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Review

Considering "Trifecta" as a Single Outcome when Comparing Robotic With Open Partial Nephrectomy: A Mathematical Model of Volume Conservation and Systematic Review

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Abstract. *Background/Aim: Trifecta represents a composite outcome reflecting the quality level of treatment in nephron sparing surgery. However, there is substantial heterogeneity concerning the criteria required for its fulfilment. The present study aimed to highlight the potential of a unified view for the different definitions of trifecta when comparing robotic and open approaches in partial nephrectomy. Materials and Methods: A systematic literature search was carried out for all relevant comparative studies published until April 2022. Trifecta definitions were clustered according to two criteria for postoperative renal function reduction. The first set as an upper limit the 10% decrease in the estimated glomerular filtration rate, while the second set as an upper limit 25 min of ischemia. To mathematically investigate the point of intersection between the above two groups, a suitable model of volume conservation equations was formulated. Results: A total of 11 studies were investigated for their methodological features and grouped accordingly. The ischemic zone volume surrounding the tumor resection site emerged as the central parameter connecting the two main definitions. Specifically, for patients with solitary renal masses, a given change in the value of one parameter resulted in a fixed change in the value of the other. Conclusion: The two main definitions of the "trifecta outcome" extracted from the international literature represent the two sides of the same coin. Thus, trifecta achievement rates could be utilized by future studies as aggregate data to yield a quantitative estimate of the comparative effect between robotic and open approaches in partial nephrectomy procedures.*

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Complete resection of primary solitary kidney tumors is the standard of treatment for renal cell carcinoma (RCC). However, newer trends in renal surgery are moving towards the approach of nephron sparing surgery (NSS) in order to maintain optimal renal function postoperatively, as this has been found to be associated with the most favorable long-term outcomes (1, 2). The evaluation of the surgical specimen margins after partial nephrectomy reflects the most effective method for determining the completeness of tumor resection (2, 3). A positive surgical margin involves the presence of cancer cells at the level of the ink-stained periphery of the specimen. However, the evaluation of postoperative renal function is much more complicated (4). The effect of surgery on postoperative renal function is determined by a set of parameters that are related to the patient but also to the resection procedure itself. The parameter of outmost importance found to be related to postoperative renal function is that of warm ischemia time (WIT), defined as the time period during which, locoregional vascular occlusion of the renal blood supply is maintained. As a parameter, the duration of warm ischemia is considered continuous, and a reasonable range within which it can regress is between 20-30 min. The literature indicated the mean value of 25 min as the maximum time of warm ischemia for optimal postoperative performance in terms of renal function (4, 5). Finally, concerning perioperative complications, the prevailing classification in the international literature according to the Clavien–Dindo classification (6, 7), seems to be effective regarding their systematic standardization, offering the potential to strictly formulate the criteria in terms of their incidence, as well as their severity of impact (4). The three aforementioned parameters, namely surgical margins, renal function diminishment, and complications rate are summarized in modern kidney surgery with the complex concept of trifecta, which has been argued to represent a quality measure in terms of the effectiveness of surgical treatment in patients with small renal masses (8, 9).

Definitional heterogeneity is a term that characterizes international literature regarding the trinity of parameters utilized for the composition of the "trifecta outcome", with the majority of authors however referring to it in general as a single concept (9-11). In the present investigation, we reviewed studies that reported data on the “trifecta outcome” achievement, showing particular interest in comparing robotic partial nephrectomy (RPN) or robotic-assisted (RAPN) and the conventional open partial nephrectomy (OPN).

The main goal of this study was to examine the different definitions of trifecta utilized by the relevant literature comparing RPN/RAPN and OPN, and to group the studies into as few clusters as possible, in order to investigate the deeper meaning of trifecta through a mathematical model of volume conservation equations. Our ultimate objective was to determine whether the results of the comparative studies included could be utilized as aggregate data by future studies to derive a quantitative estimate of the comparative effect of RPN/RAPN and OPN on the “trifecta outcome” as a single entity.

Materials and Methods

Methodology. Initially, a systematic literature search was carried out, for all studies that compare RPN/RAPN and OPN and highlight differences in the frequency of the composite outcome of trifecta achievement. The first objective included the investigation of all definitions attributed to the trifecta concept, and their classification at the minimum number of clusters. The second goal of the study was to highlight the feasibility of the complex “trifecta outcome” as a single parameter. This process aimed to investigate whether a quantitative representation of the comparative effect between the robotic and open approaches for partial nephrectomy on the “trifecta outcome”, as a single qualitative parameter, is possible from subsequent studies. The methodology was divided into four distinct parts. The first part concerns the literature search and the isolation of a set of relevant comparative studies, with data that can be used for estimating the comparative effect between the robotic and open approach in partial nephrectomy procedures as for the “trifecta outcome” frequency of achievement. The second part includes the process of grouping the studies based on the two main definitions found to prevail in the international literature concerning trifecta. The third part reflects the backbone of our analysis where we modeled partial nephrectomy with volume conservation equations in order to investigate by using mathematical notations whether or not the two main definitions can be reduced to a single conceptual parameter. In the fourth part, the relevant results of analytical procedure are presented, as well as the necessary conclusions for the potential of comparatively utilizing the respective trifecta achievement rates when examining the application of the robotic over the conventional open approach in partial nephrectomy.

Data acquisition. Regarding the first and second part of this study, a search of electronic databases was carried out using the keywords: "open", "robotic", "robot-assisted", "partial nephrectomy". The inclusion criteria were: studies only in the English language, comparative studies examining robotic or robot-assisted partial nephrectomy versus the open approach, comparative studies with useful data in both parts of the comparison for further statistical analysis, and also comparative studies which include cost analysis. The exclusion criteria were: studies that are not in English, studies that were retrieved only in the form of a summary or reports without the accompanying data or the necessary text, non-comparative studies, comparative studies with insufficient data for further statistical analysis, comparative studies which include data for only one part of the comparison, studies including patient populations with solitary kidney, and lastly studies involving pediatric patients.

The literature search procedure included all available comparative studies until December 2021. This process aimed at the extraction of all relevant reports from the “Google scholar”, “PubMed”, and the “CENTRAL” databases. Finally, and regarding the above, the open-source “R” programming language version: 4.2.0 (12), along with the “OriginPro 2017®” (13) and the “Visible Body 3D®” (14, 15) modeling software were used to configure the necessary graphical representations.

The “trifecta outcome” has been a real challenge in terms of content analysis as it is related to the adequacy of surgical treatment in the context of partial nephrectomy, which makes it an extremely important parameter for this intervention; however, the definition used by researchers in the international literature is not strictly defined. During the overview of the available literature, it was possible to derive two dominant definitions regarding trifecta. According to the first definition, the absence of positive surgical margins and complications and the absolute percentage decrement in the estimated glomerular filtration rate ($|\Delta eGFR|$) by less than or equal to 10% were incorporated in the trinity of the trifecta concept (3, 16-18). On the other hand, according to the second definition, the trinity of the trifecta outcome included the absence of positive surgical margins and complications as well as duration of ischemia time (IT) less than 25 min (2, 19-23). In the present study, we considered valid the view of Zargar and his colleagues (11), according to which both definitions mentioned above correspond to the same basic concept, which is the effectiveness of surgery in partial nephrectomy for small renal tumors and the degree of recovery of renal function in the postoperative period. In order to mathematically investigate the interconnection between two definitions we worked successively on three different levels. At the first level, a model based on the principle of volume conservation was defined and the related equations were constructed appropriately. At the second level, a series of mathematical expressions and relationships between the variables of interest were formulated, as derived from data available in the literature. Finally at the third level, the proportionality expressions that will have already been formulated are written in the form of proper equations in order to finally arrive at our definitive conclusions.

Volume conservation model. The volume conservation principle-based model is shown in Figure 1. This figure shows the area of the tumor (V_{tumor}) which is incorporated into the resection volume corresponding to the volume of the surgical specimen ($V_{specimen}$) as well as the area of the renal parenchyma around the resection site, whose functionality is considered to be extremely reduced, even down to zero, due to the application of ischemia ($V_{ischemia}$). Equation 1 describes the baseline volume balance between preoperative ($V_{preoperative}$) and postoperative ($V_{postoperative}$) renal parenchyma.

$$V_{preoperative} = V_{postoperative} + V_{specimen} \quad (1)$$

In this equation the difference in renal parenchymal volume pre- and post-surgery equals the volume of the removed surgical specimen. Subsequently, in Equation 2, a distinction is made regarding the postoperative renal parenchyma volume ($V_{postoperative}$), in functional ($V_{postop.functional}$) and non-functional ($V_{postop.non\ functional}$) parenchyma.

$$V_{postoperative} = V_{postop.functional} + V_{postop.non\ functional} \quad (2)$$

According to Mir *et al*., $V_{postoperative}$ is the determining factor for maintaining renal function postoperatively. However, ischemia also plays a prominent role in this connection, as it has been found that post-ischemia nephrons recovery is not complete (24). In another study, Simmons *et al*. claim that the loss of functional renal tissue is mainly due to resection ($V_{specimen}$) and not to the volume of the ischemic zone ($V_{ischemia}$). According to the same authors, the above two parameters practically begin to acquire the same order of magnitude after the application of at least 40 minutes of ischemia (25). In fact, it is noted that ischemia leads mainly to loss of functionality without a corresponding loss of volume, with this effect being characterized as reduction in the glomerular density (GD) (26). Based on the above, and according to Bechara *et al*., it follows that around the resection site a volume-stable zone of ischemic renal parenchyma is formed, which is particularly evident after the application of both arterial and venous clamping (27). This technique is used in a significant number of partial nephrectomy procedures with the aim of limiting intraoperative blood loss (28-31). At this point, it was hypothesized that ischemia reflects the main mechanism responsible for the loss of functional renal parenchyma around the resection site, being caused either by applying hemostasis locally with heat release, or by proximal vascular clamping during the operation. Therefore, under this assumption, Equation 3 was derived.

$$V_{postop.non\ functional} = V_{ischemia} \quad (3)$$

Substituting Equation 3 into Equation 2 finally yields Equation 4, that identifies the preoperative renal parenchymal volume ($V_{preoperative}$) as a function of the remaining functional renal parenchyma postoperatively ($V_{postop.functional}$), the zone of virtually zero renal parenchymal functionality due to ischemia ($V_{ischemia}$), as well as the volume of the surgical specimen ($V_{specimen}$).

$$V_{preoperative} = V_{postop.functional} + V_{ischemia} + V_{specimen} \quad (4)$$

Rearranging the terms of Equation 1 and utilizing Equation 4 finally leads to Equation 5.1. The latter identifies the postoperative renal parenchyma volume as a function of the preoperative renal parenchyma and the specimen volume ($V_{preoperative}$, $V_{specimen}$), as well as the residual functional parenchyma and the ischemic zone volume ($V_{postop.functional}$, $V_{ischemia}$).

$$V_{postoperative} = V_{preoperative} - V_{specimen} = V_{postop.functional} + V_{ischemia} \quad (5.1)$$

Finally, by reordering the terms of Equation 5.1 we arrive at Equation 5.2 presented below.

$$V_{preoperative} - V_{postop.functional} - V_{specimen} - V_{ischemia} = 0 \quad (5.2)$$

According to Pasichnyk *et al*., the functional renal parenchyma preoperatively is determined by the volume of the neoplastic lesion, while in the mathematical model developed by the authors the tumor volume was considered to have practically zero functionality (32). In Equation 6.1 we express the preoperative renal volume ($V_{preoperative}$) as the sum of functional ($V_{preop.functional}$) and non-functional parenchyma ($V_{preop.non\ functional}$), while in Equation 6.2 we assign the non-functional part to the lesion volume (V_{tumor}). Finally, in Equation 6.3 follows the combination of the above two equations.

$$V_{preoperative} = V_{preop.functional} + V_{preop.non\ functional} \quad (6.1)$$

$$V_{preop.non\ functional} = V_{tumor} \quad (6.2)$$

$$V_{preoperative} = V_{preop.functional} + V_{tumor} \quad (6.3)$$

Then, by combining Equations 5.2 and 6.3 we are led to the formulation of Equation 7.1.

$$V_{preop.functional} + V_{tumor} - V_{postop.functional} - V_{specimen} - V_{ischemia} = 0 \quad (7.1)$$

After the rearrangement of the terms in Equation 7.1, finally Equation 7.2 emerges.

$$V_{preop.functional} - V_{postop.functional} - (V_{specimen} - V_{tumor}) - V_{ischemia} = 0 \quad (7.2)$$

The difference: $V_{specimen} - V_{tumor}$ practically expresses the marginal zone volume of healthy renal parenchyma around the tumor that is

