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FULL PAPER

Perirenal fat stranding on CT: is there an association with bladder outlet obstruction?

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Objective: To determine the association between perirenal fat stranding (PFS) on CT and bladder outlet obstruction (BOO).

Methods: CT scans from 122 patients who had undergone urodynamic study for lower urinary tract symptoms (LUTS) were registered after exclusion of patients with renal or retroperitoneal disease. Images were independently reviewed by two radiologists and compared with those of 244 age- and sex-matched control patients without LUTS. The PFS severity was scored on a four-point scale, and the interobserver agreement was assessed with kappa statistics. The severity score and incidence was compared between the groups, and the association with baseline characteristics was analyzed. For the LUTS group, an association between PFS severity and urodynamic and laboratory data was evaluated.

Results: PFS was more frequent and more severe in the LUTS group than in the control group (p -value < 0.001); its presence was significantly associated with male gender and older age (p -value < 0.001). PFS was predominantly bilateral in both groups (80.1–93.2%). In the LUTS group, PFS severity scores were significantly correlated with the maximum flow rate, maximum detrusor pressure and estimated glomerular filtration rate (p -value < 0.001). Interobserver agreements were excellent for PFS presence ($\kappa = 0.883$) and severity ($\kappa = 0.816$).

Conclusion: Severe PFS was observed in older, male patients with LUTS. PFS severity was associated with the degree of BOO and impaired renal function.

Advances in knowledge: Recognition of PFS on the CT scan may warrant further evaluation of BOO and appropriate management to prevent renal impairment.

INTRODUCTION

Bladder outlet obstruction (BOO) is a common cause of lower urinary tract symptoms (LUTS) in males, and benign prostatic hyperplasia (BPH) is mainly attributable to BOO in male patients. Multiple mechanisms leading to increased pressure in the urinary bladder and the renal collecting system have been proposed to explain the association between chronic BOO and renal function impairment.¹ Renal function impairment secondary to BOO is preventable if cases are recognized early, but it is often difficult to identify patients at risk of renal failure. Urodynamic study is the gold standard for the diagnosis of BOO.² However, because of its invasiveness, its use for screening purposes is inappropriate.

Curvilinear areas of soft-tissue attenuation in the perirenal space have been previously described as a secondary sign of acute ureteral obstruction or image findings of various renal or extrarenal diseases by many authors.^{3–6} However, perirenal fat stranding (PFS) is commonly shown on CT in patients without acute ureteral obstruction or any other

urological condition. Some authors regarded the finding as being caused by previous inflammation or of no particular clinical significance and commented that bilateral PFS was seen in many older patients.^{4,7} Nevertheless, there has been no clear explanation as to why PFS is a common incidental finding, especially among older patients. We hypothesized that PFS could be caused by recurrently extravasated urine owing to BOO, which could increase pressure in the urinary bladder and the renal collecting system.

CT has become the primary imaging modality for the evaluation of the abdominal and pelvic area because of its widespread availability and fast scanning time. Because renal function impairment due to BOO may not be necessarily accompanied by upper tract dilatation,¹ it is difficult to predict the severity of BOO on CT. Bladder wall thickening with trabeculations may develop secondary to BOO; however, CT has limited value in assessing bladder wall thickening. The possible significance of our hypothesis on the association between PFS and BOO is that CT might suggest a warning sign indicating the degree of BOO that

may need further evaluation, which could help minimize the chances of renal function impairment induced by BOO. The purpose of this study was to determine the association between PFS on CT and BOO.

