

1 **Association of simple renal cysts and chronic kidney disease with**
2 **large abdominal aortic aneurysm**

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34 **Abstract**

35 Abdominal aortic aneurysms (AAA) primarily affect elderly men who often have many other
36 diseases, with similar risk factors and pathobiological mechanisms to AAA. The aim of this study
37 was to assess the prevalence of simple renal cysts (SRC), chronic kidney disease (CKD), and
38 other kidney diseases (e.g. nephrolithiasis) among patients presenting with AAA. Two groups of
39 patients (100/group), with and without AAA, from the Surgical Clinic Charité, Berlin, Germany,
40 were selected for the study. The control group consisted of patients who were evaluated for a
41 kidney donation (n = 14) and patients who were evaluated for an early detection of a melanoma
42 recurrence (n = 86). The AAA and control groups were matched for age and sex. Medical
43 records were analyzed and computed tomography scans were reviewed for the presence of
44 SRC and nephrolithiasis. SRC (73% vs. 57%; $p < 0.001$) and CKD (31% vs. 8%; $p < 0.001$) were
45 both more common among AAA than control group patients. On multivariate analysis, CKD, but
46 not SRC, showed a strong association with AAA. Knowledge about pathobiological mechanisms
47 and association between CKD and AAA could provide better diagnostic and therapeutic
48 approaches for these patients.

49

50 **Key words:** Abdominal aortic aneurysm, renal cyst, chronic kidney disease

51

52 **Introduction**

53 Abdominal aortic aneurysm (AAA) is the most common type of aneurysm, and is defined as an
54 abdominal aortic diameter > 3 cm [1]. According to recent literature, the prevalence of AAA has
55 decreased in the last decades and is 1–2% [2]. This change can be primarily attributed to a
56 decreased prevalence of smoking [2, 3]. The prevalence of AAA, however, increases with age
57 and is 4.1%–14.2% in men and 0.35 – 6.2% in women > 65 years [4, 5].

58

59 As AAA is asymptomatic in the majority of cases [6], it is often initially detected as an incidental
60 finding during ultrasound or computed tomography (CT) examinations. Unfortunately, many
61 AAA cases remain undetected until rupture. The mortality rate of a ruptured AAA is estimated to
62 be 74–90% [7, 8], with a 32–83% pre-hospital mortality rate [7, 9]. One way to reduce this trend,
63 is to implement a national AAA screening program to detect AAA before rupture [10]. Such a
64 program was launched successfully in the USA in 2007 [11] and in the Great Britain in 2009
65 [12].

66

67 A number of risk factors for AAA have been identified. The four primary risk factors are male
68 sex, age > 65 years, smoking and a positive family history [13-18]. Several diseases appear to
69 often co-exist with AAA, including chronic obstructive pulmonary disease (COPD) [13, 19, 20],
70 different types of hernia [20], gallstones [21], and simple renal cysts (SRC) [22]. SRC is a
71 common disease, with increased prevalence in older patients, affecting 24–27% of those > 50
72 years of age [23, 24]. In older individuals, SRCs are even more common; Carrim et al. found an
73 overall prevalence of 41% [25], while Chang et al. reported a prevalence of 35% in >60-year
74 olds [26].

75

76 The co-occurrence of AAA and SRC [22, 27] can be explained by shared risk factors, e.g. older
77 age [26, 28, 29], male sex [25, 30], hypertension [31] and smoking [26]. Ito et al. [22] stated “*the*
78 *presence of renal cysts shows the strongest independent association with AAA among patients*
79 *belonging to the 65 to 74 years old group and over 75 years old group*”. The exact pathogenesis
80 of SRC remains unclear, but it is intriguing that both diseases demonstrate increased matrix
81 metalloproteinase (MMP) levels, in the aortic wall in AAA patients [32] and in the cystic fluid in
82 patients with SRCs [33].

83

84 Given the potentially shared pathophysiology between SRC and AAA, the primary aim of this
85 study was to assess the prevalence of SRC and other kidney diseases among AAA patients,
86 and compare the results to a group of age- and sex-matched non-AAA patients from the same
87 hospital.

