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Correlation of clinical and radiological parameters of acute pyelonephritis

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Abstract
Aim and Objective: To assess the correlations between clinical and biochemical parameters with radiological severity of acute pyelonephritis.
Methodology: It was a descriptive analytical study. All patients admitted to Narayana Medical College and Hospital, Nellore, from March 2019 to December 2020 with a CT proven diagnosis of acute pyelonephritis. All the patients diagnosed to have APN based on clinical and/or radiological findings were included in this study. Diagnosis of APN was based on both clinical and radiological criteria. Clinical criteria include the presence of "classical" symptoms of APN.
Results: A sample size of 100 patients was considered for the study. But, in view of COVID pandemic, sample collection as limited to 62mong 62 patients with pyelonephritis, 30(48.4%) were males, and 32(51.6%) were females. Males were older when compared to females. The mean age of 62 patients with acute pyelonephritis was 55.47 ± 12.82 years. The total number of patients with diabetes mellitus were 19(30.65%). Patients with hypertension were 18(29.03%). 4(26.67%) patients in group 1, 9(28.13%) patients in group 2, and 5(33.33%) patients in group 3 were found to have hypertension. Classical triad of pyelonephritis was seen in 51 (82.3%) patients and was absent in 11 (17.7%) of patients. There was an association between inotrope use and severe CT grading by using the likelihood ratio test, which was statistically significant with a p-value of 0.015. Ultrasound was found to detect pyelonephritis in 18(29.03%) patients. In 44(70.97%) patients, ultrasound was found to be normal despite the presence of clinical features. HbA1C levels were similar among the three groups with a mean value of 6.48 ± 0.65, 6.53 ± 0.62, and 6.59 ± 0.77 in group 1, group 2, and group 3 patients, respectively.
Conclusion: This study showed a good correlation between clinical and radiological severity in adult patients with APN. Duration of hospital stay, presence of hypotension, and leukocytosis were associated with severe pyelonephritis.

Keywords: APN, diabetes, hypertension, CT scan, leulocytosis, radiological severity

Introduction
Most patients with acute pyelonephritis (APN) have mild symptoms and can be managed in an outpatient setting. However, around 10- 30% of patients with APN require hospitalization and may even present with life-threatening complications, including shock, septicemia, and multi-organ dysfunction syndrome [1, 2].
The British Medical Research Council Bacteriuria Committee defined APN as "a clinical syndrome of flank pain, costovertebral angle tenderness, and fever accompanied by laboratory evidence of renal infection including leukocytosis, pyuria, haematuria, bacteriuria, positive urine culture and sometimes bacteremia [3]." Radiologically, APN manifests on contrasted computed tomography (CT) scans as hypo-enhancing regions with or without renal swelling and may be focal or diffuse [4]. To standardize terminologies, Talner *et al.* suggested that all radiological parenchymal abnormalities without abscess attributable to acute infection be called APN [5].
Few data are available to correlate the clinical severity of APN with radiological severity. Much less data exist to recommend when CT imaging should be performed in patients presenting with symptoms suggestive of APN.
This study aims to assess the correlations between clinical and biochemical parameters with radiological severity of APN and define clinical predictors to identify patients with severe APN.

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Aim

To assess the correlations between clinical and biochemical parameters with radiological severity of acute pyelonephritis.

Objectives of the study

- To study the association between clinical parameters and severe CT grading
- To study the association between laboratory parameters and severe CT grading

Materials and Methods

Study design

Descriptive analytical study.

Study setting and duration

All patients admitted to Narayana Medical College and Hospital, Nellore, from March 2019 to December 2020 with a CT proven diagnosis of acute pyelonephritis.

Sample size: 100 patients

Methodology

After taking informed consent, a detailed history was taken. Demographic characteristics, physical examination findings, biochemical parameters including hemoglobin, total counts, platelet counts, serum urea, serum creatinine, serum albumin, blood culture sensitivity, urine culture sensitivity were noted. Radiological findings, including ultrasonography and CT, were entered in the proforma.