METHODS AND MATERIALS

Patient selection

This retrospective study received institutional review board approval, and the requirement for informed consent was waived. A computerized database search was performed at Korea University Anam Hospital from October 2006 through to February 2014, and a total of 205 patients (101 males and 104 females; average age, 62.7 years; age range, 20–86 years), who underwent urodynamic study for LUTS and were examined with abdominal CT between 6 months before and after the urodynamic study, were consecutively registered. Exclusion criteria were as follows: (a) patients who had a history of any kidney or urinary tract surgery or procedure; (b) patients with hydronephrosis; (c) patients who had a history of any cause of non-obstructive renal disease including renal infarction, pyelonephritis and glomerulonephritis; (d) patients with a renal mass other than a simple renal cyst; (e) patients who had undergone retroperitoneal surgery; (f) patients with disease of the retroperitoneal space; (g) patients with a large amount of ascites with or without retroperitoneal fluid; (h) patients with congenital disease with renal parenchymal malformations; and (i) patients with any clinical evidence of anatomic cause of BOO other than BPH. Of the 205 patients, 123 patients (mean age, 63.5 years; range, 20–86 years) including 63 males (mean age, 65.9 years; range, 20–86 years) and 60 females (mean age, 60.9 years; range, 26–81 years) were finally included in our study (Figure 1). To perform a case-control study, a database was searched at Korea University Anam Hospital for patients who underwent enhanced CT at our healthcare centre for screening purposes and who had no known LUTS. Among them, 246 patients (mean age, 63.5; range, 20–86 years) including 126 males (mean age, 65.9 years; range, 20–86 years) and 120 females (mean age, 60.9 years; range, 26–81 years) were matched with patients in the study group for age and sex.

Urodynamic study and clinical measures

The results of the urodynamic studies during the voiding phase were assessed by retrospective chart review. Before the urodynamic study with pressure flow analysis, uroflowmetry was performed and the maximal flow rate ($Q_{\max}$) and post-void residual (PVR) data were obtained. Pressure flow analysis was performed using two catheters; one was placed into the bladder and the other into either the vagina or the rectum. Concurrent multichannel measurement of bladder and abdominal pressures during the filling and storage phase and the voiding phase of micturition provided calculated detrusor pressure as the difference between the bladder and abdominal pressures. Detrusor pressure at maximum flow rate ($\text{Prdet}Q_{\max}$) and maximal detrusor pressure (maxPrdet) data were also obtained. Decreased $Q_{\max}$, increased $\text{Prdet}Q_{\max}$ and maxPrdet are known to be associated with BOO.^{2,8} BOO index (BOOI) was calculated according to the definition by Lim et al,⁹ which was calculated as $\text{Prdet}Q_{\max} - 2 \times Q_{\max}$. Elevated BOOI indicates BOO in male patients.² Serum creatinine level which was measured between the date on which CT scan was performed and the date on which urodynamic study was performed were obtained and the estimated glomerular filtration rate (GFR) was calculated based on the Chronic Kidney Disease Epidemiology Collaboration equation.¹⁰ Prostate volume was obtained from the chart review, where it is automatically calculated using the height, length and width of the prostate gland measured on transrectal sonography.

CT technique

Because of the nature of the retrospective study, the parameters of the CT scan were inconstant. All CT examinations were performed on 1 of 4 scanners: a 4-channel CT scanner (Volume Zoom; Siemens®, Erlangen, Germany) (detector collimation, 4×1 mm; reconstruction, 5-mm slice thickness; 120 kVp; and 130 mAs), a 64-channel CT scanner (Brilliance 64; Philips Medical Systems, Cleveland, OH) (detector collimation, 64×0.625 mm; reconstruction, 3- or 5-mm slice thickness; 120 kV; and 120–280 mAs) and two 128-channel CT scanners [SOMATOM Definition AS+; Siemens®, Erlangen, Germany] (detector collimation, 64×0.6 mm using z-flying focal spot

Figure 1. Flowchart of patient selection, inclusion and exclusion.

technology; reconstruction, 3- or 5-mm slice thickness; 100 kV; and 100–350 mAs) and Somatom Definition Flash; Siemens®, Erlangen, Germany (detector collimation, 128×0.6 mm; reconstruction, 3- or 5-mm slice thickness; and 100-kVp tube voltage using online dose modulation) (CARE Dose4D; Siemens Healthcare, Erlangen, Germany)]. CT images were obtained before contrast enhancement and/or after the administration of a non-ionic iodinated contrast material by using a power injector at a rate of $2.5\text{--}3.0\text{ ml s}^{-1}$. Contrast-enhanced CT images were obtained during breath-holding over 25–40 s (arterial phase), 50–70 s (portal phase) and/or approximately 300 s (excretory phase) after the initial administration of the contrast materials.

