World Journal of Urology
https://doi.org/10.1007/s00345-023-04415-x

TOPIC PAPER

Perioperative outcomes and risk factors for major complications associated with nephrectomy for Xanthogranulomatous pyelonephritis: a multicenter study

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Received: 21 December 2022 / Accepted: 28 March 2023

Abstract

Purpose To determine the risk factors associated with major complications in patients with histologically confirmed Xanthogranulomatous pyelonephritis (XGP) who underwent nephrectomy.

Methods A multicenter retrospective study was performed including patients who underwent nephrectomy between 2018 and 2022 with histopathological diagnosis of XGP. Clinical and laboratory parameters at the initial presentation were evaluated. Data on extension of XGP was recorded as per the Malek clinical-radiological classification. Characteristics of nephrectomy and perioperative outcomes were obtained. The primary outcome was major complications, defined as a CD ≥ grade 3 and the need for intensive care unit (ICU) admission. Secondary outcomes included the comparison of complications evaluating the nephrectomy approach (transperitoneal, retroperitoneal, and laparoscopic). A sub-analysis stratifying patients who needed ICU admission and Malek classification was performed.

Results A total of 403 patients from 10 centers were included. Major complications were reported in 98 cases (24.3%), and organ injuries were reported in 58 patients (14.4%), being vascular injuries the most frequent (6.2%). Mortality was reported in 5 cases (1.2%). A quick Sepsis-related Organ Failure Assessment (qSOFA) score ≥ 2, increased creatinine, paranephric extension of disease (Malek stage 3), a positive urine culture, and retroperitoneal approach were independent factors associated with major complications.

Conclusion Counseling patients on factors associated with higher surgical complications is quintessential when managing this disease. Clinical-radiological staging, such as the Malek classification may predict the risk of major complications in patients with XGP who will undergo nephrectomy. A transperitoneal open approach may be the next best option when laparoscopic approach is not feasible.

Keywords Xanthogranulomatous pyelonephritis · Nephrectomy · Complications · Mortality · Prognosis

Introduction

Xanthogranulomatous pyelonephritis (XGP) is an infrequent, but life-threatening, presentation of chronic granulomatous pyelonephritis, commonly associated with obstruction of the collecting system caused by infected nephrolithiasis [1]. Treatment consists of broad-spectrum antibiotics and often nephrectomy [2, 3]. Surgical intervention can be challenging due to severe diffuse inflammation and often a fibrotic reaction that obliterates anatomical landmarks, making dissection challenging and leading to a greater risk of intra and postoperative morbidity [4, 5].

Different surgical approaches have been used, including open transperitoneal, open retroperitoneal, and also minimally invasive approaches, such as laparoscopic or

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Published online: 12 May 2023

robotic-assisted [1, 4, 5]. However, none of these approaches has shown better surgical outcomes, nor fewer complications. In addition, a high rate of open conversion has been reported when performing laparoscopic nephrectomy [4, 5].

Due to the rarity of this condition and the scarcity of available literature, the factors associated with unfavorable surgical outcomes continue to be poorly understood. This study aims to determine the risk factors associated with major complications in patients with histologically confirmed XGP who underwent nephrectomy.

Materials and methods

Retrospective data were obtained from 10 centers in 5 countries. Adults above 18 years who had a nephrectomy either open or laparoscopically between 2018 and 2022 with a histopathological diagnosis of XGP were included. Ethics committee approval was obtained at each participating center. Patients managed with other therapeutic modalities, in whom nephrectomy was not performed and with incomplete medical records were excluded.

Study design

Sociodemographic characteristics including age, sex, and comorbidities were assessed. Clinical and laboratory parameters at the first presentation were evaluated. Laboratory parameters included complete blood count, biochemical tests, and urinary microbiological cultures. The cutoff values for various definitions were as follows: leukocytosis as having > 11,000/μL white blood cells in blood count, thrombocytopenia as having < 150,000/μL platelet in blood count, increased serum creatinine as creatinine level of ≥ 1.2 mg/dL, and hyperglycemia as having a serum glucose level of > 200 mg/dL. The quick Sepsis related Organ Failure Assessment (qSOFA) score was used, which is a 3-point scoring system including altered mental status, > 22 breaths/min, and hypotension (systolic blood pressure < 100 mmHg) [6]. Septic shock was defined as a profound circulatory, cellular, and metabolic abnormalities associated with sepsis [6].