Inclusion criteria

All the patients diagnosed to have APN based on clinical and/or radiological findings were included in this study.

Diagnosis of APN was based on both clinical and radiological criteria. Clinical criteria include the presence of "classical" symptoms of APN [4].

1. Fever, defined as a temperature of greater than 37.5 °C
2. Pyuria, defined as greater than ten white blood cells per high-power field of centrifuged urine
3. Presence of loin or flank pain with or without lower urinary tract symptoms. The presence of positive urine or blood cultures is not mandatory for diagnosis. Hypotension is defined as a systolic blood pressure <90mm Hg or diastolic blood pressure <40mm Hg
4. Acute kidney injury is defined as any of the following (Not Graded):
a) Increase in serum creatinine by 0.3 mg/dl within 48 hours; or
b) Increase in serum creatinine to 1.5 times baseline, which is known or presumed to have occurred within the prior seven days; or
c) Urine volume <0.5 ml/kg/h for 6 hours [6].

Exclusion criteria

1. Those without CT imaging documenting radiological evidence of acute pyelonephritis
2. Pregnant women
3. Those with prior urological intervention

Statistical analysis

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) Version 16 software.

Descriptive studies were performed for the cohort.

Univariate analyses were performed to compare clinical and biochemical variables with radiological severity of APN, using cross-tabulation and chi-square tests for categorical variables and T-tests for continuous variables.

Multivariate analysis considering radiological severity of disease as the dependent variable was performed with statistical significant factors and covariates from univariate analysis.

All tests of significance were considered statistically significant when $P<0.05$.

Results

A sample size of 100 patients was considered for the study. But, in view of COVID pandemic, sample collection as limited to 62.
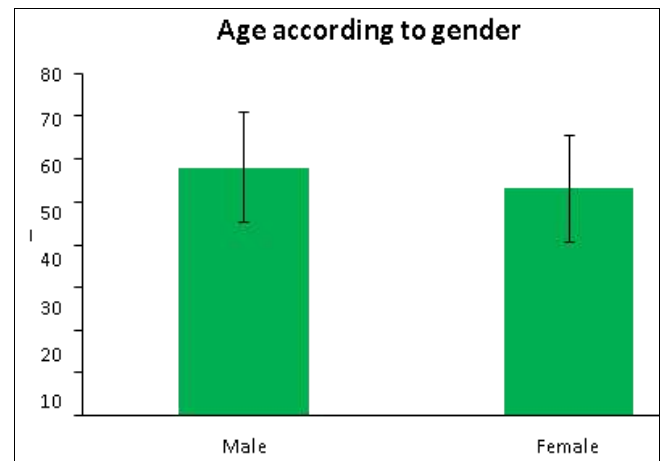

Fig 1: Mean age of patients according to gender

Table 1: Association between gender and severity of pyelonephritis by using the Likelihood Ratio test

Gender	CT grading						Likelihood ratio	p- value
	Group 1		Group 2		Group 3			
	n	%	N	%	n	%		
Male	6	40	15	46.88	9	60	1.262	0.532
Female	9	60	17	53.13	6	40		

Among 62 patients with pyelonephritis, 30(48.4%) were males, and 32(51.6%) were females. Males were older when compared to females. Females were found to have a more severe disease when compared to males. This difference was not statistically significant with a p-value of 0.532.

Table 2: Comparison of age and severity of pyelonephritis by using One-way ANOVA

(n = 50)	CT grading						"F"	p value
	Group 1		Group 2		Group 3			
	Mean	SD.	Mean	SD.	Mean	SD.		
Age	49.07	14.62	52.66	9.52	67.87	8.65	13.667	< 0.001*

The mean age of 62 patients with acute pyelonephritis was 55.47 ± 12.82 years. A majority of them were above 50 years. Patients who were categorized into group 2 and group 3 were older. This was statistically significant with a p-value < 0.00.

