a higher RENAL score were more likely to undergo an open procedure as well. On the contrary, the presence of adhesive perinephric fat did not influence the decision making. Today, this paradigm is changing, and MIS, especially robotic surgery, has been shown to be safe and feasible even for large and complex renal tumors. Data from the ROSULA Collaborative Group demonstrated robotic PN to be feasible for large renal masses, maximizing kidney function without compromising on oncological outcomes [73]. Despite the encouraging data regarding NSS for T1b-T2 tumors [74], RN is recommended when PN is not feasible [1], and our data demonstrated the role of the nephrometry score during preoperative planning. Indeed, higher RENAL and PADUA scores increased the chances of opting for RN rather than PN. Tannus et al [10] developed an "ad hoc" nephrometry score, the SARR, which assessed the relationship between tumor complexity and the odds of RN. The authors evaluated the computed tomography and magnetic resonance images of 257 patients, showing that patients with higher SARR had almost 39-fold odds to undergo RN compared with those with smaller scores [37]. This is the only study in the literature on this score.

We also assessed the predictive role of the scores regarding hilar management during tumor resection. RENAL,

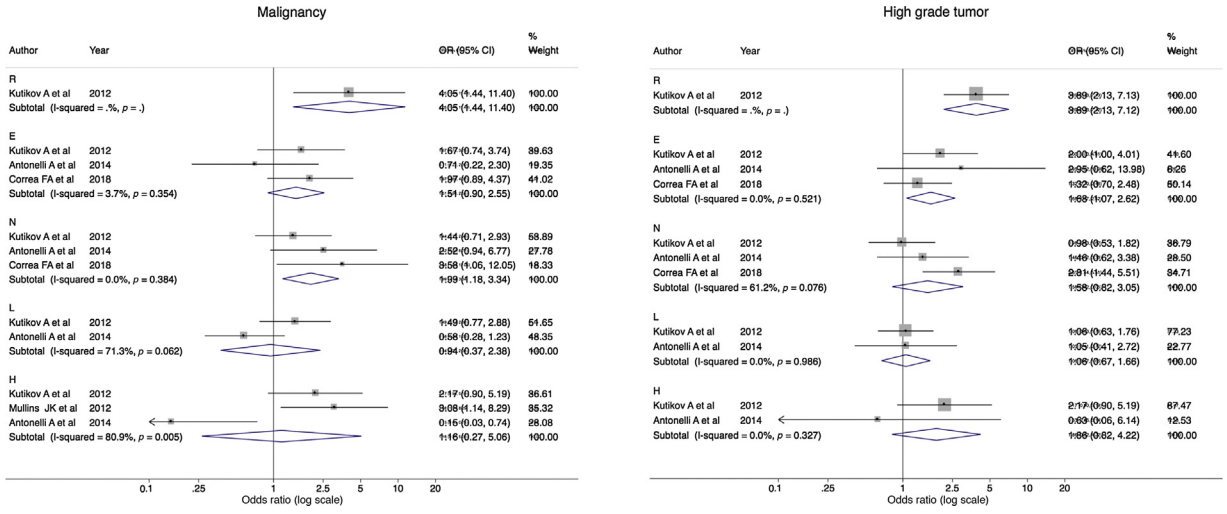

Fig. 3 – Histology predictive value of RENAL components. CI = confidence interval; OR = odds ratio; RENAL = Radius-Exophytic/Endophytic-Nearness-Anterior/Posterior-Location.