Data on the extension of XGP was recorded as per the Malek clinical-radiological classification [7] based on CT findings: (i) type 1: Disease limited to the kidney; (ii) type 2: with extension to perinephric space; and (iii) type 3: with extension to paranephric space.

Results of urine cultures and kidney urine cultures were reported for analysis using the MALDI-TOF procedure based on the guidelines of the Clinical and Laboratory Standards Institute (CLSI). The production of extended-spectrum beta-lactamase (ESBL) was performed with a double disc sensitivity test [8].

Patient management

Data on therapeutic management was collected from each center, where patients were managed based on resources, experience, and protocols of individual institutions. Ureteral stenting or percutaneous nephrostomy as initial modality for urinary diversion to relieve obstruction was indicated according to CT and clinical findings.

Characteristics of nephrectomy and perioperative outcomes were obtained. Simple nephrectomies were classified as early nephrectomy (EN) defined as surgery performed within the first 48 h of presentation and delayed nephrectomy (DN) defined as those performed anytime after 48 h of initial presentation [9].

Clavien–Dindo (CD) classification was used to report postoperative complications including need for intensive care unit admission, and mortality [10].

Primary and secondary outcomes

The primary outcome was major complications, defined as intraoperative and postoperative complications < 30 days after surgery, including local organ injuries, CD ≥ grade 3, the need for intensive care unit (ICU) admission, and death. Secondary outcomes included the comparison of complications in open transperitoneal, open retroperitoneal, and laparoscopic approaches for nephrectomy. The surgical approach was the primary approach how surgery was started. A sub-analysis for ICU admission and outcomes associated with Malek classification was performed.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the normality of quantitative variables. Continuous variables were described using mean and standard deviation (± SD). Categorical variables were described as frequencies and percentages. Student t was used for quantitative variables. Univariate analysis was performed based on sociodemographic, clinical, radiological, microbiological, and biochemical variables to determine the risk for major complications of nephrectomy using the chi-square test. Variables with significant statistical association with major complications were further analyzed in a multivariate analysis to identify independent factors related to major complications. Multivariate analysis was performed with logistic regression to find the independent odds ratio (OR) of major complications.

Statistical analysis was performed using SPSS for Windows, version 20.0 (IBM Corp. Armonk, NY), and statistical significance was set at $p < 0.05$.

Results

Four hundred and three patients met the inclusion criteria and were included. Mean age was 45.2 ± 15.4 years. There were 248 (61.5%) women. The most common presenting symptom was renal colic in 153 cases (37.9%), followed by fever (36.7%). Fifty-two (12.9%) patients had urosepsis, whilst 24 (6%) were in septic shock. Chronic kidney disease was the most common comorbidity in 281 cases (69.7%), followed by diabetes (27.8%). The majority of patients (70.9%) had anemia. Kidney stones were present in 89.3% of which staghorn stones were present in 109 (27%). Malek stage I was present in almost half of the patients, stage II in 34.5% and 16.9% had stage III. 202 patients (60.1%) had some kind of urinary diversion before nephrectomy. Complete patients characteristics are shown in Table 1.

Variables with significant association to major complications on univariate analysis (Table 2) were qSOFA ≥ 2 ($p < 0.001$, OR 3.562 [1.868–6.792]), recurrent UTI ($p = 0.01$, OR 1.939 [1.168–3.220]), renal abscess ($p < 0.001$, OR 2.939 [1.787–4.834]), staghorn stone ($p = 0.011$, OR 1.870 [1.149–3.045]), anemia ($p = 0.006$, OR 2.189 [1.245–3.851]), leukocytosis ($p = 0.012$, OR 1.867 [1.141–3.054]), increased creatinine ($p < 0.001$, OR 2.502 [1.527–4.101]), extension of disease to perinephric space ($p = 0.026$, OR 1.862 [1.079–3.214]), extension to paranephric space ($p < 0.001$, OR 5.217 [2.823–9.643]), a positive urine culture ($p < 0.001$, OR 2.615 [1.616–4.234]), ESBL agents in urine ($p = 0.002$, OR 2.838 [1.430–5.633]), and retroperitoneal approach ($p < 0.001$, OR 3.07 [1.894–4.976]).