Image analysis

CT images were independently reviewed by two radiologists (NYH and DJS, with 8 and 16 years' experience, respectively, in

abdominal CT interpretation). Two readers were blinded to the patient clinical data; however, they knew that the CT images had been obtained for either patients with LUTS or normal control patients. CT images were evaluated by using a picture archiving and communicating system (INFINITT PACS v. 3.0) (Infinit HealthCare Co., Seoul, Republic of Korea) with standard abdominal soft-tissue window settings (level, 50 HU; width, 400 HU). Axial and coronal reconstruction CT images were used for analysis when both were available. PFS was defined as linear or curvilinear soft-tissue attenuation without vascular connection distributed in the perirenal space, and Gerota's fascia was used as a generic term to describe both the anterior and posterior pararenal fascia. On CT images, the following four-point scale was defined to score the severity of PFS: 0 = no PFS, 1 = focal PFS, 2 = diffuse PFS and 3 = diffuse PFS with Gerota's fascia thickening (Figure 2). A score of 0 was considered as the absence of PFS, whereas scores ≥ 1 were regarded as the presence

Figure 2. Various degrees of perirenal fat stranding (PFS) on axial (a, c, e and g) and coronal (b, d, f and h) contrast-enhanced CT scans. (a, b) A fat tissue in the perirenal space showing homogeneous hypoattenuation (severity score of PFS = 0). The elongated hypoattenuating lesion in the sinus of the right kidney is a parapelvic cyst (asterisk). (c, d) Multifocal linear or curvilinear soft-tissue attenuations (arrows) are noted in the perirenal space (severity score of PFS = 1). (e, f) Diffuse linear or curvilinear soft-tissue attenuations (arrows) are noted in the perirenal space (severity score of PFS = 2). (g, h) Diffuse linear or curvilinear soft-tissue attenuations with Gerota's fascia thickening (arrows) are noted in the perirenal space (severity score of PFS = 3). The round hypoattenuating lesion in the left kidney is a cyst (asterisk).

of PFS. The severity scale was applied to the two kidneys, and the higher score was used as the overall score of PFS in each patient.

Statistical analysis

Interobserver agreement between the two radiologists for the severity score of PFS and for the presence of PFS was analyzed using kappa statistics. Kappa value interpretations were graded as poor ($\kappa < 0.2$), fair ($0.2 < \kappa \leq 0.4$), moderate ($0.4 < \kappa \leq 0.6$), substantial ($0.6 < \kappa \leq 0.8$) and excellent ($0.8 < \kappa \leq 1.0$). The incidence and the severity score of PFS were compared between the LUTS and the control group using the χ^2 test and Mann–Whitney U test. The association of baseline characteristics including age and sex with the severity score was assessed using the χ^2 test, Spearman's rank correlation test and Mann–Whitney U test. For patients in the LUTS group, the association between the severity of PFS and the urodynamic study, prostate volume and laboratory data was evaluated using Spearman's rank correlation test; this was first analyzed separately for male and female patients and then as a group. A p -value of <0.05 was considered statistically significant.

RESULTS

Perirenal fat stranding scores

Because of the severe streaking artefact caused by barium in the colon, one patient in the LUTS group and two corresponding patients in the control group were excluded from image analysis. Finally, 122 patients (mean age, 63.7 years; range, 20–86 years), including 62 males (mean age, 66.4 years; range, 20–86 years) and 60 females (mean age 60.9 years; range, 26–81 years), and 244 age- and sex-matched control patients without LUTS were included in the analysis. Contrast-enhanced CT images were available in 115 of 122 patients in the LUTS group; the remaining 7 patients had been subjected to non-contrast-enhanced CT only. The severity score of PFS was significantly higher in the LUTS group (mean $\pm$ standard deviation: 0.91 ± 0.918 and 0.90 ± 0.922 for Readers 1 and 2, respectively) than in the control group (0.31 ± 0.588 and 0.37 ± 0.644 for Readers 1 and 2, respectively) (p -value < 0.001 for Readers 1 and 2). The incidence of PFS was also significantly higher in the LUTS group [73/122 (59.8%) patients and 72/122 (59.0%) patients for Readers 1 and 2, respectively] than in the control group [59/244 (24.2%) patients and 68/244 (27.9%) patients for Readers 1 and 2, respectively] (p -value < 0.001 for Readers 1 and 2) (Table 1). PFS was predominantly bilateral in both the LUTS [65/73 (89.0%) patients and 58/72 (80.1%) patients for Reader 1 and 2, respectively] and the control group [55/59 (93.2%) patients and

60/68 (88.2%) patients for Readers 1 and 2, respectively]. Both in the LUTS and the control group, older age and male gender were significantly associated with a more severe PFS score (p -value < 0.001 for all comparisons) (Table 2). The κ value for interobserver agreement between the two radiologists was 0.816 (95% confidence interval: 0.76–0.87) for scoring of the severity of PFS and 0.883 (95% confidence interval: 0.83–0.93) for the presence of PFS.