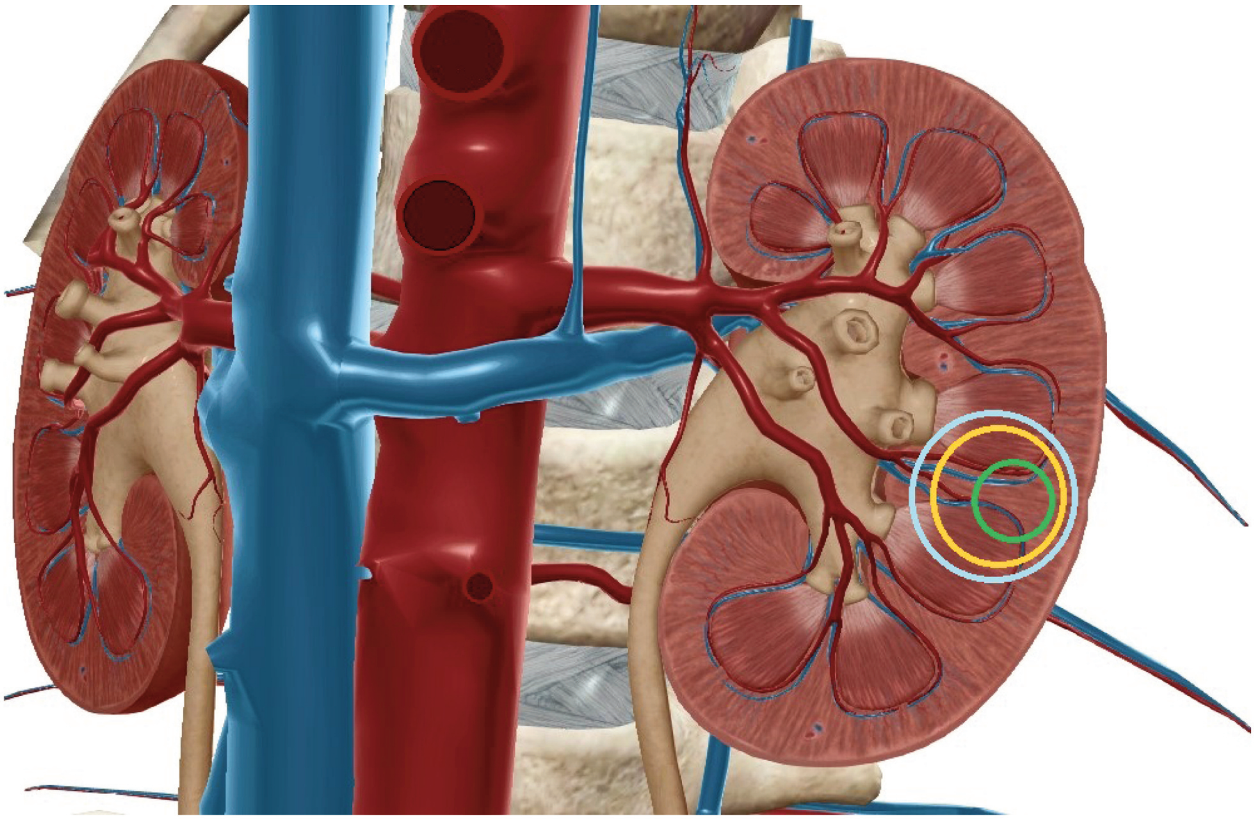


Figure 1. *Schematic representation of the renal parenchyma zones that are functionally affected after partial nephrectomy surgery. Green color corresponds to the tumor volume (V_{tumor}), yellow corresponds to the resection volume ($V_{specimen}$) and blue corresponds to the remaining renal parenchyma around the resection site, with reduced functionality due to previous application of some type of ischemia ($V_{ischemia}$). The anatomical 3D model was created via the Visible Body 3D® software.*

resected as part of the surgical specimen along with the neoplastic lesion ($\Delta V_{threshold}$). Therefore, according to the above we can arrive at Equation 7.3.

$$\Delta V_{threshold} = V_{specimen} - V_{tumor} \quad (7.3)$$

The combination of Equations 7.3 and 7.2 finally results in Equation 8.1, which is the final equation describing renal parenchyma volume balance after partial nephrectomy procedures.

$$V_{preop\,functional} - V_{postop\,functional} - \Delta V_{threshold} - V_{ischemia} = 0 \quad (8.1)$$

By rearranging the terms of Equation 8.1 we finally arrive at Equation 8.2 that is presented below.

$$V_{preop\,functional} - V_{postop\,functional} = \Delta V_{threshold} + V_{ischemia} \quad (8.2)$$

By defining the difference: $V_{preop\,functional} - V_{postop\,functional}$ as the absolute decrement in functional renal parenchyma volume (FRPV) after partial nephrectomy ($|\Delta V_{functional}|$), we are led to Equation 8.3.

$$|\Delta V_{functional}| = V_{preop\,functional} - V_{postop\,functional} \quad (8.3)$$

Substituting Equation 8.3 into Equation 8.2 finally yields Equation 9.

$$|\Delta V_{functional}| = \Delta V_{threshold} + V_{ischemia} \quad (9)$$

Equation 9 expresses the total volume balance after partial nephrectomy procedures. The above mathematical relationship defines the absolute reduction of FRPV as the sum of the ischemic zone volume around the resection site, and the volume of normal renal parenchyma contained in the surgical specimen of the operation.

By delving into the above equation, we could hypothesize that since no predefined surgical margins threshold is required in NSS procedures (33), the average proportion of normal renal parenchyma removed along with the tumor could be considered approximately constant. The above assumption implies that the quantity $\Delta V_{threshold}$ can be considered fixed among different patients undergoing partial nephrectomy. Therefore, considering the parameters: $|\Delta V_{functional}|$ and $V_{ischemia}$ as variables, while the $\Delta V_{threshold}$ parameter as a fixed term, it emerges that the change in FRPV depends on the zero-functionality zone (ZFZ) induced by the intraoperative application of ischemia among patients undergoing PN. The above position can be further supported by the assumption of uniformity in both GD as well as nephron functionality per unit of FRPV. Additionally, in order for the Equation 9 to be considered valid, the absence of complications such as the development of postoperative renal infarct away from the resection site is also necessary, as in this case the induced necrobiotic region would be added to ZFZ. An additional limitation stems from the fact that the $\Delta V_{threshold}$ term cannot be considered constant in the case of heterogeneous populations of patients with solitary and multiple renal tumors undergoing single-stage resection. Finally, an interesting observation has to do with the fact that due to the determination of the change in FRPV, the parameters of the size of the tumor as well as the level of functionality of the kidney are eliminated on a case-by-case basis.

Proportionality expressions. In this section, we focus our analysis on the key-parameters determining the two main trifecta definitions. Specifically, we are going to explore the proportionality relationships interconnecting each one of them with the volumetric terms already discussed in Equation 9. In the analysis that is to follow, the proportions are notated via the symbol "∝", as in the corresponding study of Cerbus *et al*. (34). The first part of the section is concerned with investigating the relationship between ischemia time (IT) and the ZFZ volume (ZFZV) around the resection site. Finally, in the second part, the effect of the absolute change in FRPV on the corresponding decrement in eGFR is investigated.

According to Damasceno-Ferreira *et al*. (35), about a quarter of the glomeruli are lost after the application of about 30 min of ischemia, while the limit of 20 min is the beginning of the formation of the ischemia zone. In their study dealing with the effect of the application of warm ischemia in a pig model, the researchers observed a progressive loss of nephrons with the prolongation of the ischemia duration, attributing to the above parameters a clearly proportional relationship. The response of normal renal tissue to the application of ischemia is generally considered to be homogeneous, as supported by the relevant study of Bechara *et al*. (36). In a previous study it was determined that the effect of ischemia, results in the formation of a well-defined zone characterized microscopically by the destruction of the microvascular architecture (37). This finding was linked to the hypothesis that revascularization is not particularly likely in this area (ZFZ). In another study investigating the impact of warm ischemia time (WIT) on ZFZ formation in a porcine model, de Souza *et al*. observed a significant decrease in glomerular density (GD) with prolonged application of WIT (26). GD was defined as the quotient of the number of nephrons per unit of renal parenchyma volume, while an interesting finding was the observation of a decrease in the absolute number of functional nephrons without a corresponding decrease in their distribution area. In this study, it is clearly described that the ZFZ refers to a strictly defined spatial area characterized by an almost total loss of the number of functional nephrons, while in its development the effect of ischemia time is also implied to be linear. Another interesting finding was that the serum creatinine levels remained unchanged, which was attributed to the normal function of the contralateral kidney (26). Finally, Mir and her colleagues in their related study sought to formulate a model for predicting postoperative renal function based on data on the type and duration of ischemia and the percentage of normal renal parenchyma preservation in patients submitted to PN (24). Specifically, the researchers utilized as a control variable the ratio of the percentage of preserved GFR to the percentage of preserved renal parenchyma volume (PRPV). They attributed to this variable the property of representing the proportion of nephron function recovery in the parenchyma that remains after resection of the surgical specimen. Theoretically, the recovery rate would be expected to be around 100%, however in their results it was estimated at approximately 80% with the difference been attributed to the application of WIT. The point of intersection with what we have already mentioned, concerns the PRPV, defined as the volume difference between the preoperative renal parenchyma ($V_{preoperative}$) and the surgical specimen ($V_{specimen}$), thus representing $V_{postop.functional}$. This parameter appears to decrease almost linearly with increasing ischemia duration (24). Therefore, according to Equation 5.1 ($V_{postop.functional} = V_{postoperative} - V_{ischemia}$), an equally linear increase in ZFZV ($V_{ischemia}$) emerges. Assigning the weight factor k_1 to the interaction between IT, $V_{ischemia}$ and based on the above, we can directly proceed to the assumption of the Expression 10.

$$IT \propto k_1 \cdot V_{ischemia} + \text{const} \qquad (10)$$

In the above study, the authors also investigated the relationship between PRPV and renal function as expressed through GFR, additionally to the effect of ischemia. In particular, a direct correlation was observed between the change in GFR (ΔGFR) and the proportion of PRPV. In particular, this effect was found to be much stronger than that in which IT intervenes as a prognostic factor (24). Moreover, considering the glomerular filtration rate proportional to the number of nephrons (38), it follows that in case of homogeneous GD, there is a given *d* (GFR) per unit of FRPV. In this case the total GFR is obtained as the sum of the individual *d* (GFR), and is proportionally related to FRPV. In a study of renal function in living kidney donors (LKD), Nunes-Carneiro *et al*. observed a direct correlation between the ratio of residual kidney volume (RKV) to weight (W) and the medium-term renal function, as expressed through the eGFR (39). The RKV parameter utilized by the authors, corresponds in our study to the postoperative FRPV ($V_{postop.functional}$). Upon careful review of the model developed by the authors, it becomes apparent that in case of approximating ΔeGFR through the change in FRPV ($|\Delta V_{functional}|$), then the weight of each patient is introduced as a multiplication constant to the decrement in renal function. In another related study carried out by Shinoda *et al*. in LKD it was observed that age, Body Mass Index (BMI), pre-operative GFR and preserved kidney volume (PKV) are independent predictors of postoperative GFR (40). It is noted that the PKV parameter used in the above study corresponds to that of $V_{postop.functional}$ in the present investigation. From this model we can observe the direct proportional correlation of FRPV with GFR, while it is of particular interest that the other parameters that seem to interfere, are related to individual patient characteristics, and are therefore eliminated during the determination of ΔeGFR. In the study conducted by Pasichnyk *et al*., it is explicitly stated that GFR is directly proportional to the number of nephrons or otherwise to the functional renal parenchyma (32). In the model presented by the authors for the determination of GFR, the parameters involved included the patients' age and weight, FRPV and the corresponding serum creatinine level. However, it is useful to note that creatinine concentration is expressed in units: mmol/l, while FRPV in mm^3 and therefore there is a significant difference in the order of magnitude between the above two parameters. Finally, in this case as well, it becomes evident that the parameters related to patient characteristics are eliminated during the calculation of ΔeGFR. In another model intending to estimate postoperative GFR in living kidney donors (LKD), Herts *et al*. observed that renal parenchymal volume correlates well with the level of renal function, with their relationship being strongly linear (41). Specifically, the above model resulted in an equation for determining GFR ($GFR=70.77–0.444A+0.366W+0.20V_R–37.317Cr$), in which its proportional relationship with age (A), weight (W), residual normal renal parenchyma (V_R; FRPV), and serum creatinine level (Cr) was evident. Almost identical were the conclusions drawn from a similar study conducted by Goh *et al*. aiming also to determine postoperative GFR in LKD (42). Verifying the predictive value of the respective model formulated by Herts *et al*., the authors reported that it outperforms the already available $MDRD_4$, $MDRD_6$ (43) and CKD-EPI equations which have been judged to have the highest validities among all available equations for determining GFR (44). From the above two studies, the proportional relationship that exists between GFR and FRPV as well as the level of serum creatinine in patients undergoing nephrectomy as living donors becomes evident. Focusing now on studies involving patients undergoing partial nephrectomy, we observe that the role of creatinine may not be as important as the PRPV parameter. Specifically, Simmons *et al*. investigated the effect of volume preservation on postoperative renal function of patients undergoing partial nephrectomy (45). In their conclusions, the authors stated that the preoperative functional renal parenchyma as well as its preservation rate are the primary determinants of long-term functional outcomes post PN. In fact, the correlation coefficient between the proportion of preserved FRPV and eGFR was estimated ranging from 83% to 96%, highlighting a clearly linear relationship. Finally, in another study of similar interest, Liu *et al*. aimed to preoperatively predict the level of renal function in patients submitted to partial nephrectomy by developing an image-based volumetric analysis model (46). In their model the researchers utilized three basic equations, while they also included the volume of the contralateral healthy kidney in their volumetric calculations. In the first equation ($V_{post} = V_{pre} – V_{def}$), postoperative renal volume (V_{post}) was defined as the difference between the preoperative parenchymal volume (V_{pre}) and that remaining nonfunctional after the resection (V_{def}). The above equation lies in agreement with Equation 4 of the present study with V_{post} corresponding to $V_{postop.functional}$, V_{pre} to $V_{preoperative}$, and V_{def} to the sum: $V_{specimen} + V_{ischemia}$. In their second equation, the authors defined as "*f*" the proportion of renal parenchyma preservation

$$\left(f = \frac{V_{pre} - V_{def}}{V_{pre}} \right),$$

while in their third equation they implemented a parametric adjustment (*FI*) on their original hypothesis to include the contralateral kidney in the calculations [$FI=0.5(1+f)$]. From the analysis that was carried out, a robust linear relationship emerged between GFR and V_{def}. Moreover, kidney function expressed *via* GFR was even divided into short- and long-term, with WIT being an independent prognostic indicator for the first, and V_{def} mainly affecting the second.