88

89 **Materials and methods**

90 The study was approved by the Charité Ethics Committee (approval number: EA1/309/16).

91 Since the study was a retrospective review of medical and imaging records, no informed
92 consent from the patients was required according to the study approval.

93

94 **Study groups**

95 This study was a retrospective review of patients' medical records including radiology records.

96 Two groups of patients (100/group) were compared in the study. All 200 patients had undergone
97 a computed tomography-angiography (CTA) scan. The first group included patients, who
98 underwent AAA surgery in 2004 – 2012 at Charité Clinic Campus Mitte in Berlin, Germany.
99 Surgeries were performed either as elective (unruptured AAA; n=94) or as emergency (ruptured
100 AAA; n= 6) operations. The exclusion criteria were an abdominal aortic diameter <3 cm, AAA
101 operation before 2004, diagnosis of rare genetic disorder such as Marfan syndrome or Ehlers-
102 Danlos syndrome, and the presence of any other arterial aneurysm. One AAA patient was
103 diagnosed with Marfan syndrome and was, therefore, excluded from further analyses, leaving
104 99 AAA patients for the analyses presented here. For the AAA patients, the pre-operative scans
105 were used.

106

107 The control group (n=100) included patients without AAA investigated at the Institute of

108 Radiology of Charité Clinic, Berlin, Germany, and consisted of patients who were evaluated for

109 a kidney donation in 2005 – 2014 (n = 14) and patients who were evaluated for an early
110 detection of a melanoma recurrence (n = 86). We chose this group of patients as a control
111 group for the following reasons: 1) they were also examined by abdominal CTA; 2) melanoma is
112 an age-related disease and a disease of a different organ, not the aorta; and 3) they were from
113 the same hospital system. Also, there were no differences in the mean height, weight, or BMI
114 between the AAA and control groups [34].

115

116 AAA patients and controls were matched on sex and age (± 2 years). For the AAA patients, age
117 at the time of the first AAA diagnosis was used for this analysis. If this information was missing,
118 age at the time of AAA surgery was taken. For the control group, age during the CTA scan was
119 used for the analysis.

120

121 **Clinical data**

122 For the analysis of the CTA scans, Centricity eRadCockpit Software (GE Healthcare, Chalfont
123 St Giles, Great Britain) was used. First, written reports from board-certified radiologists were
124 reviewed by one of the authors (M.M.). As SRCs are common, sometimes they were not
125 described as a diagnosis in the report. For that reason, the CTA scans were assessed again for
126 the presence of SRC (Fig 1) and kidney stones. Results were discussed with a board-certified
127 radiologist (C.E.A.).

128

129 Individual data on all study patients for all variables used in the study are available in the
130 Supplementary file.

132

133

134 **Fig. 1. Simple renal cyst detected in a CT scan.** Contrast-enhanced CT scan of the abdomen
135 in axial (A) and coronal (B) plane, arterial phase, demonstrates an AAA (arrow head) with mural
136 thrombus and patent lumen and a large hypodense mass on the lower left renal pole,
137 representing a simple renal cyst (arrow).

138

139 SRC (ICD-10: N28.1) were divided into subgroups according to their size: Group 1: ≤ 1 cm;
140 Group 2: 1.01 – 3.0 cm; Group 3: 3.1 – 5.0 cm; and Group 4: >5 cm. SRCs were also classified
141 using Bosniak Classification System: I: simple, benign cysts; II: minimally complicated benign
142 cystic lesions; III: more complicated cystic lesions; and IV: cystic carcinoma [35].

143

144 Nephrolithiasis (ICD-10: N20.0) was defined as a presence of kidney stones on the CTA scans.

145

146 Additional patient data [34] were collected from the medical records using the patient data
147 management program SAP (SAP SE, Walldorf, Germany). Information about the presence of
148 chronic kidney disease (CKD) was collected. CKD was defined as a presence of the following
149 ICD-10 diagnostic codes in the medical records: N18.1 for CKD stage 1, N18.2 for CKD stage 2,
150 N18.3 for CKD stage 3, N18.4 for CKD stage 4, N18.5 for CKD stage 5, and Z94.0 for renal
151 transplantation. Additional diseases in the same study groups are described in another study
152 [34].

