Comparing Diabetic and Nondiabetic Emphysematous Pyelonephritis and Evaluating Predictors of Mortality

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ABSTRACT. Mortality among patients with emphysematous pyelonephritis (EPN) has reduced from 78% to 21%, yet it is one of the most serious urologic emergencies. This prospective observational study aims to study and compare clinical profile, management, and outcomes in diabetic and nondiabetic patients with EPN. All patients of EPN admitted to emergency medical services were included in the study. Patients were grouped into diabetic and nondiabetic EPN, and the eventual predictors of mortality were assessed. The mean age of patients was 55.43 years, with 36 (65.7%) female patients. Mortality was found to be 18.86%. On univariate analysis, the factors significantly associated with mortality include dyspnea at presentation, altered consciousness, blood pressure <90 systolic, oliguria, decreased platelet count (<100,000/mm³), urine culture positive for *Escherichia coli*, hyponatremia (Na <132), hyperkalemia (K >5.0), higher computerized tomography (CT) grade, and emergency nephrectomy as an intervention modality (P <0.05). Mortality was comparable among diabetics and nondiabetics. Diabetics had a lower CT score and higher creatinine (>2 mg/dL) as compared to nondiabetics. Most patients having urolithiasis were nondiabetic. Although nondiabetics had a higher CT score as compared to diabetics, the mortality in nondiabetics and diabetics was equivalent. This may suggest that either diabetics have a rapid deterioration of EPN status or intercurrent metabolic factors in diabetics may contribute to mortality among diabetics. Raised serum creatinine and immunocompromised status owing to diabetes may also play a role.

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Introduction

Emphysematous pyelonephritis (EPN) is defined as a life-threatening necrotizing infection of the kidney which is characterized by the accumulation of gas in the renal parenchyma and within the surrounding tissues. It has gained special attention among the uro-
logists due to its life-threatening potential. Ever since the first case of EPN was reported in 1898 by Kelly and MacCullum, the modality of management has varied from conventional open surgical treatment to a genre of endourologic procedures such as double J stenting, percutaneous nephrostomy, in addition to systemic antibiotic therapy.1,4

Mortality among patients diagnosed with EPN has reduced from 78% to 21% due to the aggressive management protocols and accurate staging using radiological imaging.5

Although there has been a significant decrease in mortality, EPN continues to be an important preventable cause of death in the field of urology.

There have been several studies, mostly retrospective which intended to identify the clinical, biochemical, and radiologic factors responsible for mortality among patients with EPN.6–8 In 1995, Pontin et al reported 22 patients of EPN exclusively in diabetic patients.9

There have been only few case reports on non-diabetic EPN. There is no data till date comparing the cohorts of diabetic and nondiabetic EPN. This study was conducted to identify the differences in clinical presentation, investigations, and outcomes in diabetic and non-diabetic cases of EPN and to evaluate the predictors of mortality of EPN.

**Materials and Methods**

This was a prospective observational study, conducted after Institutional Ethics Committee approval in a tertiary care medical college in Mumbai from July 2015 to May 2017. All patients diagnosed to have EPN based on the presence of gas within the parenchyma or pelvicalyceal system or both on computerized tomography (CT) scan and who were willing to participate in the study, were included in the study. However, patients having the presence of gas in the kidney or pararenal space secondary to recent instrumentation or fistulous communication between the kidney and colon or small bowel were excluded. Patients lost to follow-up were also excluded.

After obtaining informed consent, data on demographic profile, clinical features, laboratory investigations, imaging studies, the follow-up details were recorded. Each patient was followed up for at least six months. Clinical features included symptoms at presentation, duration of symptoms, associated comorbidities and history of prior urologic interventions if any. On clinical examination, general physical findings such as mental status, cardiorespiratory parameters, and per abdominal findings such as guarding, local tenderness, and skin changes over the flank and back, were assessed. Laboratory variables included a complete hemogram, C-reactive protein, erythrocyte sedimentation rate, renal function tests, liver function tests, coagulation profile, urine microscopy, blood culture, urine culture, and sensitivity. Imaging studies included ultrasonography; X-ray of kidney, ureter, and bladder (KUB); and CT scan of the abdomen and pelvis with or without contrast.