From the bibliographic data discussed, it is possible to observe that in the studies dealing with patients undergoing PN and not radical surgery as kidney donors, the intrusion of the creatinine level as an additional parameter is not observed in the relevant models for the determination of GFR through FRPV. This observation can reasonably be attributed to the pronounced difference between the above procedures in terms of the volume of functional renal parenchyma removed by surgery. Therefore, in the following mathematical expressions, initially the creatinine term (Cr) is included, while after the final formulation of the proportionality relationships for the variables of interest, an appropriate assumption will be made for its elimination regarding patients undergoing partial nephrectomy. As it becomes evident in the relevant study of Herts *et al*., the effects from V_R and Cr on GFR are generally different from each other (41, 42). In the relationships listed below, k_V, k_{Cr}, refer to weighting constants of proportionality for volume and creatinine parameters respectively, in terms of the determination of eGFR. Thus, in line with the above and assuming a linear relationship among eGFR, FRPV, and Cr both pre- and postoperatively, the Expressions 11.1 and 11.2 emerge.

$$eGFR_{preoperative} \propto k_V \cdot V_{preop.functional} + k_{Cr} \cdot Cr_{preoperative} + const. \quad (11.1)$$

$$eGFR_{postoperative} \propto k_V \cdot V_{postop.functional} + k_{Cr} \cdot Cr_{postoperative} + const. \quad (11.2)$$

Then, substituting Equation 8.1 into the Expression 11.1 finally yields the Expression 11.3.

$$eGFR_{preoperative} \propto k_V \cdot (V_{postop.functional} + V_{ischemia} + \Delta V_{threshold}) + k_{Cr} \cdot Cr_{preoperative} + const. \quad (11.3)$$

Subsequently, we consider the absolute decrease in glomerular filtration rate as defined in Equation 12.

$$|\Delta eGFR| = eGFR_{preoperative} - eGFR_{postoperative} \quad (12)$$

Thus, substituting the Expressions 11.2 and 11.3 into Equation 12 finally results in Expression 13.1.

$$|\Delta eGFR| \propto k_V \cdot (V_{ischemia} + \Delta V_{threshold}) + k_{Cr} \cdot (Cr_{preoperative} - Cr_{postoperative}) + const. \quad (13.1)$$

Rearranging the terms of Expression 13.1 finally yields the Expression 13.2.

$$|\Delta eGFR| \propto k_V \cdot (V_{ischemia} + \Delta V_{threshold}) - k_{Cr} \cdot (Cr_{postoperative} - Cr_{preoperative}) + const. \quad (13.2)$$

In the above expression, the difference: $Cr_{postoperative} - Cr_{preoperative}$ reflects the absolute increase in serum creatinine postoperatively due to the loss of functional renal parenchyma and is mathematically defined in Equation 14.

$$|\Delta Cr| = Cr_{postoperative} - Cr_{preoperative} \quad (14)$$

Thus, substituting Equation 14 in the Expression 13.2 finally results in the Expression 15.1.

$$|\Delta eGFR| \propto k_V \cdot (V_{ischemia} + \Delta V_{threshold}) - k_{Cr} \cdot |\Delta Cr| + const. \quad (15.1)$$

Rendering the proportional relationship described in Expression 15.1 in the form of an equation, assuming "α" as the proportionality factor and "c" as a constant, yields Equation 15.2.

$$|\Delta eGFR| = \alpha \cdot k_V \cdot (V_{ischemia} + \Delta V_{threshold}) - \alpha \cdot k_{Cr} \cdot |\Delta Cr| + c \quad (15.2)$$

By rearranging the terms of Equation 15.2 we finally get Equation 15.3.

$$|\Delta eGFR| + \alpha \cdot k_{Cr} \cdot |\Delta Cr| = \alpha \cdot k_V \cdot (V_{ischemia} + \Delta V_{threshold}) + c \quad (15.3)$$

Finally, by rendering Equation 15.3 to reflect the proportionality relationship, we finally arrive at the Expression 15.4.

$$|\Delta eGFR| + \alpha \cdot k_{Cr} \cdot |\Delta Cr| \propto V_{ischemia} + \Delta V_{threshold} + const. \quad (15.4)$$

According to the above mathematical expression, the overall change in renal function as expressed by the absolute decrement in glomerular filtration rate and serum creatinine level adjusted by the factor $\alpha \cdot k_{Cr}$, is directly proportional to the sum of the ischemic zone volume around the resection site and the excess normal renal parenchyma that is resected along with the tumor as part of the surgical specimen. The above observation is reinforced by the position of Mir *et al*. in their relevant study, according to which preserving as much of well-vascularized healthy renal parenchyma as possible during PN procedures, represents the outmost importance strategy for maximizing postoperative renal function (24).

Linear equations. In the following, the final mathematical expressions of the previous section will first be rendered in the form of linear equations. Subsequently, the analysis is going to be extended by studying the interaction between the two parameters describing renal function (|ΔeGFR|, IT) and are involved in the various definitions of the "trifecta outcome". To achieve the investigation of the above interconnection, the variability of parameters related to renal function is controlled for all patients undergoing partial nephrectomy according to the hypotheses already declared in the concluding part of the first section. Finally, appropriate conclusions will be drawn regarding all patients with solitary renal masses undergoing PN by formulating mathematical expressions containing differentials.

Starting with the Expression 10, this can be written in the form of the linear Equation 16.1.

$$\mathrm{IT} = \alpha_1 \cdot V_{ischemia} + c_1 \quad (16.1)$$

As mentioned above, the introduction of the creatinine term in the proportionality relationships obtained in the previous section, was based on studies involving radical nephrectomy operations in living kidney donors (39-42). In these types of operations, the volume of functional renal parenchyma that is removed is much lesser compared to partial nephrectomy procedures. This statement is supported by relevant volumetric analysis studies on the effect of FRPV change on renal function decrement in patients undergoing PN (45, 46). Consequently, by neglecting the term of the absolute change in creatinine levels in Expression 15.4, the linear Equation 16.2 is finally obtained.

$$|\Delta eGFR| = \alpha_2 \cdot (V_{ischemia} + \Delta V_{threshold}) + c_2 \quad (16.2)$$

We will then explore the forms that the Equations 16.1 and 16.2 can receive for the various patients undergoing partial nephrectomy. From Equation 16.1 it appears that the change in ZFZV [$\Delta(V_{ischemia})$] occurs mainly due to the change in intraoperatively applied ischemia duration [$\Delta(IT)$]. Thus, by differentiating the above equation with respect to IT, Equation 16.3 is finally obtained.

$$\frac{\partial(V_{ischemia})}{\partial(IT)} = \frac{1}{a_1} \quad (16.3)$$

While Equation 16.3 can be approximated in a simpler form through Equation 16.4.

$$\Delta(V_{ischemia}) = \frac{1}{a_1} \cdot \Delta(IT) \quad (16.4)$$

On the other hand, in Equation 16.2 it becomes apparent that the variation in the absolute decrement in glomerular filtration rate [$\Delta(|\Delta eGFR|)$] among different patients undergoing PN is a linear combination of the change in ZFZV [$\Delta(V_{ischemia})$] and the variation in the volume of excess normal renal parenchyma excised along with the lesion [$\Delta(\Delta V_{threshold})$]. Thus, by differentiating the above equation with respect to $V_{ischemia}$, Equation 16.5 is finally obtained.

$$\frac{\partial(|\Delta eGFR|)}{\partial(V_{ischemia})} = a_2 \cdot \left(1 + \frac{\partial(\Delta V_{threshold})}{\partial(V_{ischemia})}\right) \quad (16.5)$$

As discussed above, among the various PN procedures no proportional relationship between tumor size and resection margin threshold is imposed oncologically (47). Therefore, it could be assumed that the variation of $\Delta V_{threshold}$ is relatively small among patients with solitary renal masses submitted to PN. In practice, this margin ranges around 5 mm beyond the periphery of the neoplastic lesion, while it does not seem to depend on the duration of ischemia (48). Consequently, the term

$$\frac{\partial(\Delta V_{threshold})}{\partial(V_{ischemia})}$$

in Equations 16.5 can be eliminated and therefore it can receive the form of the Equation 16.6.

$$\frac{\partial(|\Delta eGFR|)}{\partial(V_{ischemia})} = a_2 \quad (16.6)$$

While Equation 16.6 can be approximated in a simpler form through Equation 16.7.

$$\Delta(|\Delta eGFR|) = \alpha_2 \cdot \Delta(V_{ischemia}) \quad (16.7)$$

Finally, from the combination of Equations 16.3 and 16.6 it is possible to arrive at Equation 16.8.

$$\frac{\partial(|\Delta eGFR|)}{\partial(\mathrm{IT})} = \frac{a_2}{a_1} \quad (16.8)$$

While Equation 16.8 can be approximated in a simpler form through Equation 16.9.

$$\Delta(|\Delta eGFR|) = \frac{a_2}{a_1} \cdot \Delta(IT) \quad (16.9)$$

From the above equation, the direct proportional relationship that appears to exist between the two main parameters of kidney function that are incorporated in the various trifecta definitions becomes apparent. Thus, for a given change in ischemia duration $\Delta(IT)=\Delta t$, Equation 16.4 yields a corresponding change in the ischemic zone volume equal to:

$$\Delta(V_{ischemia}) = \frac{1}{a_1} \cdot \Delta t$$

Finally, from Equation 16.7 there is a corresponding change in the absolute reduction of the glomerular filtration rate equal to:

$$\Delta(|\Delta eGFR|) = \frac{a_2}{a_1} \cdot \Delta t$$

As can be seen from the calculation process of the above parameters, the sequence of effects follows the direct causality that connects the three variables according to the physiology of renal function. Expression 17.1 lists the causal sequence between the changes: $\Delta(IT)$, $\Delta(V_{ischemia})$ and $\Delta(|\Delta eGFR|)$, with the arrows connecting cause and effect in each case, while immediately above the arrows the transformation factor is also demonstrated (49).

$$\Delta(IT) \xrightarrow{1/a_1} \Delta(V_{ischemia}) \xrightarrow{a_2} \Delta\left(|\Delta eGFR|\right) \quad (17.1)$$

Finally, the transformations of the above variables in both directions of causality become apparent in Expression 17.2. In this representation the corresponding transformation factor is assigned to each arrow that connects cause and effect.

$$\Delta(IT) \underset{a_1}{\overset{1/a_1}{\rightleftarrows}} \Delta(V_{ischemia}) \underset{1/a_2}{\overset{a_2}{\rightleftarrows}} \Delta\left(|\Delta eGFR|\right) \quad (17.2)$$

By closing the present section, we finally arrived at the configuration of the Expressions 17.1 and 17.2 through the utilization of the available literature. The represented relationships describe in mathematical terms the central role played by ZFZ ($V_{ischemia}$) in shaping the postoperative renal function level of patients with solitary tumors undergoing one-stage partial nephrectomy. In fact, as can be seen from the combination of Equations 16.1 and 16.2, and Expressions 17.1 and 17.2, the ratio of the changes in each of the variables |ΔeGFR| and IT (α_2/α_1) is equal to the quotient of the effects that $V_{ischemia}$ has respectively in their determination. Consequently, it was shown that the two parameters of renal function that are utilized in the various definitions of trifecta (|ΔeGFR|, IT) have as their point of intersection the parameter $V_{ischemia}$, thus constituting two different courses for its assessment. More simply they could be characterized as the two sides of the same coin regarding the theoretical estimation of the change in renal function.

Results

The initial set of 180 reports ultimately retrieved from the international literature, yielded 11 studies describing comparative data on the “trifecta outcome” achievement rates. Of those 3 concerned the comparison between robotic and open partial nephrectomy (RPN *vs*. OPN), and 8 concerned the comparison between robot-assisted and open partial nephrectomy (RAPN *vs*. OPN). Additionally, regarding the renal function regulatory parameter utilized in each case for the definition of trifecta, 6 studies adopted the ischemia time, while the remaining 5 the estimated glomerular filtration rate change. The results of the above-described literature research are presented in the flowchart of Figure 2 according to the PRISMA statement (50).