In the multivariate analysis, a qSOFA ≥ 2 ($p = 0.004$, OR 3.36 [1.488–7.591]), increased creatinine ($p = 0.015$, OR 2.258 [1.171–4.356]), extension of disease to paranephric space ($p < 0.001$, OR 3.958 [2.077–7.543]), a positive urine culture ($p = 0.031$, OR 1.948 [1.064–3.565]), and retroperitoneal approach ($p < 0.001$, OR 3.311 [1.757–6.241]) were factors associated with major complications (Table 2).

Major complications occurred in 98 cases (24.3%). Organ injuries were reported in 58 patients (14.4%). Vascular injuries were the most frequent (6.2%). Mortality was reported in five cases (1.2%). Postoperative complications Clavien-Dindo ≥ 3 were reported in 100 cases (24.8%) (Table 3).

Table 4 shows the microbiological profile of urine and kidney urine cultures. A total of 383 urine cultures and 253 kidney urine cultures were obtained among the 403 patients. *Escherichia coli* was the most common pathogen, followed by *Proteus mirabilis* and *Klebsiella pneumoniae*. *Escherichia coli* was also the most common bacteria in

Table 1 Demographic, clinical, radiological and microbiological characteristics of the study population. ($n = 403$)

Variables	Values
Demographics	
Age; years mean ± SD	45.2 ± 15.4
Females; *n* (%)	248 (61.5)
Right side kidney; *n* (%)	207 (51.4)
Body mass index; kg/m^2, mean ± SD	24.5 ± 5.1
Days of hospitalization; days, mean ± SD	8.9 ± 6.3
Clinical presentation	
Renal colic; *n* (%)	153 (37.9)
Fever n (%) (> 38.3 °C)	148 (36.7)
Septic shock n (%) (PAM < 60)	24 (6)
Urosepsis; *n* (%)	52 (12.9)
qSOFA score	
0 points; *n* (%)	291 (72.2)
1 point; *n* (%)	54 (13.4)
2 points; *n* (%)	33 (8.2)
3 points; *n* (%)	11 (2.7)
Comorbidities	
Diabetes mellitus; *n* (%)	112 (27.8)
Hypertension; *n* (%)	116 (28.8)
Chronic kidney disease; *n* (%)	281 (69.7)
Recurrent urinary tract infections; *n* (%)	93 (23.1)
Radiological characteristics	
Pyonephrosis; *n* (%)	178 (44.2)
Renal abscess; *n* (%)	95 (23.6)
Staghorn stone; *n* (%)	109 (27)
Multiple stones; *n* (%)	133 (33)
Ureteropyelic junction stone; *n* (%)	118 (29.3)
Laboratory workup	
Anemia (Hemoglobin < 12 g/dL)	283 (70.2)
Leukocytosis (Leukocytes > 11,000/L)	130 (32.2)
Thrombocytopenia (Platelets < 150,000/L)	27 (6.7)
Increased creatinine Creatinine > 1.2 mg/dL)	99 (24.5)
Hyperglycemia (Glucose > 200 mg/dL)	54 (13.4)
Malek classification	
Limited to the kidney; *n* (%)	196 (48.6)
Extended to perirenal space; *n* (%)	139 (34.5)
Extended to pararenal space; *n* (%)	68 (16.9)
Microbiological characteristics	
Positive urine cultures; *n* (%)^2	185 (48.3)
ESBL agents in urine; *n* (%)^2	38 (9.9)
Previous urinary diversion	
Double J sent; *n* (%)	69 (17.1)
Percutaneous nephrostomy; *n* (%)	134 (33.3)
Percutaneous drainage; *n* (%)	39 (9.7)
Nephrectomy approach	
Transperitoneal; *n* (%)	210 (52.1)
Retroperitoneal; *n* (%)	193 (47.9)
Open; *n* (%)	358 (88.9)
Laparoscopic; *n* (%)	45 (11.1)

Table 1 (continued)

Variables	Values
Perioperative findings	
Operation time; minutes, mean ± SD	171.7 ± 65.1
Bleeding; mL mean ± SD	625.7 ± 810
Need of transfusions; *n* (%)	139 (34.5)
Complications (Clavien-Dindo)	
Grade I; *n* (%)	56 (13.9)
Grade II; *n* (%)	50 (12.4)
Grade IIIa; *n* (%)	11 (2.7)
Grade IIIb; *n* (%)	22 (5.5)
Grade IVa; *n* (%)	38 (9.4)
Grade IVb; *n* (%)	26 (6.5)
Grade V[1]; *n* (%)	3 (0.7)

*Considering total laparoscopic procedures as 100%. [1]Transoperative mortality. [2]A total of 383 urine culutres were collected

kidney urine cultures, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Sterile urine and kidney urine cultures were reported in 178 cases (46.4%) and 135 cases (53.5%), respectively.