153

154 **Statistical analysis**

155 For statistical analyses SPSS Statistics Version 22 for Windows (IBM, Armonk, New York, USA)
156 was used. First, a univariable analysis was carried out. For quantitative variables, the mean,

157 median, standard deviation, minimal and maximal values were determined. The categorical
158 variables were analyzed using cross-tabulation. The differences between the two groups were
159 determined using Mann-Whitney U test or chi-squared test (Fisher's exact test) where
160 appropriate. A difference was defined significant, if $p \leq 0.05$.

161

162 The univariable analysis was followed by a multivariable analysis to identify independent risk
163 factors. Significant values from the univariable analysis were included in a multiple logistic
164 regression model. This included the following parameters: ever smoker, peripheral artery
165 disease (PAD), pack years of smoking, incisional hernia, any hernia, congestive heart failure,
166 American Society of Anesthesiologists (ASA) score, diabetes mellitus, coronary bypass,
167 creatinine, COPD, current smoker, coronary artery disease, diverticulosis, platelet count [34]
168 and SRC. Parameters with >50% of the values missing were excluded from the analysis. A
169 forward and backward analysis was performed. Odds ratios (OR) and a 95% confidence
170 intervals (CI) were calculated.

171

172 **Results**

173 Our study included 99 (78 male and 21 female) AAA patients and 100 (79 male and 21 female)
174 age- and sex-matched controls. Altogether, 30.3% AAA and 8% control patients had CKD
175 diagnosis in their medical records ($p < 0.001$; Table 1). The distribution of CKD stages was also
176 statistically significantly different between the study groups ($p = 0.002$; Table 1). One AAA patient
177 received a renal transplantation due to the CKD. Nephrolithiasis was found in 2% of the AAA
178 and 7.1% of the control patients ($p = 0.1$). SRCs were found amongst 72.7% AAA patients and
179 57% controls, resulting in a statistically significant difference (Table 1; $p = 0.009$). Among AAA
180 patients, two had been diagnosed with autosomal dominant polycystic kidney disease (ADPKD)

181 and were excluded from further evaluations.

182

183 **Table 1. Comparison of simple renal cysts and chronic kidney disease between study**

184 **groups.**

Variable	AAA group		Control group		<i>p</i> ^a
	<i>With variable n</i>	<i>Data available n</i>	<i>With variable n</i>	<i>Data available n</i>	
CKD, all stages ^b	30	99	8	100	<0.001
CKD stage 1/2/3/4/5/RTX ^c	5/9/11/1/3/1	99	1/4/3/0/0/0	100	0.002
Nephrolithiasis	2	99	7	98	0.10
SRC (both right and left kidney) ^d	72	99	57	100	0.01
SRC, right kidney only	58	99	46	100	0.04
1 – 4 SRC in right kidney ^d	46	99	41	100	0.05
>5 SRC in right kidney ^d	12	99	5	100	0.05
SRC, left kidney only ^d	60	98	33	100	<0.001
1 – 4 SRC in left kidney ^d	48	98	29	100	<0.001

> 5 SRC in left kidney ^d	12	98	4	100	<0.001
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185 ^aChi-square test

186 ^bDefined as presence of ICD-10 code in medical records: N18.1 for CKD stage 1, N18.2 for
 187 CKD stage 2, N18.3 for CKD stage 3, N18.4 for CKD stage 4, N18.5 for CKD stage 5 or Z94.0
 188 for renal transplantation.

189 ^cDefined as presence of kidney stones (ICD-10: N20.0) on the CTA scans.

190 ^dDefined as presence of simple renal cysts (ICD-10: Q61.9) on the CTA scans.

191 CKD: chronic kidney disease; SRC: simple renal cyst; RTX: renal transplantation.

192

193

194 In the right kidney, SRCs were found in 58.6% of AAA patients and in 46% of controls
 195 (p=0.039). In the AAA group, 46.5% of patients had 1–4 SRCs, and 12.1% of patients had ≥5
 196 SRCs. In the control group, these numbers were 41% and 5%, respectively (p=0.048, for both
 197 comparisons). In the right kidney, SRCs ≤1 cm were significantly more common among AAA
 198 than control patients (p<0.001; Table 2).