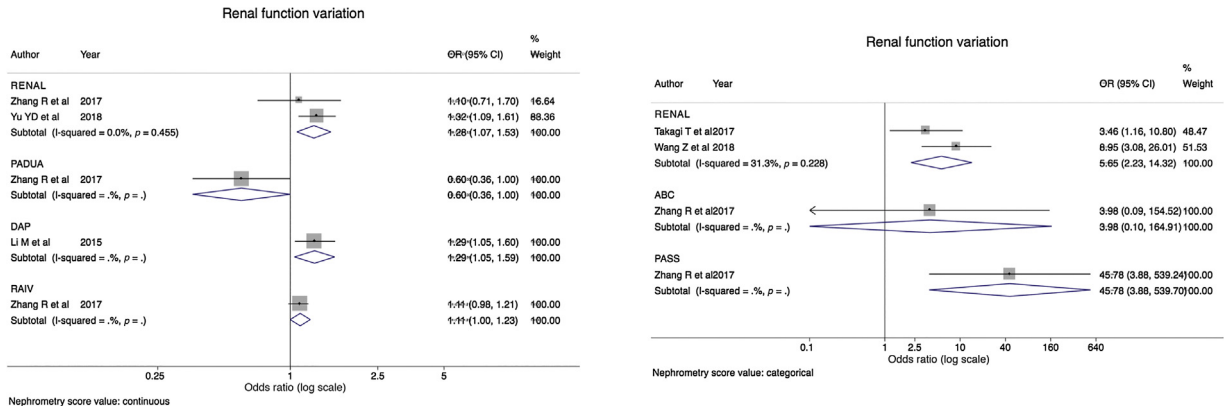

Fig. 4 – Predictive value of Nephrometry score for renal function variation. ABC = Arterial Based Complexity; CI = confidence interval; DAP = Diameter-Axial-Polar; OR = odds ratio; PADUA = Preoperative Aspects and Dimensions Used for an Anatomical; PASS = Peritumoral Artery Scoring System; RAIV = Renal and Ischemia Volume; RENAL = Radius-Exophytic/Endophytic-Nearness-Anterior/Posterior-Location.

PADUA, and ABC were predictors of hilar clamping, but the MAP score seemed to be the strongest one [72]. Data from a new randomized trial suggested a higher RENAL score to be a predictor of the transition from an off-clamp to an on-clamp robotic PN [71]. Recently, the CLAMP score has been developed to evaluate patients suitable for selective artery clamping. This is a 3D imaging–based tool that allows evaluation of the opportunity to perform e selective artery clamp, stratifying patients according to the vascular anatomy [19]. The use of scoring systems to predict the clamping technique remains poorly investigated.

Regarding surgical outcomes, a higher nephrometry score directly influenced WIT, which is a surrogate of tumor complexity [75]. Indeed, a pooled analysis of RENAL and PADUA demonstrated an increased probability of longer WIT. These data were already achieved by a large multicenter study on 227 patients. In this report, the authors concluded that patients with high-complexity RENAL and PADUA scores had 5.7- and 2.6-fold higher rates of longer WIT, respectively [54]. Besides RENAL and PADUA, only CSA, DAP, and ABC were investigated regarding the duration of ischemia time [11,49,59]. The ABC score was the only one unrelated to WIT, and this could be a consequence of its design that accounts only for tumor location, disregarding other data such as diameter, degree of depth, and longitudinal position. Interestingly, Kriegmair et al [59] evaluated a modified version of the ABC score that also included tumor diameter. The authors found that the inclusion of this parameter made the ABC an independent predictor of WIT. These data suggest that tumor dimension is one of the main parameters to consider during nephrometry score development [62].

Overall and major complications were the most investigated outcomes among the nephrometry scores. The first-generation nephrometry scores showed once again their predictive role of overall complications as both continuous and categorical variables. Kriegmair et al [76] achieved the same result in a large cohort series comparing four different scores. Interestingly, the authors analyzed NePhRO score and C-index, with the first related to complications ($p = 0.011$). These data reflected our results showing the inferiority of C-index compared with the others. In addition, except for C-index and MAP score, all the nephrometry scores appeared to be potentially independent predictors of overall and major complications. Nevertheless, RPS was underlined to be superior with 34.25-fold chances of complications for patients with a higher score. Particularly, RPS assessed the renal pelvic anatomic complexity and seemed to be strictly related to urine leak incidence and duration. Tomaszewski et al [9] speculated that the reason could be the interpretation of RPS as a surrogate of renal pelvis volume and pressure. Thus, intrarenal pelvis might present higher inner pressure, increasing the risk of rupture during tumor resection and yielding to delayed healing of urine leak. The urine leak could be a consequence of more complex tumor resection. In fact, higher nephrometry scores and complexity were related to pelvicalyceal system entry/repair. Potretzke et al [77] conducted a review of studies on urinary fistula after robotic PN, and found that pelvicalyceal system entry and tumor size were related to the development of urine leak. These two parameters could be interpreted as a reflection of tumor complexity, which could be the reason for urinary fistula incidence. Our data reflect these findings, and RENAL score and PADUA complexity were shown to be linked to pelvicalyceal system entry/repair. Potentially, a higher ABC score could indicate the risk of urinary tract effraction/repair, but only one study in our analysis reported this outcome [59].