The initial management included fluid and electrolyte management, optimization of coagulation values, sugar control, and antibiotic administration in the emergency department. Broad-spectrum antibiotics were used initially, which were changed as per the culture and sensitivity report. Based on the extent of gas on CT, patients were grouped as per classification given by Huang and Tseng:10 Type 1, gas in the collecting system only (so-called emphysematous pyelitis); Type 2, gas in the renal parenchyma (Figure 1); Type 3, extension of gas or abscess to the perinephric space (3A) or to the pararenal space (3B) (Figure 2); and Type 4, bilateral EPN or solitary kidney with EPN. Figure 3 shows emphysematous pyelitis with emphysematous cystitis.

Based on the initial assessment of clinical parameters and imaging studies, interventions required were individualized which included per urethral catheterization only, per urethral catheterization and D-J stenting, per urethral catheterization and percutaneous intervention, exploration and drainage of pus or emergency nephrectomy. Patients requiring only medical management in addition to per urethral catheterization were said to be conservatively managed. Once stabilized, the function of the
Figure 1. Patient with Grade 2 emphysematous pyelonephritis with cross-sectional and coronal cuts.

Figure 2. Computerized tomography image and postoperative specimen image of Grade III B emphysematous pyelonephritis.

Figure 3. Grade I emphysematous pyelonephritis with emphysematous cystitis.
affected kidney was assessed by a nuclear imaging and USG KUB during the follow-up at one month. Patients who had recurrent pyelonephritis and/or poorly functioning kidney were managed by delayed elective nephrectomy.

Cohorts of diabetic and nondiabetic emphysematous pyelonephritis patients were individually assessed, and univariate analysis was done to compare these two cohorts to identify the significantly different factors among the two cohorts. Univariate analysis was done using Chi-square test to assess the clinical features, laboratory tests, radiologic features and outcomes of EPN. Multivariate logistic regression was done to identify independent variables that could predict mortality. Parameters that had a significant association with mortality were noted ($P<0.05$). All the data analysis was done using Statistical Package for Social Science software version 16.0 (SPSS Inc., Chicago, IL, USA).

**Results**

Among a total of 53 patients, $36$ ($67.92\%$) were female. The mean age was $55.43 \pm 1.10$ [mean ± standard deviation (SD)].Thirty patients ($56.60\%$) had diabetes mellitus. Forty-three patients ($81.13\%$) presented with flank pain as their predominant symptom, 30 patients ($56.60\%$) presented with fever, 17 ($32.70\%$) patients had decreased urine output and 13 ($24.52\%$) had dyspnea on presentation. Five patients ($9.43\%$) had skin changes in the flank region at presentation.

*Escherichia coli* was isolated in the urine of 29 ($54.73\%$) EPN patients, whereas 11 ($20.75\%$) urine cultures grew *Klebsiella* species and 10 ($18.86\%$) grew *Proteus*. Three patients had mixed growth in culture reports. The mortality was seen in 10 patients ($18.86\%$).

As per Huang and Tseng classification, four ($7.5\%$) patients had Type 1 EPN, 23 ($43.40\%$) had Type 2 EPN, 17 ($32.13\%$) had Type 3 EPN and nine ($17\%$) had Type 4 EPN. Thirteen patients ($24.52\%$) had urolithiasis on CT scan. Among patients with urolithiasis, 11 ($84.61\%$) patients were nondiabetics. Thirty-five patients ($66.03\%$) underwent percutaneous intervention or internal drainage using D-J stent along with medical management, whereas 10 ($18.86\%$) patients underwent surgical drainage. In three patients (5.66%), ultimately, emergency nephrectomy was required. Five (9.43%) required only the medical line of management. There were no mortalities in the patients managed only medically whereas 100% mortality was observed in patients undergoing emergency nephrectomy.