These 11 comparative studies, including a total of 2,877 patients, were used to investigate the parameters that compose the concept of trifecta and the final configuration of the prevailing definitions in the international literature. Table I includes the abovementioned sample of studies, while highlighting some of their individual characteristics, such as data regarding author’s name, year of publication, duration in days, and the methodology. This table also presents the triads of parameters used to define trifecta in each study. Based upon these, the included studies were classified into two main categories. The first incorporated all studies that used as a criterion for the change of renal function, the duration of ischemia that does not exceed 25 min. The second category included all studies that adopted the 10% threshold as the criterion for the percentage change in estimated glomerular filtration rate. Figure 3 depicts in the form of pie charts, the amount of data that were utilized according to the country of origin, both at the level of studies and at that of patients. These data are also presented in the form of a map chart with color percentage scale in Figure 4, where the adequacy of the representativeness of the sample of studies at an international level becomes apparent, while the majority of the patient population came mainly from the United States, Canada and Italy. Figure 5 shows the percentages of studies and patients included in the analysis, according to whether any kind of patient characteristics matching protocol was implemented, prior to any statistical analysis procedure. From this diagram it becomes apparent that approximately 25% of the available data, as an average of both study and patient levels, were derived from studies that applied some sort of patient matching. Figure 6 shows the corresponding percentages of studies and patients, according to whether each included study was conducted as single- or multicenter. In this case, it emerges that approximately 60% of all the data, as an average from both levels, came from multicenter studies. Finally, Figure 7 presents the percentages of studies and patients included in the analysis, according to the renal function decline parameter utilized in each case as the definition of the “trifecta outcome”. By taking into account both the level of studies and that of patients, the sample of studies included was balanced regarding the aforementioned study subgroups.

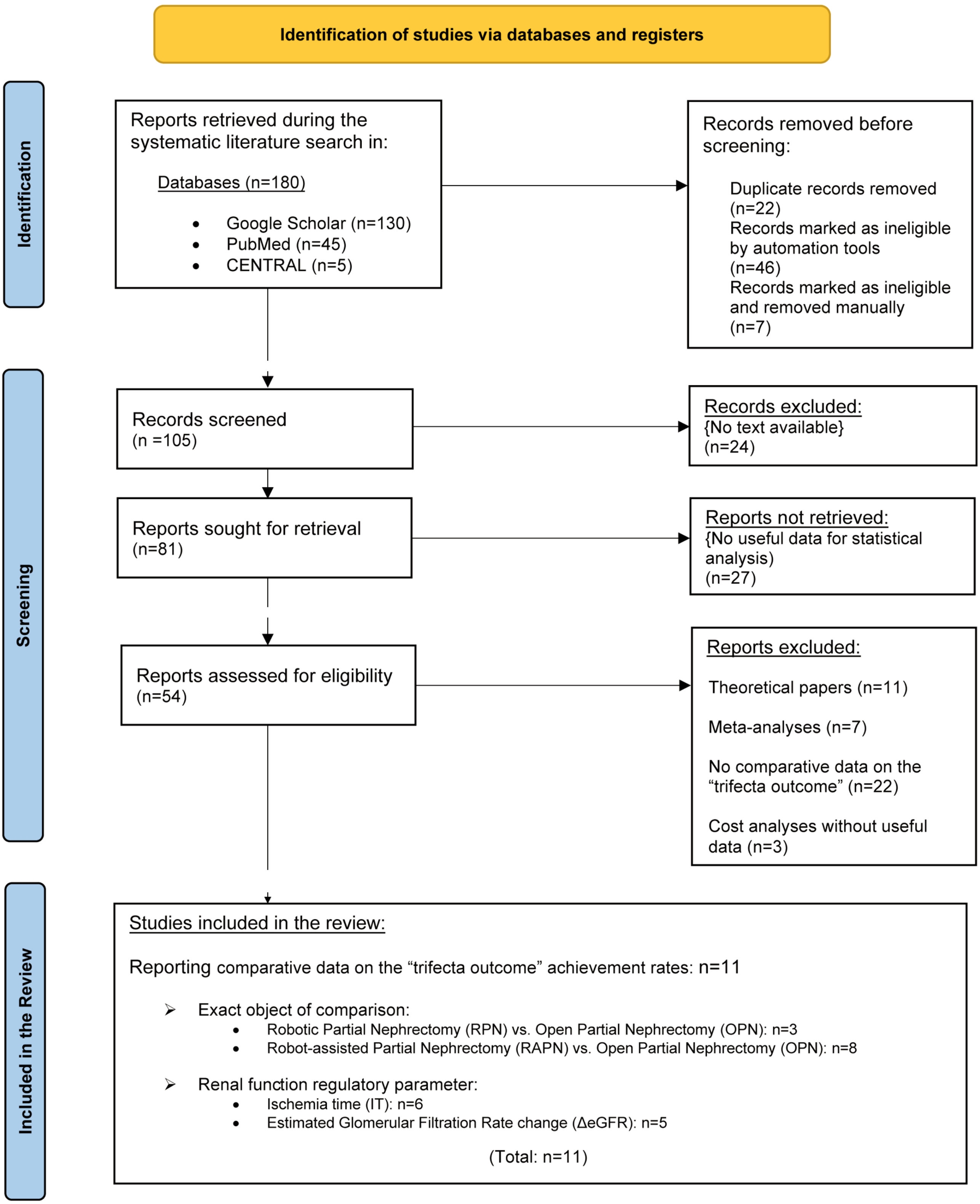


Figure 2. *Flow-chart of studies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).*

Table I. *Table of the final set of 11 studies included, providing information about the title, author, country of origin, year of publication, the study-specific definition of the "trifecta outcome", the study groups based on the renal function reduction criterion for the definition of trifecta, and other specific characteristics, such as whether each study was performed in a single or multiple centers, or whether any sort of patient characteristics matching protocol was applied, as well as the exact arms and corresponding patient populations under comparison in each study.*

Study title	Author & year (Population under comparison)	Country	Original criteria for the definition of trifecta (as reported in each respective study)	Grouping based on the renal function diminishment criterion for the definition of trifecta	Single-/ Multicenter study	Study with/ without patient matching	Experimental (n_{exp}) *vs*. Control group (n_{ctrl})
Which patients with clinical localized renal mass would achieve the trifecta after partial nephrectomy? The impact of surgical technique.	Bianchi *et al*. 2020 (23) (326 patients)	Italy	1. WIT <20 min 2. No PSM 3. No postoperative complications	IT <25 min	Single-center	Without patient matching	RAPN (n_{exp}=83) *vs*. OPN (n_{ctrl}=243)
Trifecta outcomes of partial nephrectomy in patients over 75 years old: Analysis of the Renal SURGery in Elderly (RESURGE) group.	Bindayi *et al*. 2019 (18) (477 patients)	USA	1. |ΔeGFR| <10% 2. No PSM 3. No complications of grade CD > II	|ΔeGFR| <10%	Multicenter	Without patient matching	RAPN (n_{exp}=152) *vs*. OPN (n_{ctrl}=325)
Functional and oncologic outcomes of open, laparoscopic, and robotic partial nephrectomy: A Multicenter comparative matched-pair analyses with a median 5 years follow up.	Chang *et al*. 2018 (19) (244 patients)	Korea	1. WIT <25 min 2. No PSM 3. No overall complications	IT <25 min	Multicenter	With patient matching	RAPN (n_{exp}=122) *vs*. OPN (n_{ctrl}=122)
Robotic partial nephrectomy for clinical T2a renal mass is associated with improved trifecta outcome compared to open partial nephrectomy: A single surgeon comparative analysis.	Ghali *et al*. 2020 (16) (150 patients)	USA	1. |ΔeGFR| <10% 2. No PSM 3. No complications of grade CD > II	|ΔeGFR| <10%	Single-center	Without patient matching	RPN (n_{exp}=59) *vs*. OPN (n_{ctrl}=91)
Achieving the "trifecta" with open *versus* minimally invasive partial nephrectomy.	Ghavimi *et al*. 2020 (17) (1030 patients)	Canada	1. |ΔeGFR| <10% 2. No PSM 3. No urological complications	|ΔeGFR| <10%	Multicenter	Without patient matching	RPN (n_{exp}=284) *vs*. OPN (n_{ctrl}=746)
Are there limits of robotic partial nephrectomy TRIFECTA outcomes of open and robotic partial nephrectomy for completely endophytic renal tumors?	Harke *et al*. 2018 (20) (140 patients)	Gemany	1. WIT <25 min 2. No PSM 3. No overall complications	IT <25 min	Multicenter	Without patient matching	RAPN (n_{exp}=64) *vs*. OPN (n_{ctrl}=76)

Table I. *Continued*

Table I. *Continued*

Study title	Author & year (Population under comparison)	Country	Original criteria for the definition of trifecta (as reported in each respective study)	Grouping based on the renal function diminishment criterion for the definition of trifecta	Single-/ Multicenter study	Study with/ without patient matching	Experimental (n_{exp}) *vs*. Control group (n_{ctrl})
Trifecta outcomes in open, laparoscopy or robotic partial nephrectomy: does the surgical approach matter?	Mehra *et al*. 2019 (2) (39 patients)	India	1. WIT <30 min 2. No PSM 3. No complications of grade CD > II	IT <25 min	Single-center	With patient matching	RAPN (n_{exp}=13) *vs*. OPN (n_{ctrl}=26)
Early single-center experience with robotic partial nephrectomy using the da Vinci Xi: Comparative assessment with conventional open partial nephrectomy.	Motoyama *et al*. 2019 (21) (74 patients)	Japan	1. IT <25 min 2. No PSM 3. No complications of grade CD > II	IT <25 min	Single-center	With patient matching	RAPN (n_{exp}=37) *vs*. OPN (n_{ctrl}=37)
Partial Nephrectomy in Clinical T1b Renal Tumors: Multicenter Comparative Study of Open, Laparoscopic and Robot-assisted Approach (the RECORd Project).	Porpiglia *et al*. 2016 (22) (228 patients)	Italy	1. IT <25 min 2. No PSM 3. No overall complications	IT <25 min	Multicenter	Without patient matching	RAPN (n_{exp}=95) *vs*. OPN (n_{ctrl}=133)
Comparative Outcomes and Predictive Assessment of Trifecta in Open, Laparoscopic, and Robotic-Assisted Partial Nephrectomy Cases with Renal Cell Carcinoma: A 10-Year Experience at Ramathibodi Hospital.	Soisrithong *et al*. 2021 (60) (59 patients)	Thailand	1. |ΔeGFR| <10% 2. No PSM 3. No complications of grade CD > II	|ΔeGFR| <10%	Single-center	Without patient matching	RAPN (n_{exp}=41) *vs*. OPN (n_{ctrl}=18)
Trifecta outcomes in multifocal tumors: a comparison between robotic and open partial nephrectomy.	Yerram *et al*. 2018 (3) (110 patients)	USA	1. |ΔeGFR| <10% 2. No PSM 3. No urologic complications	|ΔeGFR| <10%	Single-center	With patient matching	RPN (n_{exp}=68) *vs*. OPN (n_{ctrl}=42)

RAPN: Robot-assisted partial nephrectomy; RPN: robotic partial nephrectomy; OPN: open partial nephrectomy; min: minutes; IT: ischemia time (min); WIT: warm ischemia time (min); |ΔeGFR|: absolute percentage decrement in the estimated glomerular filtration rate post-surgery (%); PSM: positive surgical margins; CD: Clavien–Dindo classification of surgical complications (6, 7); Experimental group: RPN / RAPN; Control group: OPN.

In the first part of the analytical procedure followed, Equations 16.4 and 16.7 showed that for a given change of one regulatory parameter (IT) a fixed corresponding change in the other (|ΔeGFR|) occurs. Therefore, having proved that the two above-mentioned definitions for the "trifecta outcome" are two sides of the same coin, Equation 16.9 proved to be the mathematical representation of equivalence of the two definitions prevailing in the international literature, with the result that the general conclusion can be described by the phrase: "trifecta: two definitions - one concept" (11). The main conclusion derived from the above equations places the volume of the ischemic renal parenchyma marginal zone around the resection bed ($V_{ischemia}$) as the central parameter, which is apparently the object of estimation from the two main definitions of trifecta, regarding the term of the postoperative renal function change in patients undergoing partial nephrectomy.