199

200 **Table 2. Simple renal cysts in the right kidney classified according to their size.**

SRC classification based on size	AAA group			Control group			<i>p</i> ^a
	<i>Number of SRC per patient</i>	<i>Median SRC per patient</i>	<i>Data number of available</i>	<i>Number of SRC per patient</i>	<i>Median SRC per patient</i>	<i>Data number of available</i>	
	<i>Mean±SD</i>	<i>patient</i>	<i>n</i>	<i>Mean±SD</i>	<i>patient</i>	<i>n</i>	
≤1 cm	1.15 ± 1.86	0	97	0.50 ± 1.45	0	100	<0.001

1.1 cm – 3.0 cm	0.43 ± 0.95	0	97	0.41 ± 0.79	0	100	0.99
3.1 cm – 5.0 cm	0.10 ± 0.34	0	97	0.05 ± 0.26	0	100	0.15
>5 cm	0.02 ± 0.14	0	97	0.04 ± 0.20	0	100	0.68

201 ^aMann-Whitney U test

202 SRC, simple renal cyst

203

204 In the left kidney, SRCs were found in 61.2% of AAA and 33% of control patients ($p < 0.001$). In
 205 the AAA group, 49% of patients had 1–4 SRCs, and 12.2% of patients had ≥ 5 SRCs. In the
 206 control group, these numbers were 29% and 4%, respectively ($p < 0.001$, for both variables). In
 207 the left kidney, both small (≤ 1 cm; $p < 0.001$) and medium size (1 – 3 cm; $p = 0.020$) SRCs were
 208 significantly more common among AAA than control patients (Table 3). In the AAA group, we
 209 also found two patients with SRCs classified as Bosniak II and two patients with SRCs classified
 210 as Bosniak III. In the control group, one patient each with Bosniak II and Bosniak III were found.
 211 There were 46 (46.5%) AAA and 22 (22%) control group patients who had bilateral SRC
 212 disease, whereas 25 (25.3%) AAA and 34 (34%) control patients had SRCs in only the left or
 213 right kidney ($p = 0.001$).

214

215 **Table 3. Simple renal cysts in the left kidney classified according to their size.**

SRC classification based on size	AAA			Controls			p^a
	<i>Number of SRC per patient</i>	<i>Median Data number of availa SRC per ble,</i>	<i>Data</i>	<i>Number of SRC per patient</i>	<i>Median Data number of availa SRC per ble,</i>	<i>Data</i>	

	<i>Mean±SD</i>	<i>patient</i>	<i>n</i>	<i>Mean±SD</i>	<i>patient</i>	<i>n</i>	
≤1 cm	1.28 ± 2.08	1	96	0.37 ±1.17	0	100	<0.001
1.1 cm – 3.0 cm	0.56 ± 0.95	0	96	0.30 ± 0.73	0	100	0.02
3.1 cm – 5.0 cm	0.10 ± 0.31	0	96	0.04 ± 0.20	0	100	0.10
>5 cm	0.01 ± 0.10	0	96	0.00 ± 0.00	0	100	0.49

216 ^aMann-Whitney U test

217 SRC, simple renal cyst

218

219 In multivariable analyses, which included ever smoker, PAD, pack years, incisional hernia, any
 220 hernia, congestive heart failure, ASA score, diabetes mellitus, coronary bypass, creatinine,
 221 COPD, current smoker, coronary artery disease, diverticulosis, platelet count and SRC, we
 222 found a strong independent association between AAA and CKD (OR = 5.655; 95%CI = 1.785–
 223 17.921; p=0.003). We found no direct association between SRC and AAA (OR = 1.711; 95%CI
 224 = 0.625–4.682; p=0.296), when adjusting for other variables.

225

226 **DISCUSSION**

227 The main findings of our study were that CKD was more frequent in AAA than age- and sex-
 228 matched control patients and showed a strong association with AAA in multivariable analysis,
 229 which included ever smoker, PAD, pack years, incisional hernia, any hernia, congestive heart
 230 failure, ASA score, diabetes mellitus, coronary bypass, creatinine, COPD, current smoker,
 231 coronary artery disease, diverticulosis, platelet count and SRC. AAA patients also had a higher
 232 rate of SRC, but SRCs were not independently associated with AAA.