Open transperitoneal approach was used in 183 patients (45.4%), open retroperitoneal in 175 (43.4%), and laparoscopic approach in 45 patients (11.1%). Ten patients of the laparoscopic group (22%) required open conversion. Five patients died, of whom three cases were intraoperative. Clavien–Dindo ≥ 3 was significantly higher in the open retroperitoneal approach compared open transperitoneal and laparoscopic approach (37.7%, 13.1%, and 22.2% respectively, $p = 0.01$). Local injuries were more frequent in patients with open retroperitoneal approach (36.6%, 14.8%, and 15.6%, respectively, $p < 0.001$). Vascular injuries were the commonest damage and significantly higher in the open retroperitoneal approach, compared to the open transperitoneal and laparoscopic approach (11.4%, 1.6%, and 4.4%, respectively, $p = 0.001$). Additionally, intensive care unit admission and mortality were also significantly higher in the open retroperitoneal approach ($p = 0.007$ and $p = 0.037$, respectively) (Table 5).

More than 26% of patients that were admitted to the ICU presented with extension of disease to paranephric space compared to only 15.2% of patients that did not require admission ($p = 0.018$). These patients also reported higher qSOFA scores, higher frequency of local injuries, and increased mortality ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively) (Supplementary Table 1).

Paranephric space extension was associated with a higher frequency of surrounding organ injuries, compared to perinephric extension versus that limited to the kidney parenchyma only (29.4%, 10.1%, and 8.2%, respectively, $p < 0.001$). Comparison according to Malek classification is described in Supplementary Table 2.

Discussion

XGP was first described by Schlagenhaufer in 1916. Oberling in 1939 coined its current name, identifying the characteristic yellowish coloration of the affected kidney due to abundant lipid deposits in histopathological examination (HPE) within the cytoplasm of macrophages (Xanthoma cells) [11].

In the meta-analysis published by Harley et al. [1] the mean age was 49 years, 70% of patients were female and 28% had diabetes mellitus. Similar findings were seen in our study (Table 1). The reason for female gender predilection remains unexplained. Even though pathogenesis is not fully understood, urinary tract obstruction and infection are thought to be essential requisites and HPE indicates a chronic granulomatous process believed to incite a chronic but incomplete immune reaction [12].

Also known as inflammatory tumor, preoperative diagnosis is often confounded by clinical and imaging characteristics resembling other pathologies (Supplementary Table 3). The intense debilitating inflammatory response responsible for the clinical and surgical morbidity is represented on HPE by macrophages intermixed with a variety of inflammatory elements, including lymphocytes, plasma cells, neutrophils, multinucleated giant cells, and associated granulomatous inflammation. In cases where differentiation between XGP and renal cell carcinoma is difficult, it has been found that specimens with XGP stained positive for PAS (periodic acid Schiff) stain [13]. This phenomenon is also seen in children and was first described in 1963, by Avnet et al. [14] XGP should be included in the differential diagnosis of all children presenting with perinephric or psoas abscess, renal mass and/or non-functioning kidney associated with/or without urolithiasis [15].

The presence of associated partial or complete staghorn stone is absent in up to 48% of cases. XGP may also be associated with upper urinary tract stones in up to 69% of cases [1]. In our series, staghorn stones were seen in 27% of cases and 69.7% of patients had some degree of pre-existing chronic kidney disease.