Table 3: Comparison of diabetes mellitus and hypertension according to CT grading

(n = 62)		CT grading						Likelihood Ratio test	p- value
		Group 1		Group 2		Group 3			
		n	%	n	%	n	%		
Diabetes Mellitus	Present	8	80	20	63	8	100	6.947	0.031*
	Absent	2	20	12	38	0	0		
Hypertension	Present	4	26.67	9	28.13	5	33.33	0.185	0.911
	Absent	11	73.33	23	71.88	10	66.67		

The total number of patients with diabetes mellitus were 19(30.65%). Patients with diabetes mellitus were found to be more likely to develop severe pyelonephritis when compared to those without type 2 diabetes mellitus. 6(18.75%) patients in group 2 and 9(60%) patients in group 3 had type 2 diabetes mellitus. 4 (26.67%) patients in group 1 had type 2 diabetes mellitus. Since the likelihood ratio P-value is less than 0.05, there was a statistically significant difference in patients with diabetes mellitus among different CT grading.

Patients with hypertension were 18(29.03%). 4(26.67%) patients in group 1, 9(28.13%) patients in group 2, and 5(33.33%) patients in group 3 were found to have hypertension. There was no statistically significant difference among the three CT severity groups with respect to hypertension as the likelihood ratio P-value is greater than 0.05.

Table 4: Association between clinical features of pyelonephritis and CT grading

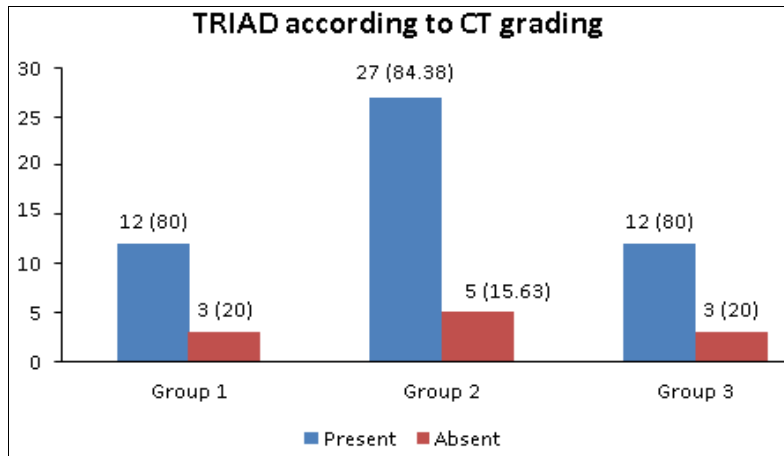| (n = 62)		CT grading						Likelihood Ratio test	p-value
		Group 1		Group 2		Group 3			
		n	%	n	%	n	%		
The classical triad of APN	Present	12	80.00	27	84.38	12	80.00	0.203	0.903
	Absent	3	20.00	5	15.63	3	20.00		
Hypotension	Present	0	0.00	2	6.25	6	40.00	12.53	0.002*
	Absent	15	100	30	93.75	9	60.00		
Inotropic support	Present	0	0.00	1	3.13	4	26.67	8.465	0.015*
	Absent	15	100	31	96.88	11	73.33		