Correlation of urodynamic and clinical data with perirenal fat stranding severity scores

The results of the analysis of the relationship between the severity score of PFS and urodynamic and clinical data are shown in Table 3. The PFS severity score showed a significant negative correlation with $Q_{\max}$ for all patients ($r = -0.368$ and -0.405 for Readers 1 and 2, respectively; p -value < 0.001) and for male patients ($r = -0.269$, p -value = 0.04 for Reader 2). The PFS severity score was also significantly correlated with $\text{Prdet}Q_{\max}$ and maxPrdet for all patients (range of r : 0.438–0.507; p -value < 0.001 for all statistical analyses) and for male patients (range of r : 0.257–0.329; p -value < 0.05 for all statistical analyses). For female patients, however, the results of the correlation analysis with urodynamic values demonstrated almost no correlation with the severity scores of PFS; only $\text{Prdet}Q_{\max}$ was significantly correlated with the PFS severity score in Reader 1 ($r = 0.345$, p -value = 0.008). BOOI was calculated only for male patients and showed significant positive correlation with the PFS severity score ($r = 0.268$ and 0.358 for Readers 1 and 2, respectively; p -value < 0.05). The results of the analysis showed a significant negative correlation between the severity score of PFS and estimated GFR for male patients ($r = -0.271$ and -0.288 for Readers 1 and 2, respectively; p -value < 0.04), for female patients ($r = -0.264$ and -0.275 for Readers 1 and 2, respectively; p -value < 0.05) and for all patients ($r = -0.346$ and -0.356 for Readers 1 and 2, respectively; p -value < 0.001). PVR and volume of the prostate gland showed no correlation with the severity score of PFS.

DISCUSSION

We proposed the hypothesis that PFS on CT could be associated with BOO. Our results supported this by demonstrating a correlation between the severity of PFS and the urodynamic parameters suggestive of BOO, especially in male patients. The kidneys are suspended in the perirenal space by the reticular bridging septa, which connect the renal capsule to the Gerota's fascia.¹¹ When a pathologic process spreads into the perirenal space along the bridging septa, PFS is seen on CT or on MR

Table 1. Incidence and severity of perirenal fat stranding (PFS) in the lower urinary tract symptoms (LUTS) and the control groups

Patients	Number (%) of patients with PFS		PFS severity score (mean $\pm$ SD)	
	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2
LUTS ($n = 122$)	73 (59.8)	72 (59.0)	0.91 ± 0.918	0.90 ± 0.922
Control ($n = 244$)	59 (24.2)	68 (27.9)	0.31 ± 0.588	0.37 ± 0.644
p -value	<0.001	<0.001	<0.001	<0.001

SD, standard deviation.

Table 2. Association of the perirenal fat stranding (PFS) severity score with age and sex

Patients	PFS severity score	Number of patients ^a		Age (years) ^b		Sex (male : female)	
		Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2
LUTS (n = 122)	0	49 (40.2)	50 (41.0)	55.2 (20–80)	55.2 (20–80)	7 : 42	7 : 43
	1	43 (35.2)	42 (34.4)	68.3 (40–81)	68.6 (40–81)	27 : 16	26 : 16
	2	22 (18.0)	22 (18.0)	70.7 (60–86)	71.0 (60–86)	20 : 2	21 : 1
	3	8 (6.6)	8 (6.6)	71.8 (61–80)	70.6 (61–80)	8 : 0	8 : 0
	p-value	–	–	<0.001	<0.001	<0.001	<0.001
Control (n = 244)	0	185 (75.8)	176 (72.1)	60.9 (20–86)	60.7 (20–81)	69 : 116	59 : 117
	1	43 (17.6)	46 (18.9)	72.1 (52–86)	70.8 (52–86)	39 : 4	44 : 2
	2	16 (6.6)	22 (9.0)	72.9 (65–80)	72.7 (61–80)	16 : 0	21 : 1
	3	0	0	–	–	–	–
	p-value	–	–	<0.001	<0.001	<0.001	<0.001

LUTS, lower urinary tract symptoms.