Univariate analysis of multiple factors and its association with mortality is shown in Table 1. Factors significantly found to be associated with mortality on univariate analysis were male gender, dyspnea at presentation, altered consciousness, systolic blood pressure (BP) <90 mm Hg, oliguria, decreased platelet count (<100,000/mm$^3$), hyponatremia (Na $<132$ mEq/L), hyperkalemia (K $>5.0$ mEq/L), higher CT grade, and requirement of emergency nephrectomy as an intervention modality ($P<0.05$). Table 2 highlights the factors independently predicting mortality on multivariate logistic regression analysis. Factors significantly found to be associated with mortality on multivariate analysis were systolic BP <90 mm Hg, decreased platelet count (<100,000/mm$^3$), hyponatremia (Na $<132$ mEq/L), higher CT grade and requirement of emergency nephrectomy. Patients with the growth of *E. coli* on urine cultures showed a significantly higher mortality in univariate as well as multivariate analysis.

The average age at presentation among patients presenting with diabetes mellitus was $56.80 \pm 1.06$ (mean ± SD) (range 29–74), and those among nondiabetics was $53.65 \pm 1.34$ (mean ± SD) (range 34–80). There was no significant difference in initial clinical presentation and management protocols among these two cohorts.

Table 3 highlights the differences in clinical profile, laboratory tests, and radiologic features among EPN patients with diabetes and those without diabetes.

Figure 4 identifies the differences in their CT grades at presentation. As noted in the graph, significantly higher number of nondiabetic
Table 1. Univariate analysis showing predictors of mortality in emphysematous pyelonephritis.

| Variables                        | Total records | Mortality | \( P \) |
|----------------------------------|---------------|-----------|---------|
| Number                           | 53            | 10        |         |
| Age in years                     |               |           |         |
| <50                              | 16            | 1         | 0.122   |
| \( \geq 50 \)                    | 37            | 9         |         |
| Gender                           |               |           |         |
| Male                             | 17            | 7         | 0.004   |
| Female                           | 36            | 3         |         |
| History of diabetes mellitus     |               |           |         |
| Yes                              | 30            | 7         | 0.342   |
| No                               | 23            | 3         |         |
| Dyspnea at presentation          |               |           |         |
| Yes                              | 9             | 4         | 0.032   |
| No                               | 44            | 6         |         |
| Altered consciousness            |               |           |         |
| Yes                              | 8             | 5         | 0.001   |
| No                               | 45            | 5         |         |
| BP                               |               |           |         |
| \( \leq 90 \)                    | 7             | 5         | 0.000   |
| \( >90 \)                        | 46            | 5         |         |
| Oliguria                         |               |           |         |
| Yes                              | 6             | 5         | 0.000   |
| No                               | 47            | 5         |         |
| White blood cell counts/\( \text{mm}^3 \) |               |           |         |
| \( \leq 3,000 \)                 | 42            | 6         | 0.095   |
| \( >13,000 \)                    | 11            | 4         |         |
| Thrombocytopenia (Platelets \( <100,000/\text{mm}^3 \)) |               |           |         |
| Yes                              | 6             | 5         | 0.000   |
| No                               | 47            | 5         |         |
| Serum sodium (mEq/L)             |               |           |         |
| \( \leq 132 \)                   | 46            | 5         | 0.000   |
| \( \leq 32 \)                    | 7             | 5         |         |
| Serum potassium (mEq/L)          |               |           |         |
| \( \leq 5.5 \)                   | 44            | 3         | 0.000   |
| \( >5.5 \)                       | 9             | 7         |         |
| Serum creatinine (mg/dL)         |               |           |         |
| \( \leq 2 \)                     | 27            | 6         | 0.524   |
| \( >2 \)                         | 26            | 4         |         |
| Urine culture                    |               |           |         |
| \( E. \text{coli} \)            | 29            | 9         | 0.041   |
| \( \text{Klebsiella} \)          | 14            | 1         |         |
| \( \text{Proteus species} \)     | 10            | 0         |         |
| Urolithiasis on CT scan          |               |           |         |
| Yes                              | 40            | 8         | 0.711   |
| No                               | 13            | 2         |         |
| CT classification (Huang and Tseng) |               |           |         |
| I                                | 4             | 0         | 0.03    |
| II                               | 23            | 4         |         |
| III                              | 17            | 1         |         |
| IV                               | 9             | 5         |         |