233

234 Our study demonstrated a strong association between AAA and CKD with 30.3% of the AAA
235 and only 8% of the age- and sex-matched control patients diagnosed with CKD. The AAA
236 patients also exhibited a more advanced CKD stage. Previously published studies reported a
237 wide range of CKD prevalence (3–65%) among AAA patients [20, 36-39]. Alnassar et al. [36]
238 and Pitoulias et al. [40] found no significant difference in the prevalence of CKD between AAA
239 and PAD patients [20, 36]. However, patients with a large AAA (>5.5 cm) had a significantly
240 higher rate of CKD than patients with a small AAA (13% vs. 2%) [20]. Approximately half
241 (54.3%) of the AAA patients in our study had a large AAA (>5.5 cm) and all were operated on
242 for AAA, and the rate of CKD was over four times as high as the rate in the study of Pitoulias et
243 al [20]. Furthermore, similar to the findings by Chun et al. [38] and Takeuchi et al. [39], our study
244 demonstrated an independent association of AAA and CKD in multivariable analysis, not seen
245 in the study by Pitoulias et al. [20].

246
247 We estimated the prevalence of SRC to be 72.7% in the AAA and 57% in the control group.
248 Based on previous literature, the SRC prevalence in general population varies 4.2–41% [25,
249 28], which is lower than in the current study (Table 4). Similarly, the SRC prevalence among
250 AAA patients in the current study was higher than in most of the previous studies, which
251 reported a prevalence of 38–69% among AAA patients and 18–45% for controls [20, 22, 27, 41-
252 43]. A recent study by Brownstein et al. [43] analyzed a total of 35,498 patients who underwent
253 both chest and abdominal CT imaging during a 4-year period. Altogether 18% of these patients
254 had SRC and 2.6% had AAA. Compared with the matched population without SRC, patients
255 with SRC demonstrated an increased prevalence of AAA (8% vs. 3%). They were also more
256 likely to have thoracic, ascending and descending aortic aneurysms or dissections [43]. Five
257 previous studies found an independent association between AAA and SRC in a multivariable
258 analysis [20, 22, 27, 41, 43], but we could not confirm this in our study. However, three of those
259 studies [22, 41, 43] examined a significantly larger patient group.

260 **Table 4. Prevalence of SRC in AAA and control patients in published studies.**

Study reference	Number of AAA/controls	Prevalence of SRC (%)		Univariate analysis		Multivariate analysis	
		AAA	Controls	p value	OR (95%CI)	p value	OR (95%CI)
Current study	99/100	73	57	0.008	NA	0.30	1.71 (0.63 – 4.68)
Pitoulis et al. [20]	10/60	69	27	<0.001	0.16 (0.08 – 0.33)	<0.001	0.23 (0.11 – 0.48)
Ito et al. [22]	16/102 ^a	38 ^a	29 ^a	0.56 ^a	NA	0.002 ^b	4.15 ^b (1.72 –
	56/88 ^b	63 ^b	37 ^b	0.002 ^b		0.02 ^c	10.03)
	52/81 ^c	56 ^c	38 ^c	0.05 ^c			3.00 ^c (1.16 – 7.73)
Song et al.[41]	271/1,387	55 ^d	19 ^d	0.001 ^d	NA	0.04	2.64 (1.05 – 6.63)
		56 ^e	29 ^e	0.03 ^e			

Spanos et al. [42]	100/100	63	45	NA	NA	0.02 ^f	NA
Yaghoubian et al. [27]	100/100	54	30	0.0006	2.73 (1.53 – 4.9)	0.03 ^f	2.05 ^f (1.08 – 3.88)

261 ^aPatients <65 years.

262 ^bPatients 65 – 74 years.

263 ^cPatients >75 years.

264 ^dData for the entire sample group.

265 ^eData for the matched group.

266 ^fAAA as predictive factor for SRC.