In XGP, the relationship between nephrolithiasis and urinary tract infection (UTI) is complex and difficult to analyze both from a pathophysiological and clinical point of view [16]. Ripa et al. proposed that UTI and kidney stone disease are mutually coexisting and reciprocally causal [17]. Infected nephrolithiasis is traditionally considered to be a consequence of a UTI by urease-producing bacteria, mostly of *Proteus* spp, which is traditionally described as the most common causative microorganism in XGP. A limited

Table 2 Univariate and multivariate analysis of factors associated with the development of complications after nephrectomy for xanthogranulomatous pyelonephritis ($n=403$)

	No major complications ($n=305$)	Major complications ($n=98$)	Univariate		Multivariate	
			P value	OR (CI 95%)	*P* value	OR (CI 95%)
Demographics						
Age; years mean ± SD	44.8 ± 15.7	46.4 ± 14.4	0.368	1.6 (1.912–5.149)*		
Females; *n* (%)	191 (62.6)	57 (58.2)	0.43	1.205 (0.758–1.916)		
Body Mass Index; kg/m^2, mean ± SD	24.1 ± 5	25.6 ± 5.2	0.659	1.5 (0.176–2.84)*		
Clinical presentation						
Fever; *n* (%) (> 38.3 °C)	104 (34)	44 (44.9)	0.106	1.465 (0.921–2.332)		
Urosepsis; *n* (%)	34 (11.1)	18 (18.4)	0.064	1.793 (0.961–3.345)		
qSOFA ≥ 2 points; *n* (%)	22 (7.2)	22 (22.4)	**< 0.001**	**3.562 (1.868–6.792)**	**0.004**	**3.360 (1.488–7.591)**
Comorbidities						
Diabetes mellitus; *n* (%)	81 (26.6)	31 (31.6)	0.329	1.28 (0.779–2.101)		
Hypertension; *n* (%)	80 (26.2)	36 (36.7)	0.054	1.633 (0.998–2.648)		
Chronic kidney disease; *n* (%)	219 (71.8)	62 (63.3)	0.11	0.676 (0.418–1.094)		
Recurrent urinary tract infections; *n* (%)	61 (20)	32 (32.7)	**0.01**	**1.939 (1.168–3.220)**	0.145	1.652 (0.841–3.245)
Radiological characteristics						
Renal abscess; *n* (%)	56 (18.4)	39 (39.8)	**< 0.001**	**2.939 (1.787–4.834)**	0.231	1.516 (0.768–2.991)
Staghorn stone; *n* (%)	72 (23.6)	37 (37.8)	**0.011**	**1.870 (1.149–3.045)**	0.089	1.683 (0.924–3.065)
Multiple stones; *n* (%)	103 (33.8)	30 (30.6)	0.563	0.865 (530–1.413)		
Ureteropyelic junction stone; *n* (%)	89 (29.2)	29 (29.6)				
Laboratory workup						
Anemia (Hemoglobin < 12 g/dL)	203 (67)	80 (81.6)	**0.006**	**2.189 (1.245–3.851)**	0.122	1.738 (0.862–3.504)
Leukocytosis (Leukocytes > 11,000/L)	88 (28.8)	42 (42.8)	**0.012**	**1.867 (1.141–3.054)**	0.867	1.055 (0.566–1.964)
Thrombocytopenia (Platelets < 150,000/L)	18 (6)	9 (9.1)	0.252	1.630 (0.702–3.784)		
Increased creatinine (Creatinine > 1.2 mg/dL)	61 (20.2)	38 (38.8)	**< 0.001**	**2.502** (1.527–4.101)	**0.015**	**2.258 (1.171–4.356)**
Hyperglycemia (Glucose > 200 mg/dL)	36 (11.8)	18 (18.3)	0.184	1.531 (0.814–2.878)		
Malek classification						
Limited to the kidney; *n* (%)	166 (54.4)	30 (30.6)				
Extended to perirenal space; *n* (%)	104 (34)	35 (35.7)	**0.026**	**1.862 (1.079–3.214)**	0.076	1.676 (0.948–2.962)
Extended to pararenal space; *n* (%)	35 (11.5)	33 (33.7)	**< 0.001**	**5.217 (2.823–9.643)**	**< 0.001**	**3.958 (2.077–7.543)**
Microbiological characteristics						
Positive urine culture; *n* (%)	138 (45.2)	67 (68.4)	**< 0.001**	**2.615 (1.616–4.234)**	**0.031**	**1.948 (1.064–3.565)**
ESBL agents in urine; *n* (%)	21 (6.9)	17 (17.3)	**0.002**	**2.838 (1.430–5.633)**	0.773	1.070 (0.675–1.696)
Previous urinary decompression; *n* (%)	144 (47.2)	48 (49)	0.761	1.073 (0.681–1.692)		
Nephrectomy approach						
Retroperitoneal approach; *n* (%)	126 (41.3)	67 (68.4)	**< 0.001**	**3.07 (1.894–4.976)**	**< 0.001**	**3.311 (1.757–6.241)**