\( P <0.05 \) considered significant. \( E. \text{coli} \) : \text{Escherichia coli}, CT: Computerized tomography.

EPN presented with Type 4 EPN on CT, whereas Type 2 EPN was the most common finding in diabetics EPN. Diabetes mellitus was not found to be associated with increased risk of mortality. Diabetic EPN patients had a significantly higher creatinine values and lower CT scores at admission.

\textit{Proteus} species were isolated in the urine of 10 patients, nine of which were diabetic (90%).

Significantly higher number of nondiabetic EPN patients had associated urolithiasis. Figure 5 shows various modalities used in the management of EPN and their associated mortality.

**Discussion**

EPN is caused by a process of gas formation which requires a pathogenic organism proficient of acid fermentation in local necrotic tissue in the presence of hyperglycemic environment.\(^{11}\) Hence, diabetes mellitus has been known to be the most common associated factor with up to 95% of patients with EPN having underlying uncontrolled diabetes mellitus...
at the time of presentation.\textsuperscript{8,12} Our study had 30 patients (56.60%) with diabetes mellitus. Thus, as opposed to previous studies, our study supported the role of other etiologies in EPN, which have been mentioned in recent literature.\textsuperscript{13} The mean age of our study population was 55.6 years (range; 29–80 years) which was comparable with the age group of patients in other studies, however, male to female ratio (1:2.11) was lower in our study, whereas male to female ratios varying from 1:3 to 3:43 were found in other studies.\textsuperscript{9,10} EPN is commonly associated with \textit{E. coli} organisms and was isolated in nearly 70% of the reported cases.\textsuperscript{14,15} \textit{Proteus mirabilis}, \textit{Klebsiella pneumonia}, Group D \textit{Streptococcus},

| Variables | Odds ratio (95% confidence interval) | \( P \) |
|-----------|------------------------------------|-----|
| Age in years | <50 | 1.034 (0.319–1.46) | 0.871 |
| Gender | Male | 1.019 (0.301–1.211) | 0.916 |
| History of diabetes mellitus | Yes | 0.679 (0.126–1.132) | 0.176 |
| Dyspnea at presentation | Yes | 0.976 (0.921–1.32) | 0.911 |
| Altered consciousness | Yes | 1.138 (0.273–1.113) | 0.57 |
| Blood pressure | <90 | 0.482 (0.026–0.654) | 0.006 |
| Oliguria | Yes | 0.977 (0.371–1.214) | 0.917 |
| White blood cell counts (/mm\(^3\)) | ≤3,000 | 1.138 (0.566–1.311) | 0.631 |
| Thrombocytopenia (Platelets <100,000/mm\(^3\)) | Yes | 0.039 (0.064–0.414) | 0.029 |
| Serum sodium (meq/L) | >132 | 2.118 (1.932–3.356) | 0.003 |
| Serum potassium (meq/L) | ≤5.5 | 0.612 (0.136–1.345) | 0.059 |
| Serum creatinine (mg/dL) | ≥2 | 1.552 (0.058–1.23) | 0.088 |
| Urine culture | \textit{E. coli} | 8.434 (6.10–11.561) | 0.001 |
| | \textit{Klebsiella} & | |
| | \textit{Proteus species} & | |
| Urolithiasis on CT scan | Yes | 0.765 (0.346–1.21) | 0.346 |
| CT classification (Huang and Tseng) | I | 0.032 (0.011–0.87) | 0.027 |
| | II | | |
| | III | | |
| | IV | | |
| Management | Double J stenting | 1.869 (1.233–2.561) | 0.005 |
| | Percutaneous nephrostomy | | |
| | Percutaneous drainage and DJ | | |
| | Open surgical drainage | | |
| | Open nephrectomy | | |