267 NA, no data available; CI, confidence interval; OR, odds ratio; SRC, simple renal cyst.

268

269 An important difference between our study and the previous studies on SRCs is that in our
270 study patients were not stratified according to age, which could explain our negative results in
271 the multivariable analysis. Ito et al. [22] found an association between AAA and SRC in their
272 multivariable analysis, but only in patients >65 years. Another important factor is the age of
273 patients with and without SRC. Prior studies have confirmed that SRC develops mostly at older
274 age [24, 25, 28, 29, 41, 42], and Ito et al. [22] and Yaghoubian et al. [27] found a significant
275 difference in the age of patients with and without SRC .

276

277 Our study showed an asymmetric distribution of SRCs between the left and right kidney. In
278 controls, the right kidney was more often affected than the left kidney (46% vs. 33%), whereas
279 in the AAA group, both kidneys were affected as often (58.6% vs. 61.2%). One previous study
280 demonstrated that a bilateral appearance of SRC increased the risk of hypertension (OR = 3.48,
281 95%CI = 2.12–5.71) [44]. Also the presence of multiple SRC (≥ 2) was associated with an
282 increased risk of hypertension [44]. Previous studies have also examined the correlation
283 between SRC size and hypertension, but an association with hypertension was found only for
284 SRCs > 1 cm in diameter [44].

285

286 SRC and AAA share some common risk factors, e.g. older age, male sex and hypertension [25,
287 26, 28, 29, 31, 45], and some studies also mention smoking as a possible risk factor for SRC
288 [26]. Molecular studies suggest that MMPs play a role in the pathophysiology of SRC and AAA
289 [33]. Furthermore, one study on 108 autopsies showed a correlation between the diameter of
290 the abdominal aorta and the number of SRC [46].

291

292 Further research on kidney diseases and AAA is not only of academic, but also of clinical
293 interest. Nowadays, the majority of AAA are repaired using endovascular aneurysm repair

294 (EVAR), which requires a contrast agent administration, known to be nephrotoxic. Only one
295 study has investigated the kidney function in patients with SRC after EVAR [42], and found that
296 patients with SRC had slightly higher creatinine levels, both before and after surgery, but the
297 difference was not statistically significant [42]. There was no significant difference in the
298 creatinine levels after EVAR [42], leading to the conclusion that kidney function is not affected
299 by the presence of SRC. As we have reported previously, in the current study population, the
300 AAA group patients had significantly higher creatinine levels than the control group patients [34].
301

302 Nephrolithiasis is a common problem in the elderly population. A higher prevalence of
303 nephrolithiasis has been reported in patients with SRC [26] and ADPKD [47]. The relationship
304 between renal stones and AAA has not been investigated previously. As SRC and ADPKD
305 appear frequently in AAA patients [22, 27], one might expect that nephrolithiasis affects AAA
306 patients as well. In our study population, we found no association between AAA and
307 nephrolithiasis. Nonetheless, when examining a patient with a renal colic, one should consider a
308 symptomatic or ruptured AAA as a potential differential diagnosis.
309

310 The association between AAA and CKD also requires further research by examining the role
311 CKD plays on the development and progression of AAA. It has been reported that blood vessel
312 walls in patients with CKD are thinner, which can increase the risk for rupture [48]. The co-
313 occurrence of AAA and CKD also has several clinical implications, since CKD increases the rate
314 of complications after surgery [49]. The clot inside the aneurysm sac can also impair the blood
315 perfusion of renal arteries (e.g. by embolization).
316

317 The main limitation of our study is the fact that this was a retrospective single-center study with
318 a small number of patients and controls. Another possible limitation is the fact that the control
319 group consisted of patients with melanoma and those evaluated for kidney donation and their

320 comorbidity profile might not be representative of the general population. Also, our study
321 evaluated patients with larger AAAs which were treated surgically. This might have caused a
322 selection bias and the results might not be representative of all AAA patients. A major
323 advantage of our study was matching of patients and controls on sex and age minimizing the
324 confounding effects attributed to these factors.