Another consequence of tumor complexity is the risk of intraoperative conversion to RN. In our review, few analyses reported these data [37,59,65,66], and pooled estimation underlined the RENAL score correlation with conversion rate. Nevertheless, the MAP score overcame the RENAL score. Indeed, patients with a higher MAP score and a higher MAP risk had, respectively, 7.66- and 3.29-fold higher risks to be converted to RN. It might be speculated that a higher MAP score could be a consequence of advanced disease, prompting the surgeon to convert the case to a radical one [78].

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The potential role of nephrometry scores to predict malignancy and tumor grade was postulated by Kutikov et al [31]. The authors evaluated each RENAL score component on a cohort of 525 patients and found that $R = 3$, $E = 2$, and $L = 3$ were predictors of malignant histology and high-grade tumors. Equally, we found $R = 3$, $E = 2$, and hilar location as predictors of malignancy. Correa et al [64] hypothesized that tumor growth within the inner renal environment could promote its progression, explaining the major aggressiveness of hilar and endophytic masses. Notably, high-stage, hilar-located renal tumors, especially clear cell carcinomas, showed a higher expression of GLUT5, which is related to glucose metabolism and neoplasm growth [79].

In terms of functional outcomes, the RENAL score was not an independent predictor of new-onset CKD. On the contrary, it was found to be linked to postoperative renal function variation, as well as PADUA and PASS. The latter, which is a 3D rendering–based score assessing peritumoral artery volume, was demonstrated to be the strongest predictor of eGFR variation. The authors found that tumors with higher PASS scores were more likely to have higher RENAL scores too. Consequently, resection could be more difficult, requiring longer ischemia time and larger healthy parenchyma removal [80]. The aforementioned reasons could unfold the strong relationship between PASS and renal function variation. Zhang et al [16] developed a mathematical score to evaluate the acute ipsilateral renal dysfunction after PN: the Spectrum score. This interesting score is based on the following formula: (observed peak SCr – $SCr_{ideal\text{-}peak}$)/($SCr_{worstcase\text{-}peak}$ – $SCr_{ideal\text{-}peak}$); its modified version, proposed by Lee et al [81], quantified acute ipsilateral renal dysfunction and renal recovery after PN (beta –0.515, $p < 0.001$). This novel tool could better forecast renal function variation, but available data are still weak to consider it as an effective predictor.

Overall, RENAL and PADUA seem to represent the best tools to report complexity and prediction of morbidity. Despite other nephrometry scores being promising, their role in predicting specific outcomes does not outperform these first-generation scores.

This study presents limitations. The reports included were all retrospective and of intermediate quality, and the only randomized trial did not address the topic specifically [71]. Moreover, a cumulative analysis was possible only for a limited number of scores and a limited number of outcomes. Therefore, a narrative review was adopted to summarize some of the outcomes. In addition, it was not possible to account for open, laparoscopic, or robotic procedures, so the results might be reliable for one technique but not for the other. The interobserver variability could have influenced the results, but these data were not accountable again. Last, most of the literature available comes from repeat publications from the same working group; therefore, one can argue that some data could have been assessed within the same cohort, translating into an additional bias. Notwithstanding these limitations, the main strength of this study is its design as a systematic review and meta-analysis that makes it depart from the previous descriptive ones.

4. Conclusions

The literature on nephrometry scoring systems is sparse, and it is mostly focused on RENAL and PADUA. These two scores are easy to calculate, and they carry a good correlation with most of the outcomes for which they have been assessed. RPS, SARR, and PASS can offer a better predictive value for pelvicalyceal entry/repair and urine leak, surgical approach, and renal function variation, respectively. Nevertheless, the implementation of other nephrometry scores based on mathematical models is limited by their complexity and lack of evidence supporting their predictive value. Up to date, the RENAL and PADUA scores can be regarded as the standards for reporting complexity and prediction of morbidity, whereas other newer tools did not show better performance than the first-generation ones. The present findings can aid in further research effort in this field and foster the development of better predictive tools.

Author contributions: Riccardo Autorino 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: Veccia, Autorino.
Acquisition of data: Veccia, Antonelli.
Analysis and interpretation of data: Veccia, Autorino.
Drafting of the manuscript: Veccia, Autorino.
Critical revision of the manuscript for important intellectual content: Autorino, Veccia, Antonelli, Uzzo, Novara, Kutikov, Ficarra, Simeone, Mirone, Hampton, Derweesh, Porpiglia.
Statistical analysis: Veccia.
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Supervision: Autorino, Antonelli, Uzzo, Novara, Kutikov, Ficarra, Simeone, Mirone, Hampton, Derweesh, Porpiglia.
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Appendix A. Supplementary data

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