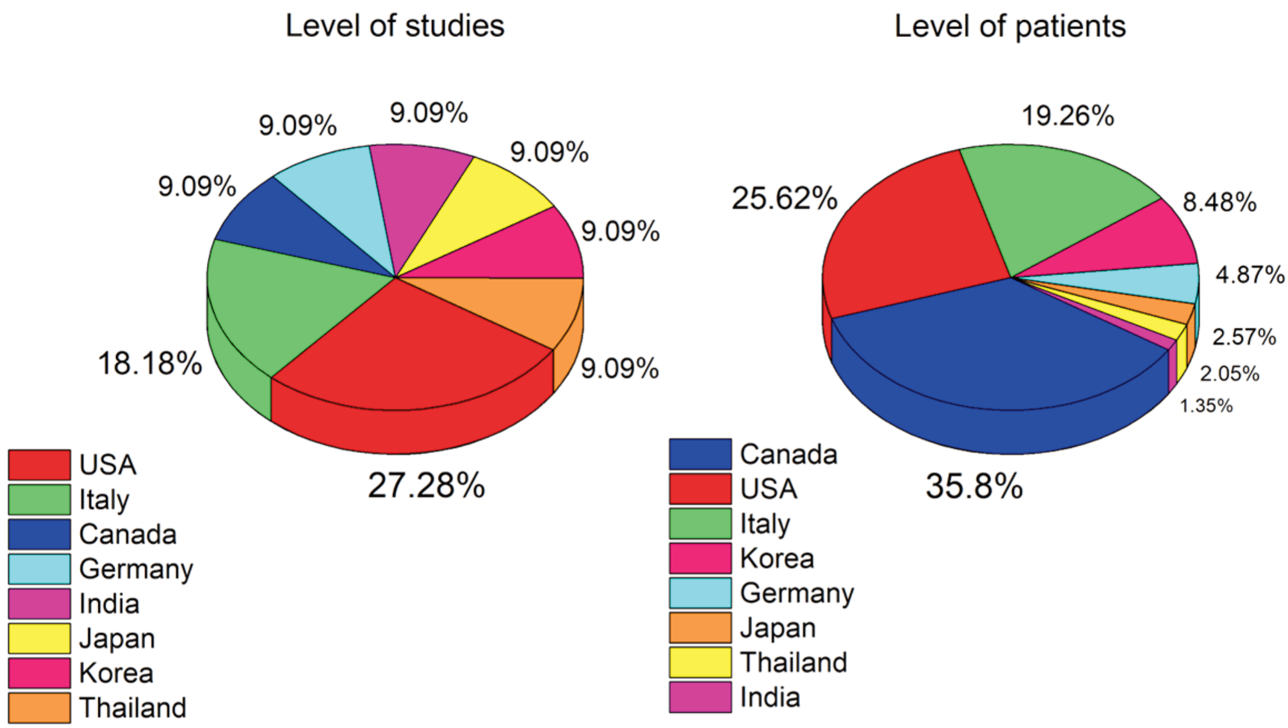
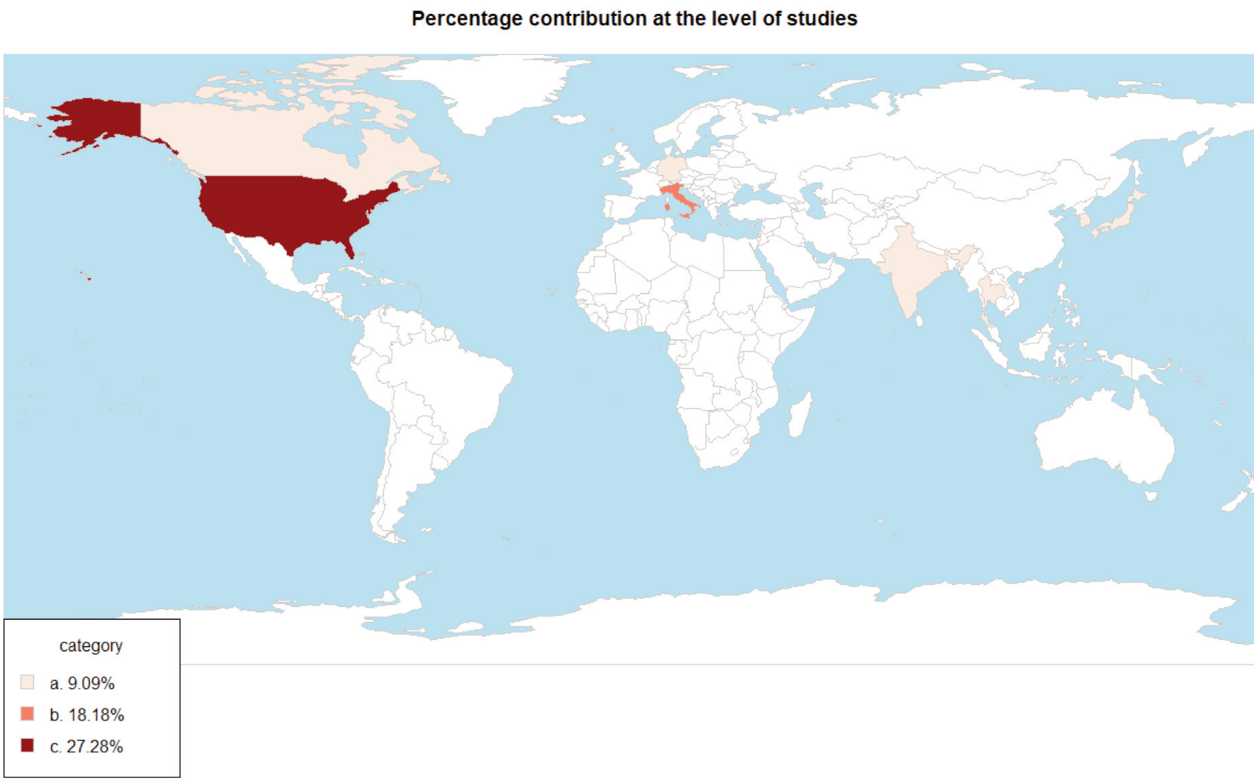


Figure 3. *Pie charts describing the amount of data that were utilized, according to the country of origin, both at the level of studies and at the level of patients.*

All comparative data between robotic and open partial nephrectomy studied are briefly summarized in Table II. By carefully observing the differences between the two approaches regarding the trifecta achievement rates, as well as the individual sub-parameters incorporated in its various definitions, none of them seems to perform superiorly over the other. Specifically, regarding the trifecta achievement rates, three are those studies that describe statistically significant differences between robotic and open partial nephrectomy. Bianchi *et al*. in 2020 (23) attempted to formulate a nomogram to predict the achievement of the trifecta outcome in patients who underwent open, laparoscopic, and robotic-assisted partial nephrectomy. In this study no differences were observed between the characteristics of patients, while in the definition of trifecta, warm ischemia time (WIT) was restricted at 20 min. In their results the researchers observed that RAPN outperforms OPN in terms of the trifecta outcome achievement rate (69.9% *vs*. 49%, p=0.003). In a similar study, Ghali *et al*. in 2020 (16) evaluated clinical T2 stage (cT2) patients who underwent robotic and open partial nephrectomy. As a criterion of renal function in the trifecta definition, an upper limit of 10% was set for the absolute change in estimated glomerular filtration rate (|ΔeGFR|). The characteristics between patients of the two groups did not differ significantly, while no differences were neither observed in the percentage of positive surgical margins or the absolute decrease in GFR. However, the robotic approach was associated with a significantly higher trifecta achievement rate (47.5% *vs*. 34%, p=0.047). A careful evaluation of the results of this study, shows only a marginally significant benefit on the part of RAPN. Finally, Motoyama *et al*. in 2019 (21) compared data of patients who underwent RAPN and OPN. In the above study, a patient matching protocol was implemented at a ratio of 1:1, while the criterion of limiting the duration of ischemia to 25 minutes was used to define trifecta. In their conclusions, the authors describe a significantly higher rate of its achievement with the adoption of the robotic approach over open surgery (91.9% *vs*. 62.2%, p=0.0057), while no difference was observed in terms of the median ischemia duration. Moving on to the individual sub-parameters of the trifecta outcome, we observed that only two studies emerged with statistically significant differences between robotic and open partial nephrectomy regarding the percentages of patients where positive surgical margins were found. In fact, these studies report conflicting results. The first study was described earlier and concerns the one conducted by Bianchi *et al*. in 2020 (23). In their results the



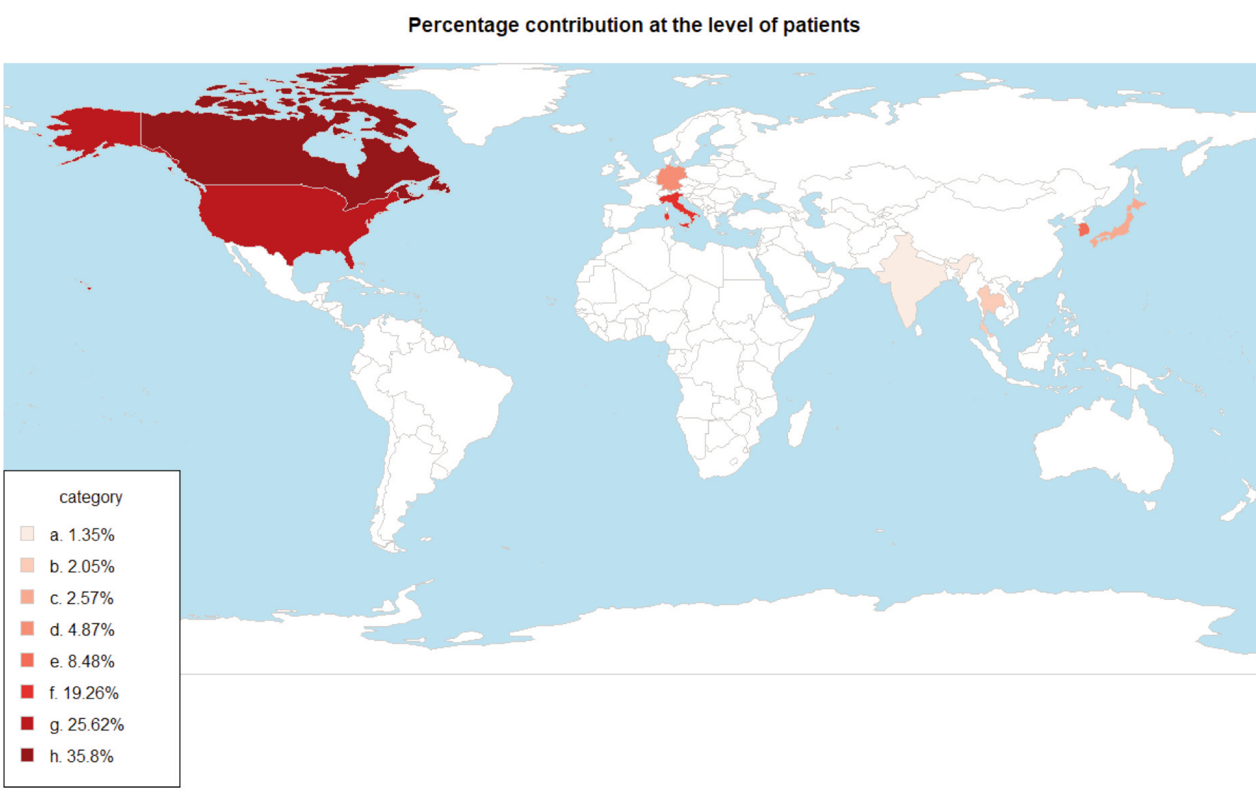


Figure 4. *Map charts describing presenting in a color percentage scale the amount of data that were utilized, both at the level of studies and at that of patients*.

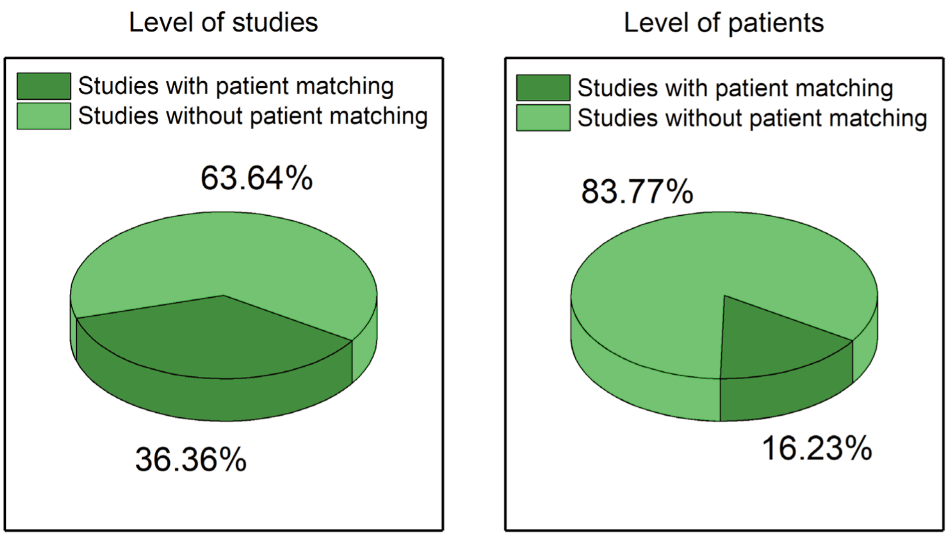


Figure 5. *Pie charts showing the percentage distribution of data utilized, at both the study and patient levels, according to whether any patient characteristics matching protocol was applied.*

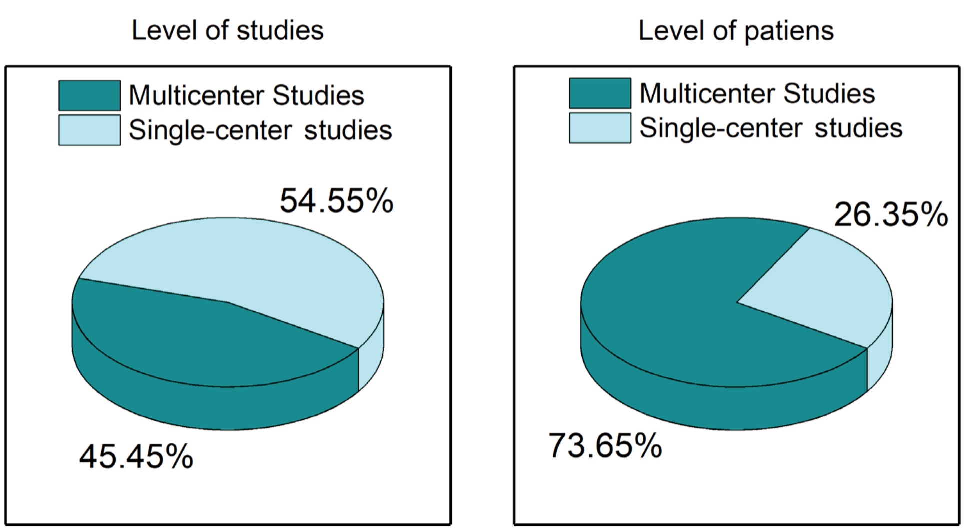


Figure 6. *Pie charts showing the percentage distribution of data utilized, at both the study and patient levels, according to whether they were derived from single-/multicenter studies.*

researchers describe the statistically significant superiority of RAPN over OPN regarding the outcome of positive surgical margins rates (3.6% *vs.* 11.5%, *p*=0.01). On the contrary, the second study was conducted by Ghavimi and colleagues in 2020 (17), with the authors considering the "trifecta outcome" as an overall measure of effectiveness of the surgical treatment provided in patients with clinical stage T1 (cT1) renal masses through nephron-sparing surgery (NSS). Specifically, groups of patients who underwent open, laparoscopic, and robotic partial nephrectomy were compared, while their baseline characteristics were comparable. The "|ΔeGFR| <10%" criterion was used to define trifecta, while no difference was observed regarding the frequency of its achievement between RPN and OPN (47% *vs.* 53%, *p*=0.194). However, a significant difference was observed in the rates of positive surgical margins, with open surgery having the advantage in this case (RPN: 11% *vs.* OPN: 6%, *p*=0.018). Subsequently, regarding the sub-parameter of complication rates, relatively low heterogeneity was observed among the final sample of studies that was