*Differences between means (CI 95%)

Bold represent statistical significant values, defined as $p<0.05$

number of strains of other gram-negative bacteria may also produce urease, which is often associated with XGP infections [12]. *Escherichia coli* is the main non-urease bacteria. Others include *Staphylococcus aureus*, group B *Streptococcus*, *Candida* spp, *Klebsiella* spp, and *Bacteroides* spp. [18]. Although many XGP patients have pyuria, bacterial growth in their bladder urine has been demonstrated in only two-thirds and hence renal tissue cultures must be taken during surgery for appropriate treatment [19].

Table 3 Major complications (intraoperative and postoperative)

	Number (%)
Clavien-Dindo ≥ 3	100 (24.8)
Organ injuries	58 (14.4)
Vascular injury	25 (6.2)
Colonic injury	16 (3.9)
Pleural injury	9 (2.2)
Duodenum injury	4 (1)
Spleen injury	4 (1)
Intensive care unit admission	60 (14.9)
Mortality	5 (1.2)

Table 4 Microbiological profile of urine and kidney cultures

	Number (%)
Urine cultures ($n = 383$)	
Sterile	178 (46.4)
Escherichia coli	109 (28.4)
Proteus mirabilis	27 (7)
Klebsiella pneumoniae	20 (5.2)
Polymicrobial	19 (4.9)
Pseudomonas aeruginosa	14 (3.6)
Enterococcus faecalis	6 (1.5)
Others[1]	10 (2.6)
Kidney cultures ($n = 253$)	
Sterile	135 (53.5)
Escherichia coli	61 (24.1)
Klebsiella pneumoniae	11 (4.3)
Pseudomonas aeruginosa	9 (3.5)
Proteus mirabilis	8 (3.1)
Polymicrobial	6 (2.4)
Staphylococcus aureus	6 (2.4)
Candida spp	5 (1.9)
Morgagnella morgagni	5 (1.9)
Others [2]	7 (2.7)

[1]Candida spp (3), Enterobacter cloacae (2), Staphylococcus aureus (3), Citrobacter freundii (1), Gardenela vaginalis (1). [2] Enterococcus faecalis (2), Enterobacter cloacae (2), Streptococcus constellatus (1), Corynebacterium spp (1), Pasteurella pneumotropica (1)

Our study differs whereby the most commonly isolated pathogen was *E. coli* (28.4%), followed by Proteus mirabilis (7%) and Klebsiella pneumoniae (5.2%). In addition, we found negative bacterial cultures in 46.8% of patients. Perhaps they had already been treated with antibiotics before culture.

Radiological findings and histopathology characteristics in XGP

XGP is also called the "great MIMIC" [16] or Pseudotumor [18] as it is commonly confused with renal cell carcinoma and imaging characteristics often resemble other renal lesions as well (Supplementary Table 1) due to its similarity in clinical and radiographic features, as well as the ability to invade adjacent structures and organs. Imaging remains a cornerstone for diagnosis, surgical planning, and prognosis. CT scan is the main imaging tool, as it provides highly specific findings and accurate assessment of the extrarenal extent of disease. Classic findings on CT include a loss of normal renal parenchyma, an enlarged kidney, paradoxical contracted scarred renal pelvis, and dilated calyces resulting in a multiloculated appearance resembling the paw print of a bear (bear's paw sign). XGP is often associated with the presence of staghorn stones. In some cases, there is a perinephric extension with thickening of Gerota's fascia with calcification better delineated only on CT scan [19].