325
326 A better understanding about the pathophysiology of AAA will facilitate the development of
327 pharmacotherapies for AAA. Also, this knowledge could be used for a better risk stratification.
328 By introducing a national screening program in every country, AAA could be detected earlier. It
329 is also important to consider the possible complications arising from CKD, both after open
330 aneurysm repair, and EVAR. This group of patients should be given special attention and risk
331 factor analysis should be carried out. The risk of rupture should be high enough to justify the risk
332 of surgery. Further research is also needed on patients with small AAA who develop problems
333 in kidney function. It remains to be determined if renal function is also affected by an expansion
334 and different types of AAA where the renal arteries are involved.

335
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337 commercial, or not-for-profit sectors.

338
339 **Data Availability Statement:** All relevant data are within the paper and the files part of the
340 Supporting Information.

341
342 **Supporting information**

343 S1 File. Dataset containing all information on every patient included in the study (Excel format).

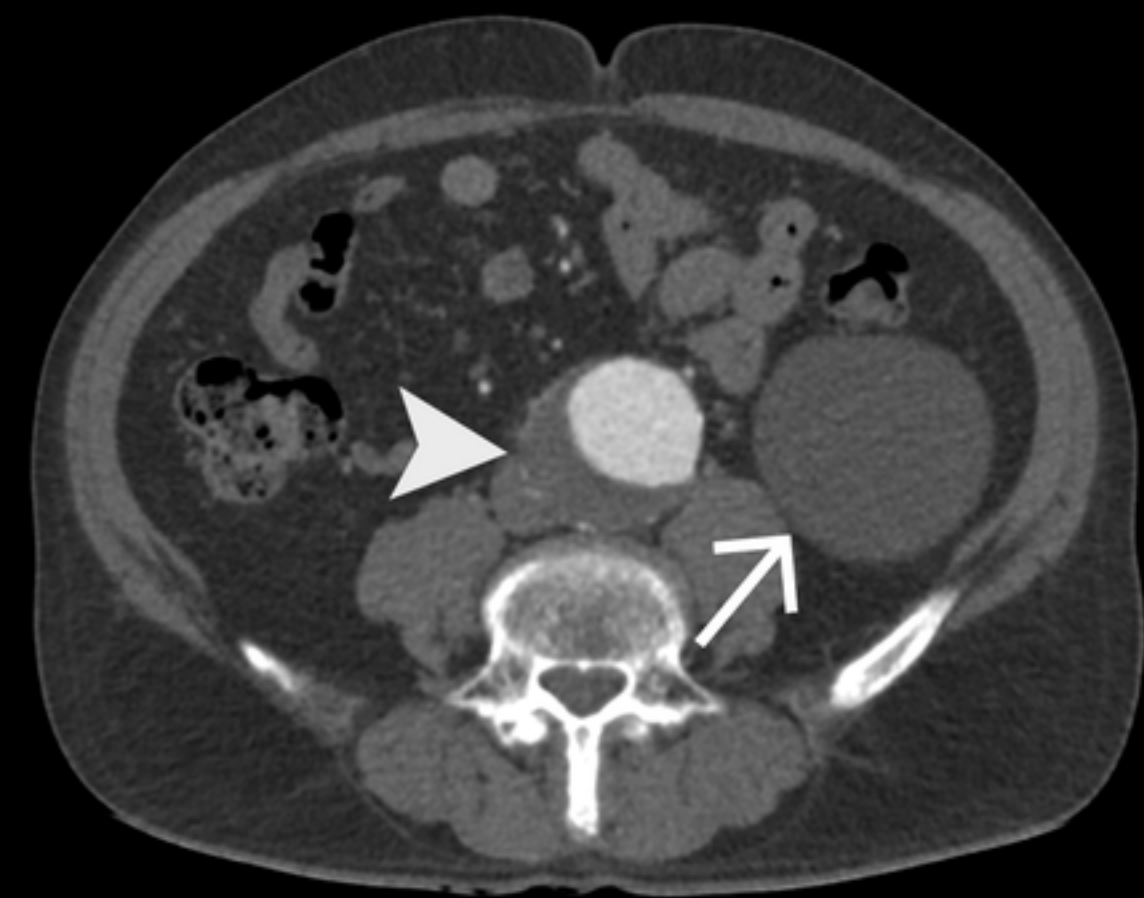
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A**B**

Figure