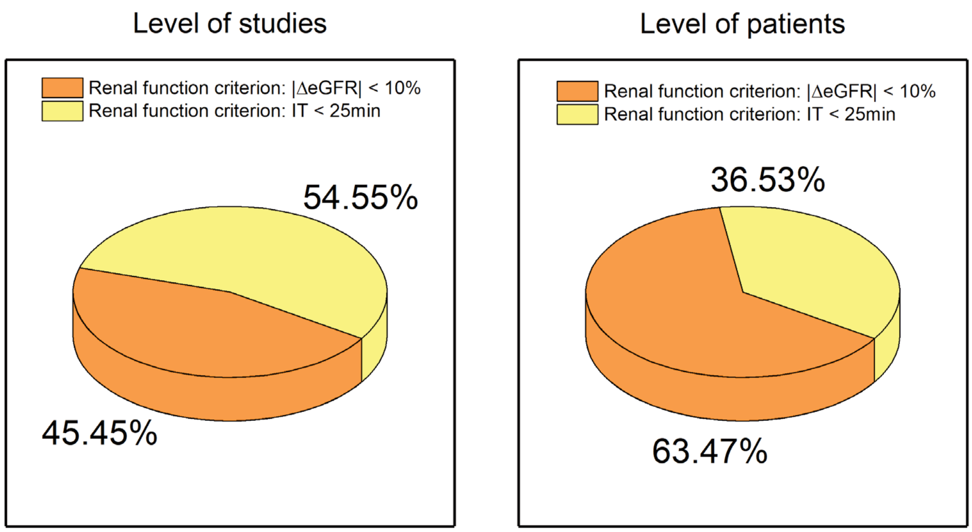


Figure 7. *Pie charts showing the percentage distribution of data utilized, at both the study and patient levels, according to the trifecta definitions clustering.*

isolated. In particular, 8 of the 11 studies (72.7%) contained coherent data concerning the incidence of major postoperative complications, two contained comparative data concerning exclusively urological complications (18.2%), and finally one described the incidence of in general postoperative complications (9.1%). In this case, only one study was found with a statistically significant difference between robotic and open partial nephrectomy in terms of the incidence of severe postoperative complications. The study in question was reported earlier and was conducted by Ghali *et al*. in 2020 (16). In their results the authors describe an advantage of RPN over open surgery (5.1% *vs*. 16.5%, *p*=0.041), with this result being considered in its essence as marginally statistically significant. The last section of data analyzed concerns the renal function of patients undergoing robotic *versus* open partial nephrectomy. Also, regarding this field of outcomes, all the assembled studies consistently presented data regarding the duration of ischemia and the proportion of patients in whom eGFR preservation was achieved in a percentage greater than or equal to 90%. For this group of sub-parameters, three were the studies that contained statistically significant differences. Chang *et al*. in 2018 (19) aimed to investigate surgical outcomes in patients who underwent OPN, LPN and RAPN for a follow-up period with a median of five years. In this study, patients were matched with a one-to-one ratio, while no differences were observed in their baseline characteristics. The "WIT ≤25 min" criterion was utilized to define trifecta, while its achievement rates did not differ significantly between RAPN and OPN (61.5% *vs*. 64.5%, *p*=0.387). On the other hand, the mean duration of ischemia was shorter in the group of patients who underwent partial nephrectomy with the adoption of the robotic approach (22±14.6 min *vs*. 27.1±13.2 min, *p*=0.018). Furthermore, Harke *et al*. in 2018 (20) studied patients with completely endophytic renal tumors who underwent RAPN and OPN. In this study as well, there were no significant differences between the two groups of patients, apart from the fact that more patients with a solitary kidney were included in the open surgery group. It is notable that also in this case the criterion "WIT ≤25 min" was utilized to define the "trifecta outcome". In the results of the study, there was no significant difference in the trifecta achievement rates between RAPN and OPN (75% *vs*. 68.4%, *p*=0.39). On the other hand, the median duration of ischemia was found to be shorter for the RAPN group (13 min *vs*. 18 min, *p*=0.001). Finally, Porpiglia *et al*. in 2016 (22) published a series of results obtained from the "RECORd" clinical study. Their article aimed to compare surgical outcomes between patients with clinical stage T1b (cT1b) renal tumors who underwent OPN, LPN, and RAPN. Trifecta was defined according to criterion: "IT <25 min". Baseline characteristics between the patients of different groups were comparable, while no significant difference was noted in the trifecta achievement rates between RAPN and OPN (69.5% *vs*. 62.4%, *p*=0.27). In contrast, the median duration of ischemia was determined to be longer in the RAPN group (18 min *vs*. 16 min, *p*=0.004).

Based on the above, it can be concluded that from the body of the available international literature we are unable to reach at a solid conclusion regarding the superiority or not of robotic partial nephrectomy over open surgery in terms of the "trifecta outcome" achievement rates. Likewise, neither

Table II. *Table containing comparative data from all included studies, regarding the achievement rates of the "trifecta outcome", as well as its individual sub-parameters in each arm under comparison.*

Study (Renal function parameter cluster)	Trifecta achievement rate (%)			Positive surgical margins rate (%)			Complications rate (%)			Impact on renal function		
	RPN/RAPN	OPN	*p*-Value	RPN/RAPN	OPN	*p*-Value	RPN/RAPN	OPN	*p*-Value	RPN/RAPN	OPN	*p*-Value
Bianchi *et al*. 2020 (23) (IT <25 min)	**69.9%**	**49%**	**0.003**	**3.6%**	**11.5%**	**0.01**	Severe Complications (%) 22.2%	20.2%	0.60	WIT (min); median (IQR) 14 (10-17) min	14 (9-17) min	>0.05
Bindayi *et al*. 2019 (18) (|ΔeGFR| <10%)	42.1%	38.5%	0.591	5.3%	3.4%	0.47	Urological Complications (%) 7.2%	5.8%	0.715	|ΔeGFR| <10% (%) 48%	42.8%	0.953
Chang *et al*. 2018 (19) (IT <25 min)	61.5%	64.8%	0.387	2.5%	1.6%	0.416	Severe Complications (%) 5.7%	7.3%	0.07	WIT (min); mean (SD) **22 (14.6) min**	**27.1 (13.2) min**	**0.018**
Ghali *et al*. 2020 (16) (|ΔeGFR| <10%)	**47.5%**	**34%**	**0.047**	3.4%	1.1%	0.561	Severe Complications (%) **5.1%**	**16.5%**	**0.041**	|ΔeGFR| <10% (%) 54.2%	47.2%	0.504
Ghavimi *et al*. 2020 (17) (|ΔeGFR| <10%)	47%	53%	0.194	**11%**	**6%**	**0.018**	Urological Complications (%) 3%	3%	0.595	|ΔeGFR| <10% (%) 52%	59%	0.105
Harke *et al*. 2018 (20) (IT <25 min)	75%	68.4%	0.39	0%	2.6%	N/A	Severe Complications (%) 10.9%	11.8%	0.87	IT (min); median (IQR) **13 (11-15) min**	**18 (12-23) min**	**0.001**
Mehra *et al*. 2019 (2) (IT <25 min)	61.53%	71.3%	0.73	7.7%	3.8%	N/A	Severe Complications (%) 15.4%	7.7%	N/A	WIT (min); median 27 min	23 min	0.923
Motoyama *et al*. 2019 (21) (IT <25 min)	**91.9%**	**62.2%**	**0.0057**	0%	8.1%	0.24	Severe Complications (%) 2.7%	2.7%	1.00	IT (min); median (range) 17 (8-39) min	19 (6-54) min	0.06
Porpiglia *et al*. 2016 (22) (IT <25 min)	69.5%	62.4%	0.27	2.5%	6.8%	0.16	Severe Complications (%) 1.1%	5.3%	0.09	IT (min); median (IQR) **18 (15-24) min**	**16 (14-20) min**	**0.004**
Soisrithong *et al*. 2021 (60) (|ΔeGFR| <10%)	64.71%	64.29%	0.502	4.88%	0%	0.999	Severe Complications (%) 7.32%	11.11%	0.675	|ΔeGFR| <10% (%) 32.35%	43.75%	0.388
Yerram *et al*. 2018 (3) (|ΔeGFR| <10%)	14.7%	17%	0.83	20%	20.6%	0.95	Overall Postoperative Complications (%) 32.4%	37.2%	0.70	|ΔeGFR| <10% (%) 72.6%	61.9%	0.36

RAPN: Robot-assisted partial nephrectomy; RPN: robotic partial nephrectomy; OPN: open partial nephrectomy; min: minutes; IT: ischemia time (min); WIT: warm ischemia time (min); |ΔeGFR|: absolute percentage decrement in the estimated glomerular filtration rate post-surgery (%), N/A: missing data. Significant *p*-Values are given in bold.

of the two aforementioned approaches seems to excel with respect to the sub-parameters that make up the definition of trifecta. Therefore, there is a need to construct and perform thorough meta-analyses, accompanied by appropriate subgroup analyses, meta-regression analyses, but also sensitivity analyses, with the integration of the maximum possible number of studies. In particular, this is the specific field to which the present study contributes. In the present article, by utilizing the principle of volume conservation we have formulated a model of mathematical equations, through which it has become possible to highlight the straight relationship connecting the two main definitions of trifecta found in the relevant literature. Consequently, with the knowledge offered by this study, the possibility is given in later meta-analyses to integrate the maximum possible number of studies, regardless of whether for the definition of trifecta the renal function parameter concerns either the duration of ischemia or the absolute change in the estimated glomerular filtration rate. At this point it is worth emphasizing that a necessary condition for the above is the formation of appropriate subgroups, whose analysis will be able to investigate any heterogeneity originating from the principle on the basis of which the "trifecta outcome" is defined in each case.

Discussion

In the present study, we reviewed the different definitions for the “trifecta outcome” that were adopted in a total of 11 comparative studies investigating any differences between RPN/RAPN and OPN concerning the frequency of its achievement. After the appropriate clustering of the included studies, considering the postoperative renal function change as the main parameter, we were led to the development of a mathematical model of volume conservation equations that allowed a thorough analysis and comparison between the two definitions found to be prevalent in the international literature. After completing the above process, we agreed with the theoretical position that has been supported in the relevant study by Zargar *et al*. (21) according to which regardless of the definition used for the consolidation of the “trifecta outcome” in each case, the concept that is represented is common.

From a thorough review of the mathematical model of volume conservation equations we developed, it was observed that the changes in both the estimated glomerular filtration rate and the ischemia duration can be used just as effectively for the assessment of partial nephrectomy’s effect on the extent of the ischemic zone around the resection site. The latter also represents the target-parameter related to the description of the postoperative renal function change included in the various definitions of trifecta in the international literature.

The term trifecta has been introduced into modern kidney surgery practice as an efficacy parameter after PN procedures. Therefore, concerning PN, the general definition of trifecta includes negative surgical margins, absence of major urological or non-urological, complications, and acceptable postoperative renal function (3). Thus, the therapeutic efficacy of PN is now defined in the context of the three terms that constitute the definition of trifecta (triple effect → tripleffect → tri-fect-a) (2). One way to verify the oncological completeness of the resection, involves the histopathological analysis of the surgical specimen. In this sense, a negative surgical margin corresponds practically to the complete resection of the neoplastic tumor, while a positive one indicates a surgical failure in terms of the completeness of the resection. Regarding the safety of PN, it is usually assessed using the modified classification of complications according to the Clavien – Dindo scale (6, 7), which contributes to the detection and systematic recording of adverse events and complications that are inextricably linked to the surgical intervention. The goal behind identifying and maintaining renal function at the highest possible level during the immediate postoperative period, shapes the driving force towards the widespread adoption of PN and the establishment of absolute indications for its implementation. A potentially adverse effect on renal function after PN may be driven by multiple factors related to the patient, the surgical intervention, as well as independent tumor characteristics. In a related study, Mir *et al*. (51) showed that the long-term effects on renal function depend to a large extent on the size of the tumor, which is a non-modifiable parameter. On the other hand, the most important potentially modifiable surgical parameter that affects postoperative renal function, refers to the duration of intraoperatively applied ischemia (51). Many aspects and surgical techniques have been described and evaluated over time, with the main goal of reducing the ischemic damage to the remaining renal parenchyma in PN procedures mostly during warm ischemia, with maneuvers such as the selective clamping technique (52-55). According to this view, the maximum recipient duration of ischemia is set at 20 min, with this value being considered a clinically acceptable cut-off value, to ensure adequate maintenance of renal function postoperatively. However, the optimal threshold for the application of warm ischemia is still controversial, a fact that has led to the development of techniques such as the zero-ischemia technique or clampless partial nephrectomy (5, 56-59), to avoid the application of any type of intraoperative ischemia.