^aData are number of patients, with percentages in parentheses.

^bData are means, with range in parentheses.

images. PFS is associated with a wide spectrum of conditions including acute ureteral obstruction, pyelonephritis, post-operative change, acute pancreatitis and metastasis.^{5,6,12} There are two possible explanations for PFS in cases of acute ureteral obstruction. When the ureter becomes obstructed, the increased intrapelvic pressure results in a microscopic rupture at the calyceal fornix, which is the area of least resistance, and pyelosisinus backflow of urine may occur.^{13,14} Extravasated urine from the renal hilum enters the perirenal space and infiltrates along the bridging septa.¹⁵ The second possible explanation is that thickening of the bridging septa may result from lymphatic dilation and extravasation.^{15,16} If the dilated renal pelvis compresses the hilar lymphatics, the lymph flow will divert to the perinephric lymphatics, which run along the fibrous septa of the perinephric space. The former explanation may account for PFS in patients with chronic BOO without hydronephrosis. Unlike acute ureteral obstruction, which causes absorption of the extravasated urine after the acute phase, recurrently extravasated urine owing to chronic BOO may cause low-grade inflammation and bridging septa fibrosis, which is shown as PFS on CT.

LUTS has been used as a general term to refer to the storage disturbances (with or without voiding disturbances) that are highly prevalent, especially among elderly males and females.^{17,18} We showed that PFS is more frequent and more severe in patients with LUTS than in control. We also showed that older age and male gender were associated with a higher severity score of PFS. Epidemiology and gender-specific aetiologies of LUTS may offer a possible explanation. LUTS in males is primarily attributed to BPH and it is closely correlated with ageing because the incidence of BPH increases with age. In females, however, in addition to the influence of ageing, menopause and childbirth add complexity to the aetiology of LUTS, with BOO accounting for a small portion of the symptoms.¹⁹ In addition, PFS was shown predominantly bilaterally in patients with LUTS and control groups in our study. This is a natural

result because BOO causes bilateral renal injury. However, 7–21% of patients showed unilateral involvement. Gershman et al¹⁴ mentioned that fornical rupture can occur unilaterally because unequal compliance of the urinary tracts may result in disproportional transmission of back pressure to the renal pelvis.

Under normal physiological conditions, urine is transported to the low-pressure urinary bladder through the ureterovesical junction. In the early phase, BOO is compensated by the hypertrophy of the bladder wall smooth muscle, causing bladder wall thickening with trabeculations and increased intravesical pressure.²⁰ This can lead to functional or anatomical ureterovesical junction obstruction or vesicoureteral reflux, eventually impairing renal function.¹ There have been studies demonstrating the association between BOO and renal failure.^{1,21} Chronic BOO may require surgical treatment if BOO is at risk of inducing renal injury. Although upper tract dilatation in BOO is an indicator of the need for surgical intervention, its sensitivity is known to be low.^{1,22} Several parameters including the prostate or transitional zone volume, PVR volume and urinary flow rate can be obtained using non-invasive diagnostic testing. However, they have limited value for the aetiological evaluation or definite diagnosis of BOO; instead, they only raise suspicion of BOO.^{2,23} Urodynamic study with pressure flow analysis remains the gold standard for diagnosing BOO, making it essential before surgical intervention of BOO, despite its invasiveness. CT is widely used in the field of abdominal and pelvic imaging and even for periodic medical check-up. Our study demonstrated that the severity score of PFS on CT was correlated with decreased estimated GFR and urodynamic parameters, but not with PVR or prostate volume. Based on the results of our study, PFS on CT without any other cause may appropriately reflect the severity of BOO, especially in male patients.