Two forms of the disease are recognized both macroscopically and on imaging: [20] Diffuse (90%) and focal or tumefactive form (10%). The former is more common and staged by Malek and Elder into three different stages according to the extent of involvement in the nearby tissues [21]. Harley et al. [1] argued that this classification was rarely used in clinical practice and that no correlation can be made between stages and mortality rate. In our study, from the 10 centers included, Malek classification was available for all 403 patients and had a significant bearing. On multivariate analysis, stage 3 (paranephric extension) was significantly associated with major complications during surgery. The review by Harley et al. also reported a total of 18 deaths within 1 year of diagnosis, resulting in a weighted proportion of 1436 deaths per 100,000 patients (95% CI 292–2579). The heterogeneity of this analysis was low ($I2 = 0\%$). However, no subset analysis was available for the 18 deaths on their clinical and radiological presentation to infer concrete conclusions. In our study, none of the patients had bilateral XGP, which is very rare and fatal, [22] but the 3 deaths that happened intraoperatively were stage 3 Malek classification. Even in the ICU subset, Malek stage 3 had the worst outcomes (Table 5). We considered that this clinical-radiological classification might be a significant factor both for prognosis and from a surgical standpoint.

Surgical approaches for nephrectomy

Of the 403 nephrectomies, the open approach was preferred in 88.9% ($N = 358$), and laparoscopic (LN) in 11.1% ($N = 45$) with a conversion rate of 22% ($N = 10$), which was much lesser than the Meta-Analysis of Harley et al. reporting laparoscopic approach in 34% ($N = 138$) with a 13% conversion rate. [1] A minimally invasive approach in XPG is a new trend with robotic and laparoscopic advances. Several publications on the LN approach for XPG have reported lower blood loss, a shorter hospital stay, and better pain management and ICU admission.

Table 5 Comparison of complications with different approaches of nephrectomy

Complications	Approach of nephrectomy			*p* value
	Open transperitoneal ($n=183$)	Open retroperitoneal ($n=175$)	Laparoscopic ($n=45$)	
Clavien-Dindo ≥ 3; *n* (%)	24 (13.1)	66 (37.7)	10 (22.2)	0.01
Local Injuries; *n* (%)	27 (14.8)	64 (36.6)	7 (15.6)	< 0.001
Vascular injury; *n* (%)	3 (1.6)	20 (11.4)	2 (4.4)	0.001
Colonic injury; *n* (%)	3 (1.6)	11 (6.3)	2 (4.4)	0.078
Pleural injury; *n* (%)	1 (0.5)	6 (3.4)	2 (4.4)	0.103
Duodenum injury; *n* (%)	0 (0)	3 (1.7)	1 (2.2)	0.178
Spleen injury; *n* (%)	0 (0)	3 (1.7)	1 (2.2)	0.178
Intensive care unit admission; *n* (%)	20 (10.9)	37 (21.1)	3 (6.7)	0.007
Mortality; *n* (%)	0 (0)	5 (2.9)	0 (0)	0.037
Conversion to open surgery*; *n* (%)	NA	NA	10 (22.2)	NA

[2, 3, 23] In our series, mean operation time was shorter than other series 171.7 ± 65.1 min vs 193.16 min (123–320 min) for Asali M et al. [24] and 304 min for Vanderbink et al. [4] but higher than Hemal AK et al. 100 min and whose main approach was retroperitoneal [25]. Mean blood loss of 625.7 ± 810 ml in our series was lower than 737.1 ± 606.8 ml for Vanderbink et al. [4] Bercowsky et al. reported a mean blood loss of 260 ml [5] and reported that experience, laparoscopic and a retroperitoneal approach were the key factors to minimizing blood loss. Our series had a transfusion rate of 35.5%, which was higher than the 26.6% reported by Asali et al. [24] Several studies suggest that the midline transperitoneal technique provides more working space and is easier to interpret anatomically. However, the flank retroperitoneal approach has the advantage of direct access to the renal artery and has a lower risk of vascular complications, which is noted to be the principal surgical complication followed by colonic injury [4, 24, 25].

The transperitoneal approach was preferred in 51.2% and the retroperitoneal approach in 48.8% of patients. Due to the intense peri-inflammatory response in XGP, nephrectomy is complex and technically demanding due to contiguous organ involvement and obliterated planes for dissection by inflammatory tissue and the term simple nephrectomy is often a misnomer [2, 3, 23]. Even a well-trained and experienced surgeon often needs conversion to open surgery and en-bloc stapling of the renal hilum may help decrease the operative duration and reduces the risk of vascular injury. Often, patients have complications, prolonged hospital stay and may also need further management in the ICU. Even in our study, 14.9% ($n=60$) of patients needed admission to ICU postoperatively with a reported 24.8% CD3 and above complications. In our study, the open transperitoneal approach reported lesser vascular and other organ injuries (CD > 3) than the laparoscopic and retroperitoneal approaches. On the other hand, the retroperitoneal approach subset had more vascular injuries with higher rates of ICU admission and significant mortality (Table 3).