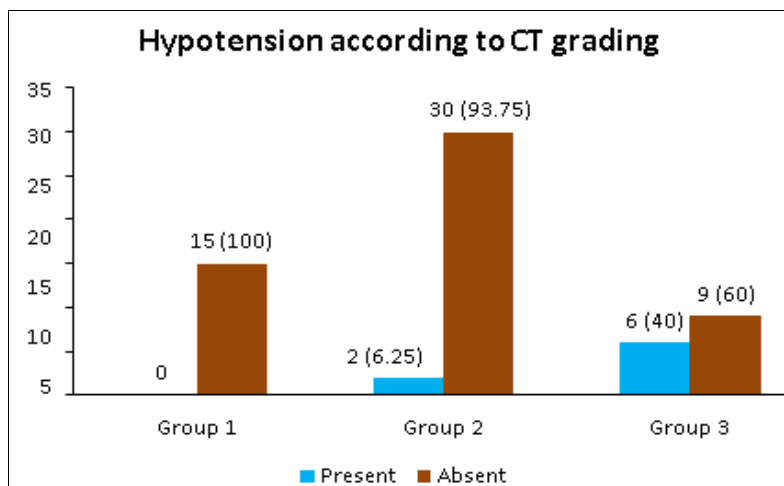**Fig 2:** Association between classical triad of pyelonephritis and CT grading

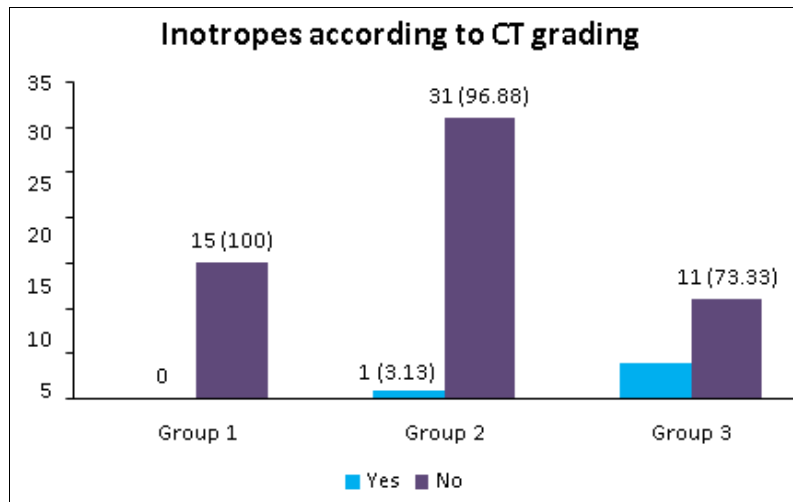**Fig 3:** Association between hypotension and CT grading

Fig 4: Association between inotropic support and CT grading

Classical triad of pyelonephritis was seen in 51 (82.3%) patients and was absent in 11 (17.7%) of patients. Patients with the clinical triad of pyelonephritis were found to have more severe pyelonephritis radiologically when compared to those without the classical triad. This was not found to be statistically significant with a likelihood ratio of 0.203 (p value=0.903).

Among the total population, 8(12.9%) patients had hypotension at admission, and 54(87.1%) patients had normal blood pressure at admission. Patients who had hypotension were more likely to develop severe pyelonephritis when compared to those without hypotension. None of the patients in group 1 had hypotension, while 2 (6.25%) of patients in group 2 and 6(40%) of patients in group 3 had hypotension. Since the likelihood ratio P-value is less than 0.05, there was a statistically significant difference in frequency of hypotension among different CT grading.

Among the total population, 5(8.06%) patients required inotropes. No patient in group 1 required inotropes, one patient in group 2, and 4 patients in group 3 required inotropic support. There was an association between inotrope use and severe CT grading by using the likelihood ratio test, which was statistically significant with a p-value of 0.015.

Table 5: Comparison of Duration of fever and hospital stay according to CT Grading

(n = 62)	Group 1		Group 2		Group 3		Kruska l Wallis "H" test	P value
	Median	IQR	Media n	IQR	Median	IQR		
Duration of fever [Days]	2.5	1.5 to 3.5	3.5	2.63 to 4.38	4.5	3.5 to 6.5	14.511	0.001*
Duration of hospital stay [Days]	5.5	4.5 to 8	9.25	8 to 10.38	14.5	8 to 17	26.582	< 0.001*

The median duration of fever was 2.5 (interquartile range 1.5-3.5) days for group 1 patients, 3.5 (interquartile range 2.63-4.38) days for group 2 patients, and 4.5 (interquartile range 3.5-6.5) days for patients in group 3. Duration of fever was higher for patients with higher CT grades. This was statistically significant on univariate analysis using the Kruskal Wallis "H" test with a p-value of 0.001.