In modern kidney surgery practice, the concept of trifecta is often used to assess surgical adequacy and practically shapes the goals of PN (22). Two main definitions of trifecta prevail in the international literature, the first of which includes the triple fulfillment of negative surgical margins, the absence of surgical complications of grade less than or equal to II according to the Clavien – Dindo classification (6, 7), and maintenance of the postoperative glomerular filtration rate at a magnitude greater than or equal to 90% of its preoperative value. The second definition for accessing postoperative renal function, utilizes instead of the change in glomerular filtration rate, the ischemia time interval applied intraoperatively. In this case, trifecta is defined as the trinity of achieving negative surgical margins, absence of major complications, and avoidance of prolonging the duration of ischemia beyond 25 min. However, the parameters affecting the trifecta achievement rates have not yet been clearly defined (60). The above three sub-objectives, despite the existence of multiple definitions in the international literature, recently have been incorporated into a single term called "trifecta outcome", which as a concept, has emerged from the strategy of surgical treatment of prostate cancer with radical prostatectomy (RP) (22). In addition to trifecta, an alternative concept, that of MIC (margin - ischemia - complications), has been proposed in the literature (4, 10, 61). In this sense, the three main objectives of partial nephrectomy are also incorporated in the MIC concept, including the complete removal of tumor cells, as expressed through negative surgical margins, the preservation of preoperative renal function to the maximum possible extent postoperatively, and the reduction in general complications rates (5).

The primary limitation of this study concerns the incorporation of a relatively small number of studies from the main body of the international literature referring to the trifecta outcome. The reason for this contract is the intention to explore the different definitions of trifecta when comparing RPN/RAPN *vs*. OPN, in order to determine the potential of utilizing its incidence as a compact variable. The successful integration of the prevailing definitions theoretically enables the approximation of the comparative effect between the above two surgical approaches in terms of the frequency of achieving trifecta by subsequent meta-analyses, providing them with the advantage of maximizing the total number of studies included. A second limitation is derived from Equations 16.4 and 16.7. The fixed terms in these equations (α_1, α_2) practically reflect the degrees to which the two main definitions of trifecta found in the international literature interact with the central parameter of the marginal ischemic volume ($V_{ischemia}$). In the best-case scenario, the above terms are both equal to 1, which implies that the effect terms from each of the two parameters on the configuration of the boundary zone area are equal to each other. However, the control over the achievement or not of the "trifecta outcome" is carried out through the selection of appropriate cut-off values for each of the two regulatory parameters of renal function ($|\Delta eGFR|$, IT). Thus, in future studies, the relevant investigation remains as to whether the cut-off value of 10% with respect to the percentage change in the estimated glomerular filtration rate, and that of 25 min concerning the ischemia duration, are ultimately the optimal, so that the two main definitions to converge definitively in the description of a single entity. Finally, the third limitation stems from the individual assumptions made in the relevant subsections of "Materials and Methods". Specifically, these concern the hypotheses of uniformity in glomerular density, a relatively small variation in $\Delta V_{threshold}$, the comparison of uniform patient populations with the same number of renal tumors undergoing one-stage resection, the absence of adverse events such as the development of renal infarct, as well as the negligible increase in serum creatinine postoperatively, compared to the corresponding decrease in eGFR.

Conclusion

Three are the main conclusions that derive from the present study. The first is that the two main definitions found in the international literature regarding the "trifecta outcome", are essentially like the two sides of the same coin. The second conclusion is related to the intention of both definitions to give an estimate for the volume of the ischemic zone around the point of excision, which turned out to be the central parameter that affects the change of renal function after partial nephrectomy in patients with solitary tumors. Finally, the third conclusion reveals the theoretical possibility of grouping comparative data regarding the frequency of trifecta achievement to determine a quantitative estimate of the comparative effect between RPN/RAPN and OPN. In this case it is worth noting that in future studies, in addition to the analysis of aggregate data, it will be necessary to formulate a relevant subgroup analysis based on the two main definitions of trifecta described above, in order to investigate for any differences between them, and also to make the analytical process as complete as possible.

Conflicts of Interest

All Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Sotirios Artsitas (SA) has given substantial contributions to the conceptualization, data curation, formal analysis, data investigation, methodology implementation, project administration, acquisition of resources, software utilization, procedure validation, visualization of results, original draft formulation, as well as the final review & editing of the present study. Dimitrios Artsitas (DA) has given substantial contributions in data curation, formal analysis, data investigation, project administration, acquisition of resources, as well as procedure validation. Ioanna Segkou (IS) has given substantial contributions in data curation, formal analysis, acquisition of resources, procedure validation, as well as original draft formulation. Gerasimos Tsourouflis (GT) has given substantial contributions in conceptualization, methodology implementation, software utilization, procedure validation, as well as critical review of the final manuscript. Dimitrios Dimitroulis (DD) has given substantial contributions in supervision, as well as critical review of the final manuscript. Nikolaos Nikiteas (NN) held the position of general supervisor during the elaboration of the present study.

References

1 Banapour P, Abdelsayed GA, Bider-Canfield Z, Elliott PA, Kilday PS and Chien GW: Nephrometry score matched robotic *vs*. laparoscopic *vs*. open partial nephrectomy. J Robot Surg *12(4)*: 679-685, 2018. PMID: 29556868. DOI: 10.1007/s11701-018-0801-x

2 Mehra K, Manikandan R, Dorairajan LN, Sreerag S, Jain A and Bokka SH: Trifecta outcomes in open, laparoscopy or robotic partial nephrectomy: does the surgical approach matter? J Kidney Cancer VHL *6(1)*: 8-12, 2019. PMID: 31149561. DOI: 10.15586/jkcvhl.2019.115

3 Yerram NK, Dagenais J, Bryk DJ, Nandanan N, Maurice MJ, Mouracade P, Kara O and Kaouk JH: Trifecta outcomes in multifocal tumors: a comparison between robotic and open partial nephrectomy. J Endourol *32(7)*: 615-620, 2018. PMID: 29790375. DOI: 10.1089/end.2018.0134

4 Buffi N, Lista G, Larcher A, Lughezzani G, Ficarra V, Cestari A, Lazzeri M and Guazzoni G: Margin, ischemia, and complications (MIC) score in partial nephrectomy: a new system for evaluating achievement of optimal outcomes in nephron-sparing surgery. Eur Urol *62(4)*: 617-618, 2012. PMID: 22704367. DOI: 10.1016/j.eururo.2012.06.001

5 Mearini L, Nunzi E, Vianello A, Di Biase M and Porena M: Margin and complication rates in clampless partial nephrectomy: a comparison of open, laparoscopic and robotic surgeries. J Robot Surg *10(2)*: 135-144, 2016. PMID: 27083923. DOI: 10.1007/s11701-016-0584-x

6 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL and Makuuchi M: The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg *250(2)*: 187-196, 2009. PMID: 19638912. DOI: 10.1097/SLA.0b013e3181b13ca2

7 Dindo D, Demartines N and Clavien PA: Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg *240(2)*: 205-213, 2004. PMID: 15273542. DOI: 10.1097/01.sla.0000133083.54934.ae

8 Bai N, Qi M, Shan D, Liu S, Na T and Chen L: Trifecta achievement in patients undergoing partial nephrectomy: a systematic review and meta-analysis of predictive factors. Int Braz J Urol *48(4)*: 625-636, 2022. PMID: 34115456. DOI: 10.1590/S1677-5538.IBJU.2021.0095

9 Hung AJ, Cai J, Simmons MN and Gill IS: "Trifecta" in partial nephrectomy. J Urol *189(1)*: 36-42, 2013. PMID: 23164381. DOI: 10.1016/j.juro.2012.09.042

10 Zargar H, Porpiglia F, Porter J, Quarto G, Perdona S, Bertolo R, Autorino R and Kaouk JH: Achievement of trifecta in minimally invasive partial nephrectomy correlates with functional preservation of operated kidney: a multi-institutional assessment using MAG3 renal scan. World J Urol *34(7)*: 925-931, 2016. PMID: 26546072. DOI: 10.1007/s00345-015-1726-x

11 Zargar H, Autorino R, Akca O, Brandao LF, Laydner H and Kaouk J: Minimally invasive partial nephrectomy in the age of the 'trifecta'. BJU Int *116(4)*: 505-506, 2015. PMID: 25901967. DOI: 10.1111/bju.12698

12 Giorgi FM, Ceraolo C and Mercatelli D: The R language: an engine for bioinformatics and data science. Life (Basel) *12(5)*: 648, 2022. PMID: 35629316. DOI: 10.3390/life12050648

13 Seifert E: OriginPro 9.1: scientific data analysis and graphing software-software review. J Chem Inf Model *54(5)*: 1552, 2014. PMID: 24702057. DOI: 10.1021/ci500161d

14 Schwartzman G and Ramamurti P: Visible Body Human Anatomy Atlas: Innovative anatomy learning. J Digit Imaging *34(5)*: 1328-1330, 2021. PMID: 34341897. DOI: 10.1007/s10278-021-00496-5

15 Ackerman MJ: The Visible Human Project: From body to bits. IEEE Pulse *8(4)*: 39-41, 2017. PMID: 28715313. DOI: 10.1109/MPUL.2017.2701221

16 Ghali F, Elbakry AA, Hamilton ZA, Yim K, Nasseri R, Patel S, Eldefrawy A, Ryan S, Bradshaw AW, Meagher M, Bree K, Reddy M, Lee HJ and Derweesh IH: Robotic partial nephrectomy for clinical T2a renal mass is associated with improved trifecta outcome compared to open partial nephrectomy: a single surgeon comparative analysis. World J Urol *38(5)*: 1113-1122, 2020. PMID: 31701211. DOI: 10.1007/s00345-019-02994-2

17 Ghavimi S, Saarela O, Pouliot F, Rendon RA, Finelli A, Kapoor A, Moore RB, Breau RH, Lavallee L, Lacombe L, Fairey A, Jewett M, Liu Z, Tanguay S and Black PC: Achieving the "trifecta" with open *versus* minimally invasive partial nephrectomy. World J Urol *39(5)*: 1569-1575, 2021. PMID: 32656670. DOI: 10.1007/s00345-020-03349-y

18 Bindayi A, Autorino R, Capitanio U, Pavan N, Mir MC, Antonelli A, Takagi T, Bertolo R, Maurer T, Ho Rha K, Long JA, Yang B, Schips L, Lima E, Breda A, Linares E, Celia A, De Nunzio C, Dobbs R, Patel S, Hamilton Z, Tracey A, Larcher A, Trombetta C, Palumbo C, Tanabe K, Amiel T, Raheem A, Fiard G, Zhang C, Castellucci R, Palou J, Ryan S, Crivellaro S, Montorsi F, Porpiglia F and Derweesh IH: Trifecta outcomes of partial nephrectomy in patients over 75 years old: analysis of the REnal SURGery in elderly (RESURGE) group. Eur Urol Focus *6(5)*: 982-990, 2020. PMID: 30799289. DOI: 10.1016/j.euf.2019.02.010

19 Chang KD, Abdel Raheem A, Kim KH, Oh CK, Park SY, Kim YS, Ham WS, Han WK, Choi YD, Chung BH and Rha KH: Functional and oncological outcomes of open, laparoscopic and robot-assisted partial nephrectomy: a multicentre comparative matched-pair analyses with a median of 5 years' follow-up. BJU Int *122(4)*: 618-626, 2018. PMID: 29645344. DOI: 10.1111/bju.14250

20 Harke NN, Mandel P, Witt JH, Wagner C, Panic A, Boy A, Roosen A, Ubrig B, Schneller A, Schiefelbein F, Wagener N, Honeck P, Schoen G, Hadaschik B, Michel MS and Kriegmair MC: Are there limits of robotic partial nephrectomy? TRIFECTA outcomes of open and robotic partial nephrectomy for completely endophytic renal tumors. J Surg Oncol *118(1)*: 206-211, 2018. PMID: 29878367. DOI: 10.1002/jso.25103

21 Motoyama D, Aki R, Matsushita Y, Tamura K, Ito T, Sugiyama T, Otsuka A and Miyake H: Early single-center experience with robotic partial nephrectomy using the da Vinci Xi: Comparative assessment with conventional open partial nephrectomy. Curr Urol *13(1)*: 13-18, 2019. PMID: 31579214. DOI: 10.1159/000499300

22 Porpiglia F, Mari A, Bertolo R, Antonelli A, Bianchi G, Fidanza F, Fiori C, Furlan M, Morgia G, Novara G, Rocco B, Rovereto B, Serni S, Simeone C, Carini M and Minervini A: Partial nephrectomy in clinical T1b renal tumors: Multicenter comparative study of open, laparoscopic and robot-assisted approach (the RECORd project). Urology *89*: 45-51, 2016. PMID: 26743388. DOI: 10.1016/j.urology.2015.08.049

23 Bianchi L, Schiavina R, Borghesi M, Chessa F, Casablanca C, Angiolini A, Ercolino A, Pultrone CV, Mineo Bianchi F, Barbaresi U, Piazza P, Manferrari F, Bertaccini A, Fiorentino M, Ferro M, Porreca A, Marcelli E and Brunocilla E: Which patients with clinical localized renal mass would achieve the trifecta after partial nephrectomy? The impact of surgical technique. Minerva Urol Nefrol *72(3)*: 339-349, 2020. PMID: 31619030. DOI: 10.23736/S0393-2249.19.03485-4