Outcomes of patients needing postoperative ICU care

After surgical exploration, 60 patients needed prolonged ICU care. Of significant note in this subset analysis, 26.7% of the patients were of Malek 3 classification, (versus 15.2% of the entire cohort), 13.3% had a qSOFA score of 3 points or more at presentation (vs 0.9% of the entire cohort), 61.7% had a retroperitoneal approach (vs 40.2% of the entire cohort) with 35% of ICU admissions (vs 8.5% of cohort) having CD3 and above injuries and 4 of the 5 patients in ICU died (supplementary Table 1). For the first time, we have been able to identify that these aforementioned parameters are negative prognostic indicators and urologists must consider counseling these significant findings in the acute management of such patients.

Study limitations

As with all retrospectively pooled multicenter data, there are limitations of bias, recording, and reporting the data. Missing variables and the lack of uniformity in management influences the outcomes of any study. However, as this global study reflects real word practice we have made several important deductions. Our study once again reiterates that proper radiological planning and classification are quintessential. Urologists should offer when possible a laparoscopic approach in experienced hands, or else an open transperitoneal approach may be adopted with adequate care to minimize the risk of organ injuries. This was in concordance with a 38% incidence of CD3 and above postoperative complications reported by Addison et al. [26] Our study indeed refutes the conclusion of Harley et al. [1] that current patients with XGP experience a lower mortality rate than historically reported. In our series, five patients died due to complications alone and we don't have a long-term follow-up of the other patients to report 1-year disease-specific mortality. Further, in their meta-analysis, they have been unable to list the probability of which patient subgroups either by radiological or clinical presentation have the highest possibility of a prolonged moribund course of recovery involving ICU care. Our pooled multicenter global data is the first of its kind that reflects the real-world modern presentation and practice of this disease and the high-grade complications we can expect during surgical intervention. Identification of which patients are likely to need ICU, a poor indicator of outcomes for this disease, has uniquely been outlined in this multicenter study.

Conclusion

XGP is a clinical, radiological, and surgical dogma. We strongly advocate using the Malek classification as in our study stage 3 disease needing nephrectomy had the highest probability of major complications and for ICU admission and mortality. A transperitoneal open approach may be the best option when the laparoscopic approach is not feasible or performed by non-expert laparoscopic surgeons, especially in patients with more extensive disease and other risk factors for major complications. Counseling patients on these above factors is quintessential when managing this pathology.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00345-023-04415-x.

Authors contributions JI Robles-Torres: protocol/project development, data analysis, manuscript writing/editing, data analysis; LR García-Chairez: protocol/project development, data collection or management; D Castellani: protocol/project development, data analysis, manuscript writing/editing; JV Enrriquez-Ávila: data collection or management; JF Monzón-Falconi: data collection or management, manuscript writing/editing; A Esqueda-Mendoza: data collection or management; JP Flores-Tapia: data collection or management; ML Wroclawski: data collection or management, manuscript writing/editing; HO Duarte-Santos: data collection or management; D Ragoori: data collection or management, manuscript writing/editing; N Gadzhiev: data collection or management, manuscript writing/editing; A Mahajan: data collection or management; S Kumar: data collection or management, manuscript writing/editing; M Farooq: Data collection or management; A Ganpule: Data collection or management; Y Tanidir: Data collection or management, Manuscript writing/editing; PN Maheshwari: data collection or management; VA Gite: data collection or management, manuscript writing/editing; MM Sinha: data collection or management; BK Somani: data collection or management, manuscript writing/editing; A Gutiérrez-González: protocol/project development, manuscript editing; V Gauhar: protocol/project development, Data analysis, Manuscript writing/editing.

Data availability Data supporting Tables 1–5 and Supplementary Tables are not publicly available in order to protect patient privacy.

Declarations

Conflict of interest None of the authors have a conflict of interest or funding source to declare.

Research involving human participants and/or animals This retrospective study involving human participants was in accordance with the ethical standards of the institutional research committee of each center involved and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Ethics Committee of each center was obtained for this study.

Informed consent The study is exempt from the application of informed consent to the study subjects.

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Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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