\textit{E. coli}: \textit{Escherichia coli}, CT: Computerized tomography.
and coagulase-negative *Staphylococcus* have also been isolated in patients with EPN. In our study, *E. coli* was isolated in the urine of the majority of patients; other organisms include *Klebsiella* and *Proteus*. *E. coli* isolated in urine showed an increased risk of mortality which has not been previously mentioned in meta-analysis.

In 2007, a meta-analysis conducted by Falagas et al alerted clinicians about the associated increased mortality risk in patients with Type I EPN, bilateral EPN, concomitant thrombocytopenia, and conservative treatment. In addition, the study showed that increased serum creatinine level, disturbance of consciousness, and hypotension (systolic BP <90 mm Hg) may also impact the fatality of such patients, though with limited evidence. In our study, the clinical parameters that were found to be associated with mortality independently on multivariate analysis were, systolic BP <90 mm Hg at admission, decreased platelet count (<100,000/mm$^3$), hyponatremia (Na <132 mEq/L), higher CT grade and emergency nephrectomy as an intervention modality. However, as the CT type of EPN described by Wan et al, was used in the meta-analysis, the CT type could not be compared. There was no significant difference in the final outcome based on the radiological classification.

Diabetes mellitus has been extensively studied for its association with EPN. Although

Table 3. Univariate analysis comparing cohort of diabetic and nondiabetic emphysematous pyelonephritis.

| Variables                        | Diabetic EPN | Nondiabetics EPN | P   |
|----------------------------------|--------------|------------------|-----|
| Number                           | 30           | 23               |     |
| Age in years                     |              |                  |     |
| <50                              | 7            | 10               | 0.119 |
| ≥50                              | 23           | 13               |     |
| Gender                           |              |                  |     |
| Male                             | 10           | 7                | 0.822 |
| Female                           | 20           | 16               |     |
| Dyspnea at presentation          |              |                  |     |
| Yes                              | 5            | 4                | 0.944 |
| No                               | 25           | 19               |     |
| Altered consciousness            |              |                  |     |
| Yes                              | 4            | 4                | 0.682 |
| No                               | 26           | 19               |     |
| Blood pressure                   |              |                  |     |
| ≤90                              | 5            | 2                | 0.395 |
| >90                              | 25           | 21               |     |
| Oliguria                         |              |                  |     |
| Yes                              | 4            | 2                | 0.597 |
| No                               | 26           | 21               |     |
| White blood cell counts(/mm$^3$) |              |                  |     |
| ≤13,000                          | 23           | 19               | 0.580 |
| >13,000                          | 7            | 4                |     |
| Thrombocytopenia (Platelets <100,000) | Yes | 4 | 2 | 0.597 |
| No                               | 26           | 21               |     |
| Serum sodium (mEq/L)             |              |                  |     |
| >132                             | 25           | 21               | 0.395 |
| ≤132                             | 5            | 2                |     |
| Serum potassium (mEq/L)          |              |                  |     |
| >5.5                             | 7            | 2                | 0.159 |
| ≤5.5                             | 23           | 21               |     |
| Serum creatinine (mg/dL)         |              |                  |     |
| >2                               | 11           | 152              | 0.039 |
| ≤2                               | 19           | 8                |     |
| Urine culture                    |              |                  |     |
| *E. coli*                        | 16           | 14               | 0.047 |
| *Klebsiella*                     | 5            | 8                |     |
| *Proteus* species                | 9            | 1                |     |
| Urolithiasis on CT scan          |              |                  |     |
| Yes                              | 2            | 11               | 0.000 |
| No                               | 28           | 12               |     |
| Mortality                        |              |                  |     |
| Yes                              | 7            | 3                | 0.342 |
| No                               | 23           | 20               |     |

$P <0.05$ considered statistically significant.