The median duration of hospital stay was 5.5 (interquartile range 4.5-8) days for group 1 patients, 9.25 (interquartile range 8-10.38) days for group 2 patients, and 14.5 (interquartile range 8-17) days for patients in group 3. Duration of fever was higher for patients with higher CT grades. This was statistically significant on univariate analysis using the Kruskal Wallis "H" test with a p-value of <0.001.

Table 6: Comparison of HbA1c and albumin according to the CT Grading

(n = 62)	Group 1		Group 2		Group 3		"F"	P value
	Mean	SD.	Mean	SD.	Mean	SD.		
Albumin [gm/dl]	3.44	0.40	3.07	0.30	2.37	0.41	35.935	< 0.001*
HbA1C [%]	6.48	0.65	6.53	0.62	6.59	0.77	0.096	0.908

Hypoalbuminemia was more severe in patients with higher CT grades. Mean serum albumin levels were 3.44±0.4 (gm/dl) in group 1 patients, 3.07±0.3 (gm/dl) in group 2 and 2.37±0.41 (gm/dl) in group 3 as shown in figure 22. This difference was found to be statistically significant on univariate analysis by one-way ANOVA test with a p- value of <0.001.

HbA1C levels were similar among the three groups with a mean value of 6.48±0.65, 6.53±0.62, and 6.59±0.77 in group 1, group 2, and group 3 patients, respectively. There was no statistical difference between HbA1C levels among the three groups by one-way ANOVA test with a p-value.

Among the total population, anemia was found in 25(40.32%) patients. 6(40%) patients in group 1, 13(40.63%) patients in group 2 and 6(40%) of patients in group 3 had anemia. On univariate analysis, there was no statistical association between anemia and CT grading by chi-square test with a p-value of 0.999.

Abnormal total leukocyte count was seen in 30 patients. Leukocytosis was found in 19(30.65%) patients, and leukocytopenia was found in 11(17.74%) patients. 4 (26.67%) patients in group 1, 8 (25%) patients in group 2, and 7 (46.67%) patients in group 3 had leukocytosis. 1(6.67%) patient in group 1, 2 (6.25%) patients in group 2 and 8 (53.33%) patients in group 3 had leukocytopenia. Abnormal leukocyte count was found to have a statistically significant association on univariate analysis by using a likelihood ratio test with a p-value of <0.001%.

Among the total population, thrombocytopenia was found in 23(37.1%) patients. 5(33.33%) patients in group 1, 12(37.5%) patients in group 2 and 6(40%) of patients in group 3 had thrombocytopenia. On univariate analysis, there was no statistical association between thrombocytopenia and CT grading by chi-square test with a p- value of 0.929.

Leukocyturia was found in 31(50%) patients. Leukocyturia was not significantly different among the three groups by using a chi-square test with a p-value of 0.879.

Renal dysfunction was observed in 15(24.19%) patients. There was no significant difference found among the three groups based on renal dysfunction on univariate analysis with a p-value of 0.644.

Increased CRP was seen in 27(43.55%) patients. There was no statistically significant difference in the CRP levels among the three groups by chi-square test with a p-value of 0.934.

Ultrasound was found to detect pyelonephritis in 18(29.03%) patients. In 44(70.97%) patients, ultrasound was found to be normal despite the presence of clinical features. There was no statistically significant difference found in the detection of APN by ultrasound in the three groups.

Positive urine culture was found in 29(46.77%) patients. There was no significant difference in positive urine culture among the three groups by chi-square test on univariate analysis.

Blood culture was positive in 7 (11.29%) patients. A higher number of patients in group 3 (26.67%) had positive blood culture when compared to those in group 1 (13.33%) and group 2 (3.13%). However, this difference was not statistically significant by the chi-square test with a p-value of 0.06.