There were some limitations to this study. First, this study was retrospective, with potential for selection bias. Second, PFS was not histopathologically confirmed. Third, only non-contrast-

Table 3. Spearman's correlation test of urodynamic and clinical data with perirenal fat stranding (PFS) severity score in the lower urinary tract symptoms (LUTS) group

Urodynamic and clinical data		All patients (<i>n</i> = 122)		Male patients (<i>n</i> = 62)		Female patients (<i>n</i> = 60)	
		Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2
Q _{max}	Number of patients	116		59		57	
	Mean ± SD (range)	14.6 ± 9.3 (3.1–55.0)		11.5 ± 6.9 (3.1–40.0)		17.8 ± 10.4 (4.0–55.0)	
	<i>r</i>	−0.368 ^a	−0.405 ^a	−0.193	−0.269 ^a	−0.188	−0.253
	<i>p</i> -value	<0.001 ^a	<0.001 ^a	0.143	0.040 ^a	0.160	0.057
PVR	Number of patients	102		58		44	
	Mean ± SD (range)	71.6 ± 174.9 (1.0–1600.0)		60.4 ± 75.6 (1.0–400.0)		86.3 ± 252.7 (1.0–1600.0)	
	<i>r</i>	0.134	0.156	−0.145	−0.142	0.222	0.292
	<i>p</i> -value	0.180	0.118	0.279	0.286	0.147	0.054
PrdetQ _{max}	Number of patients	120		62		58	
	Mean ± SD (range)	37.9 ± 25.9 (−9.0–123.0)		50.1 ± 28.6 (11.0–123.0)		24.8 ± 13.9 (−9.0–66.0)	
	<i>r</i>	0.507 ^a	0.465 ^a	0.257 ^a	0.321 ^a	0.345 ^a	0.169
	<i>p</i> -value	<0.001 ^a	<0.001 ^a	0.043 ^a	0.011 ^a	0.008 ^a	0.205
maxPrdet	Number of patients	100		62		38	
	Mean ± SD (range)	56.7 ± 3.9 (12.0–155.0)		68.2 ± 33.4 (23.0–155.0)		38.0 ± 25.5 (12.0–154.0)	
	<i>r</i>	0.480 ^a	0.438 ^a	0.300 ^a	0.329 ^a	0.115	−0.118
	<i>p</i> -value	<0.001 ^a	<0.001 ^a	0.018 ^a	0.009 ^a	0.490	0.482
BOOI	Number of patients	–		59		–	
	Mean ± SD (range)	–		45.5 ± 38.5 (−46.0–148.8)		–	
	<i>r</i>	–	–	0.268 ^a	0.358 ^a	–	–
	<i>p</i> -value	–	–	0.040 ^a	0.005 ^a	–	–
Estimated GFR	Number of patients	120		62		58	
	Mean ± SD (range)	81.4 ± 19.8 (35.0–171.0)		79.4 ± 21.5 (35.0–171.0)		83.4 ± 17.8 (37.4–117.5)	
	<i>r</i>	−0.346 ^a	−0.356 ^a	−0.271 ^a	−0.288 ^a	−0.264 ^a	−0.275 ^a
	<i>p</i> -value	<0.001 ^a	<0.001 ^a	0.033 ^a	0.023 ^a	0.045 ^a	0.036 ^a
Prostate volume	Number of patients	–		46		–	
	Mean ± SD (range)	–		50.9 ± 27.9 (7.0–124.0)		–	
	<i>r</i>	–	–	−0.041	0.042	–	–
	<i>p</i> -value	–	–	0.786	0.784	–	–

BOOI, bladder outlet obstruction; GFR, glomerular filtration rate; maxPrdet, maximal detrusor pressure; PrdetQ_{max}, detrusor pressure at maximum flow rate; PVR, post-void residual; Q_{max}, maximal flow rate; *r*, Spearman's correlation coefficient; SD, standard deviation.

^aStatistically significant.

enhanced CT images were available in some patients of the LUTS group. However, many previous studies have mentioned that non-contrast-enhanced CT was good for the evaluation of PFS.^{4,6,16} Fourth, a further limitation of this study was that the evaluation of PFS was difficult in people who were thin because the perirenal fat tissue is scarce in these patients. Lastly, different parameters and CT scanner models may affect the severity of PFS.

In conclusion, the present study revealed that PFS with no explainable reason on CT was associated with older age and male

gender, and its severity was associated with the degree of BOO and renal function impairment, especially in male patients. Recognition of this finding may warrant further evaluation of the aetiology of BOO and appropriate management to prevent renal impairment.

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