EPN: Emphysematous pyelonephritis, *E. coli*: *Escherichia coli*, CT: Computerized tomography.
it has been the single most important contributing factor, no association was found between diabetes mellitus and mortality in patients with EPN.8 Our study also could not find any significant association between diabetes mellitus and mortality. Another significant finding was that about 43% of patients in our study were nondiabetics. This could be due to extensive use of CT scan for evaluation of patients presenting with acute febrile illness with flank pain in the emergency department. This gave us an opportunity to compare the cohorts of diabetics and nondiabetics. Both these cohorts had similar age groups with similar initial clinical presentation. However, diabetic EPN patients had a significantly higher creatinine values. Also when CT scores were compared, the majority of nondiabetics had a CT classification of Type 4 whereas the majority of diabetics had CT Type 2 at presentation.

Although diabetes was not found to be significantly associated with mortality, 70% of patients who eventually succumbed had diabetes.
Hence, despite similar initial clinical presentations, similar management protocols and in fact lower CT type, it was found in our study that diabetics had a relatively higher mortality. This may hint that certain metabolic derangements associated with diabetes mellitus may contribute to the eventual outcome in patients with EPN.

Furthermore, significantly higher number of nondiabetic patients with EPN had urolithiasis. Thus, it may be proposed that urolithiasis may be the most important contributing factors in the pathogenesis of EPN among the nondiabetic cohort. This may also mean that pathogenesis among the nondiabetic cohort needs further to be analyzed and early stone clearance may help decrease the incidence of EPN among the nondiabetic cohorts.

The limitation of this study includes a lack of assessment of few important parameters such as preadmission glycemic control and proteinuria which have been found to be associated with prognosis in EPN. Long-term follow-up and thereby noting the eventual need for nephrectomy of the involved kidney in all patients could not be assessed.

The accepted treatments of EPN previously have been emergency nephrectomy and/or open surgical drainage together with antibiotic therapy. With advances in the minimal invasive drainage of renal parenchyma and pelvis, more patients are being successfully treated with endourologic procedures such as double J stenting, percutaneous, and pig-tailing of surrounding collections. In our study, majority of patients (66.03%) underwent percutaneous intervention or internal drainage in concordance with the recent norm.

There were no mortalities in the patients managed medically only whereas 100% mortality was observed in patients undergoing emergency nephrectomy. A meta-analysis published by Aboumarzouk et al in 2014 also had lower mortality in patients undergoing medical management and percutaneous drainage. However, the meta-analysis by Falagas et al mentions increased mortality with a conservative management approach. This contradictory finding in our study could be due to the fact that patients who were hemodynamically stable and had either Type 1 or Type 2 on CT classification were subjected to conservative approach and this, therefore, emphasizes the need of patient selection for conservative management.

In addition, emergency nephrectomy was done as a salvage procedure in our study following the failure of percutaneous measures thereby explaining the mortality rate. The aggressive management is advisable in patients having the parameters predicting mortality. This needs to be confirmed by a larger multi-institutional prospective study. This study will help individualize the various treatment options based on the predictors of mortality. This study also makes a pathway for devising a scoring system and thereby would help frame an algorithm in early aggressive management of EPN.

**Conclusion**

The factors significantly associated with mortality on multivariate analysis include BP <90 systolic, decreased platelet count (<100,000/mm^3), urine culture positive for *E. coli*, hyponatremia (Na <132), higher CT grade at admission and emergency nephrectomy as an intervention modality (P <0.05). In addition, significantly higher number of nondiabetic patients with EPN had urolithiasis. Diabetic patients had a lower CT grade and higher creatinine values as compared to nondiabetic patients.

**Conflict of interest:** None declared.

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