Discussion

The present study is an observational study conducted in a tertiary care teaching hospital. In the present study, all the patients with acute pyelonephritis, who satisfied all the inclusion and exclusion criteria, admitted in the department of Nephrology, were followed up throughout the course in the hospital were analyzed to identify the correlation between clinical and radiological parameters (CT severity). In univariate analysis, older age, history of type 2 diabetes mellitus, investigatory parameters including increased total counts and decreased albumin, hypotension during the hospital stay, the requirement of inotrope support in management, prolonged duration of fever, and duration of hospitalization were significantly associated with increased CT severity of APN. In multivariate analysis, increased total counts, hypotension during the hospital stay, and prolonged duration of hospitalization were independent determinants of increased CT severity of APN.

In this study, the study population comprised of all age groups, starting from the age of 24 years to the age of 79 years, with the mean age being 55.47±12.81 years. On analysis of CT severity based on age, it was noted that the mean age for patients with mild CT grade was 49.07±14.62, moderate CT grade was 52.66±9.51, and that for severe CT grade was 67.87±8.65, which was higher in severe CT grade patients and there was a statistically significant correlation. Acute pyelonephritis (APN) is the most common cause of community-acquired bacteremia in hospitalized elderly patients [7, 8].

In our study, of the total 62 patients studied, females had a slight increase in incidence with 51.6% of the total study population that is 32 patients, and males comprised 48.4%, which was 30 patients. Though this is contrary to most other studies, studies conducted in the Indian population have shown an increased prevalence of APN in men. In a study conducted by Buonaiuto et al., [9] authors found an increased prevalence of pyelonephritis in males when compared to females. A study conducted by Efstathiou SP et al. [2] found a higher incidence of pyelonephritis in females when compared to males (55% in females versus 45% in males). However, this difference was not statistically significant (p-value = 0.79). Søgaard et al. [10] conducted a retrospective study among 15070 patients age greater than 50 years in Denmark, found a higher incidence of pyelonephritis in women than men (59% versus 41%). Venkatesh et al. [11] conducted a study in 100 patients with pyelonephritis and found that pyelonephritis was more common among females (62%). Gopal et al. [12] conducted a retrospective study in 100 patients older than 60 years in a tertiary care center in South India. They found a higher incidence of pyelonephritis in older men. In Chung VY et al. [13], male sex was found to be an independent predictor for mortality in patients with APN, which is inconsistent with our study.

In a comparison of comorbidities in our study, a predominant number of the study population that is 69.35% which was 43 patients were non-diabetics. In a comparison of CT severity of APN based on prior diabetic status, 60% of severe CT grade had diabetes mellitus, and there was a statistically significant correlation. The common predisposing factor for UTI is diabetes mellitus. In comparison to non- diabetics, epidemiological studies have shown that the relative risk of UTI in diabetics increases by a factor of 1.2-2.2 [14]. Geerling SE et al. stated an increased adherence of Escherichia coli to diabetic uroepithelial cells, and this was due to higher levels of glycosylated hemoglobin (HbA1c). Due to impaired production of cytokines, the Escherichia coli infection does not cause symptomatic urinary tract infection (UTI) in diabetic.

In our study, we found that diabetic patients were at increased risk of severe CT grade of APN, but a higher HbA1c level is not associated with increased severity of disease, which is in concordance with a study done by Lim SK and Ng FC and others [15].

In our study, on investigating for complete hemogram, increased total counts were seen in 30.65% of the total study population that is 19 patients, 17.74% of the total population that is 11 patients had decreased total counts, and the remaining 51.61% of the total population that is 32 patients had total counts in the normal limits. On multivariate analysis using ordinal logistic regression analysis, the elevated total count was independently associated with severe CT grade of APN. These findings in this study were consistent with the study done by Lim SK and Ng FC [16], where a total white count of greater than 20000 was found as an independent clinical predictor of severe APN.