24 Mir MC, Campbell RA, Sharma N, Remer EM, Simmons MN, Li J, Demirjian S, Kaouk J and Campbell SC: Parenchymal volume preservation and ischemia during partial nephrectomy: functional and volumetric analysis. Urology *82(2)*: 263-268, 2013. PMID: 23791213. DOI: 10.1016/j.urology.2013.03.068

25 Simmons MN, Lieser GC, Fergany AF, Kaouk J and Campbell SC: Association between warm ischemia time and renal parenchymal atrophy after partial nephrectomy. J Urol *189(5)*: 1638-1642, 2013. PMID: 23159462. DOI: 10.1016/j.juro.2012.11.042

26 de Souza DB, de Oliveira LL, da Cruz MC, Abílio EJ, Costa WS, Pereira-Sampaio MA and Sampaio FJ: Laparoscopic partial nephrectomy under warm ischemia reduces the glomerular density in a pig model. J Endourol *26(6)*: 706-710, 2012. PMID: 22192102. DOI: 10.1089/end.2011.0412

27 Bechara GR, Damasceno-Ferreira JA, Abreu LA, Costa WS, Sampaio FJ, Pereira-Sampaio MA and Souza DB: Glomerular loss after arteriovenous and arterial clamping for renal warm ischemia in a swine model. Acta Cir Bras *31(11)*: 753-758, 2016. PMID: 27982263. DOI: 10.1590/S0102-865020160110000008

28 Cao J, Zhu S, Ye M, Liu K, Liu Z, Han W and Xie Y: Comparison of renal artery *vs*. renal artery-vein clamping during partial nephrectomy: a system review and meta-analysis. J Endourol *34(4)*: 523-530, 2020. PMID: 32098499. DOI: 10.1089/end.2019.0580

29 Blum KA, Paulucci DJ, Abaza R, Eun DD, Bhandari A, Delto JC, Krane LS, Hemal AK and Badani KK: Main renal artery clamping with or without renal vein clamping during robotic partial nephrectomy for clinical T1 renal masses: perioperative and long-term functional outcomes. Urology *97*: 118-123, 2016. PMID: 27569452. DOI: 10.1016/j.urology.2016.08.028

30 Funahashi Y, Kato M, Yoshino Y, Fujita T, Sassa N and Gotoh M: Comparison of renal ischemic damage during laparoscopic partial nephrectomy with artery-vein and artery-only clamping. J Endourol *28(3)*: 306-311, 2014. PMID: 24099438. DOI: 10.1089/end.2013.0446

31 Ginzburg S, Uzzo R, Walton J, Miller C, Kurz D, Li T, Handorf E, Gor R, Corcoran A, Viterbo R, Chen DY, Greenberg RE, Smaldone MC and Kutikov A: Residual parenchymal volume, not warm ischemia time, predicts ultimate renal functional outcomes in patients undergoing partial nephrectomy. Urology *86(2)*: 300-305, 2015. PMID: 26199171. DOI: 10.1016/j.urology.2015.04.043

32 Pasichnyk SM, Pasichnyk MS, Lychkovsky AE, Stakhovsky EO, Gozhenko AI, Shatnyi SV and Pasichnyk MA: Predicting changes in glomerular filtration rate in patients with kidney cancer using a mathematical model. Exp Oncol *43(2)*: 185-188, 2021. PMID: 34190518. DOI: 10.32471/exp-oncology.2312-8852.vol-43-no-2.16214

33 Lee J, Kim J, Kim JC, Ham WS, Han WK, Rha KH, Choi YD and Jang WS: Evaluation of the surgical margin threshold for avoiding recurrence after partial nephrectomy in patients with renal cell carcinoma. Yonsei Med J *63(2)*: 173-178, 2022. PMID: 35083903. DOI: 10.3349/ymj.2022.63.2.173

34 Cerbus RT and Goldburg WI: Information content of turbulence. Phys Rev E Stat Nonlin Soft Matter Phys *88(5)*: 053012, 2013. PMID: 24329356. DOI: 10.1103/PhysRevE.88.053012

35 Damasceno-Ferreira JA, Bechara GR, Costa WS, Pereira-Sampaio MA, Sampaio FJB and Souza DB: The relationship between renal warm ischemia time and glomerular loss. An experimental study in a pig model. Acta Cir Bras *32(5)*: 334-341, 2017. PMID: 28591362. DOI: 10.1590/s0102-865020170050000002

36 Bechara GR, Damasceno-Ferreira JA, Abreu LAS, Costa WS, Sampaio FJB, Pereira-Sampaio MA and de Souza DB: Glomerular morphology and renal function after warm ischemia by main artery or selective clamping in a porcine model. Urol Int *99(3)*: 262-266, 2017. PMID: 28355603. DOI: 10.1159/000458762

37 Moran K, Mulhall J, Kelly D, Sheehan S, Dowsett J, Dervan P and Fitzpatrick JM: Morphological changes and alterations in regional intrarenal blood flow induced by graded renal ischemia. J Urol *148(2 Pt 1)*: 463-466, 1992. PMID: 1635158. DOI: 10.1016/s0022-5347(17)36629-6

38 Abitbol CL, DeFreitas MJ and Strauss J: Assessment of kidney function in preterm infants: lifelong implications. Pediatr Nephrol *31(12)*: 2213-2222, 2016. PMID: 26846786. DOI: 10.1007/s00467-016-3320-x

39 Nunes-Carneiro D, Madanelo M, Silva F, Pestana N, Ribeiro C, Gil-Sousa D, Martins S, Almeida M, Dias L, Malheiro J, Cavadas V, Castro-Henriques A, Fraga A and Silva-Ramos M: Remaining kidney volume indexed to weight as a strong predictor of estimated glomerular filtration rate at 1 year and mid-term renal function after living-donor nephrectomy – a retrospective observational study. Transpl Int *33(10)*: 1262-1273, 2020. PMID: 32608073. DOI: 10.1111/tri.13683

40 Shinoda K, Morita S, Akita H, Washizuka F, Tamaki S, Takahashi R, Oguchi H, Sakurabayashi K, Mizutani T, Takahashi Y, Hyodo Y, Itabashi Y, Muramatsu M, Kawamura T, Asanuma H, Kikuchi E, Jinzaki M, Shiraga N, Nakagawa K, Oya M, Shishido S and Sakai K: Preserved kidney volume, body mass index, and age are significant preoperative factors for predicting estimated glomerular filtration rate in living kidney donors at 1 year after donation. Transplant Proc *51(5)*: 1306-1310, 2019. PMID: 31076152. DOI: 10.1016/j.transproceed.2019.01.142

41 Herts BR, Sharma N, Lieber M, Freire M, Goldfarb DA and Poggio ED: Estimating glomerular filtration rate in kidney donors: a model constructed with renal volume measurements from donor CT scans. Radiology *252(1)*: 109-116, 2009. PMID: 19435940. DOI: 10.1148/radiol.2521081873

42 Goh YS, Wu MW, Tai BC, Lee KC, Raman L, Teo BW, Vathsala A and Tiong HY: Comparison of creatinine based and kidney volume based methods of estimating glomerular filtration rates in potential living kidney donors. J Urol *190(5)*: 1820-1826, 2013. PMID: 23770137. DOI: 10.1016/j.juro.2013.05.117

43 Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F and Chronic Kidney Disease Epidemiology Collaboration: Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med *145(4)*: 247-254, 2006. PMID: 16908915. DOI: 10.7326/0003-4819-145-4-200608150-00004

44 Musso CG, Álvarez-Gregori J, Jauregui J and Macías-Núñez JF: Glomerular filtration rate equations: a comprehensive review. Int Urol Nephrol *48(7)*: 1105-1110, 2016. PMID: 27052619. DOI: 10.1007/s11255-016-1276-1

45 Simmons MN, Fergany AF and Campbell SC: Effect of parenchymal volume preservation on kidney function after partial nephrectomy. J Urol *186(2)*: 405-410, 2011. PMID: 21680004. DOI: 10.1016/j.juro.2011.03.154

46 Liu J, Tian C, Zhang Z, Zhou G, Shi B, Zhao H and Jiang X: Correlation between preoperatively predicted and postoperatively observed renal function using an imaging-based

approach: A retrospective cohort study. Oncol Lett *20(1)*: 501-508, 2020. PMID: 32565975. DOI: 10.3892/ol.2020.11584

47 Ghoneim IA and Fergany AF: Minimally invasive surgery for renal cell carcinoma. Expert Rev Anticancer Ther *9(7)*: 989-997, 2009. PMID: 19589037. DOI: 10.1586/era.09.59

48 Daugherty M and Bratslavsky G: Surgical techniques in the management of small renal masses. Urol Clin North Am *44(2)*: 233-242, 2017. PMID: 28411915. DOI: 10.1016/j.ucl.2016.12.009

49 Kanani HH and Klapa MI: Data correction strategy for metabolomics analysis using gas chromatography-mass spectrometry. Metab Eng *9(1)*: 39-51, 2007. PMID: 17052933. DOI: 10.1016/j.ymben.2006.08.001

50 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P and Moher D: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ *372*: n71, 2021. PMID: 33782057. DOI: 10.1136/bmj.n71

51 Mir MC, Ercole C, Takagi T, Zhang Z, Velet L, Remer EM, Demirjian S and Campbell SC: Decline in renal function after partial nephrectomy: etiology and prevention. J Urol *193(6)*: 1889-1898, 2015. PMID: 25637858. DOI: 10.1016/j.juro.2015.01.093

52 Furukawa J, Miyake H, Hinata N, Muramaki M, Tanaka K and Fujisawa M: Renal functional and perioperative outcomes of selective *versus* complete renal arterial clamping during robot-assisted partial nephrectomy: early single-center experience with 39 cases. Surg Innov *23(3)*: 242-248, 2016. PMID: 26459499. DOI: 10.1177/1553350615610648

53 Desai MM, de Castro Abreu AL, Leslie S, Cai J, Huang EY, Lewandowski PM, Lee D, Dharmaraja A, Berger AK, Goh A, Ukimura O, Aron M and Gill IS: Robotic partial nephrectomy with superselective *versus* main artery clamping: a retrospective comparison. Eur Urol *66(4)*: 713-719, 2014. PMID: 24486306. DOI: 10.1016/j.eururo.2014.01.017

54 Viprakasit DP, Derweesh I, Wong C, Su LM, Stroup SP, Bazzi W, Strom KH and Herrell SD: Selective renal parenchymal clamping in robot-assisted laparoscopic partial nephrectomy: a multi-institutional experience. J Endourol *25(9)*: 1487-1491, 2011. PMID: 21902518. DOI: 10.1089/end.2010.0667

55 Porpiglia F, Fiori C, Checcucci E, Amparore D and Bertolo R: Hyperaccuracy three-dimensional reconstruction is able to maximize the efficacy of selective clamping during robot-assisted partial nephrectomy for complex renal masses. Eur Urol *74(5)*: 651-660, 2018. PMID: 29317081. DOI: 10.1016/j.eururo.2017.12.027

56 Gill IS, Eisenberg MS, Aron M, Berger A, Ukimura O, Patil MB, Campese V, Thangathurai D and Desai MM: "Zero ischemia" partial nephrectomy: novel laparoscopic and robotic technique. Eur Urol *59(1)*: 128-134, 2011. PMID: 20971550. DOI: 10.1016/j.eururo.2010.10.002

57 Satkunasivam R, Tsai S, Syan S, Bernhard JC, de Castro Abreu AL, Chopra S, Berger AK, Lee D, Hung AJ, Cai J, Desai MM and Gill IS: Robotic unclamped "minimal-margin" partial nephrectomy: ongoing refinement of the anatomic zero-ischemia concept. Eur Urol *68(4)*: 705-712, 2015. PMID: 26071789. DOI: 10.1016/j.eururo.2015.04.044

58 Forbes E, Cheung D, Kinnaird A and Martin BS: Zero ischemia robotic-assisted partial nephrectomy in Alberta: Initial results of a novel approach. Can Urol Assoc J *9(3-4)*: 128-132, 2015. PMID: 26085870. DOI: 10.5489/cuaj.2448

59 Rizkala ER, Khalifeh A, Autorino R, Samarasekera D, Laydner H and Kaouk JH: Zero ischemia robotic partial nephrectomy: sequential preplaced suture renorrhaphy technique. Urology *82(1)*: 100-104, 2013. PMID: 23806396. DOI: 10.1016/j.urology.2013.03.042

60 Soisrithong C, Sirisreetreerux P, Sangkum P, Kijvikai K, Viseshsindh W, Kongchareonsombat W, Leenanupunth C, Kochakarn W and Jenjitranant P: Comparative outcomes and predictive assessment of trifecta in open, laparoscopic, and robotic-assisted partial nephrectomy cases with renal cell carcinoma: a 10-year experience at Ramathibodi Hospital. Res Rep Urol *13*: 425-435, 2021. PMID: 34235099. DOI: 10.2147/RRU.S316824

61 Ubrig B, Roosen A, Wagner C, Trabs G, Schiefelbein F, Witt JH, Schoen G and Harke NN: Tumor complexity and the impact on MIC and trifecta in robot-assisted partial nephrectomy: a multi-center study of over 500 cases. World J Urol *36(5)*: 783-788, 2018. PMID: 29380129. DOI: 10.1007/s00345-018-2191-0

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