In our study, on investigating liver function tests, it was noted that the mean albumin value for severe CT grade of APN was 2.37±0.41 gm/dl, 3.07±0.29 gm/dl for moderate CT grade, and that of mild CT grade was 3.44±0.40 gm/dl which was low in severe grade and had statistically significant correlation. A persons' nutritional status may be represented by serum albumin and is associated with morbidity and mortality in older patients [17].

In the current study, 12.90% (8 patients) of the total study population developed hypotension during the course in the hospital. On performing multivariate analysis using ordinal logistic regression technique, hypotension was independently associated with severe CT grade of APN. It has been hypothesized, in an attempt to contain the infection, the adhesion of bacteria to the renal cells disrupts the protective barrier, which leads to localized infection, hypoxia, ischemia, and clotting. Bacterial toxins, inflammatory cytokines, and other reactive processes further lead to complete pyelonephritis and, in many cases, systemic symptoms of sepsis and shock [18]. This finding was similar to the study done by Lim SK and Ng FC [16], where hypotension was found as an independent clinical predictor of severe APN.

In this study, among the eight patients who developed hypotension during the course in the hospital, five patients that are 8.06% of the total study population, required inotropic support. The other three patients with hypotension did not require inotropic support. On univariate analysis requirement of inotropic support showed a statistical correlation with CT severity grading. However, in multivariate analysis requirement of inotropic support was not statistically significant. These findings were in concordance with the study done by Lim SK and Ng FC[16], where the requirement of inotropes was significant in univariate analysis. Hsu CY *et al.* [19] showed that the need for inotropes was a useful clinical indicator of severe infection and sepsis.

In this study, among the study population, the duration of fever during admission was recorded, and the median duration of fever in patients with severe CT grading was 4.5 days, in those with moderate CT grade was 3.5 days and in those with mild CT grade was 2.5 days. It was found that a higher duration of fever was found to be associated with more severe CT grading. This was found to be statistically significant on univariate analysis using the Kruskal Wallis "H" test. This finding was similar to that found in the study done by Lim SK and NG FC [16], where longer duration of fever was found in patients in Groups 2 and 3 compared with Group 1, but the maximum temperature was not shown to be statistically different among the three groups.

In this study, among the study population, duration of hospitalization was noted, and the median duration of hospital stay was 14.5 days in patients with severe CT grading, 9.25 days in those with moderate CT grade, and those with mild CT grade was 5.5 days showing that the duration of hospitalization increased with increased CT severity which showed statistically significant correlation. On multivariate analysis using ordinal logistic regression technique, duration of hospital stay was independently associated with severe CT grade of APN. The study done by Paick *et al.* [20] showed an increase in mean hospital stay with an increase in grade of APN on CT. In the study done by Lim SK and Ng FC [16], a longer duration of hospitalization was associated with more severe disease. In the study by Chung VY *et al.* [13], bacteremia, suppurative pyelonephritis, and shock were significant in multivariate analysis for a long hospital stay.

In our study, 46.77% of the total study population that is 29 patients had positive urine cultures, and the remaining 53.23% of the total population that is 33 patients, were negative. The culture positivity was almost similar in all the three groups and was not statistically significant, which was in concordance with the study done by Lim SK and Ng FC [16], where urine culture was positive in only 40.8% of patients and culture positivity was not significantly different among the three groups.

Limitation of the study
1. The sample size in this study might be small for a better correlation of clinical, investigatory, and radiological profile.
2. As this study was conducted in a tertiary care hospital, patients presenting to this hospital may not accurately represent the general population.
3. CT severity scoring was based on previous studies, and there is a need for a validated CT scoring system.

Conclusion
This study showed a good correlation between clinical and radiological severity in adult patients with APN. Duration of hospital stay, presence of hypotension, and leukocytosis were associated with severe pyelonephritis.

Acknowledgment

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