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**Research Article**

# Urinary Lithogenic Risk Profiles and Pharmacological Intervention Outcomes in Recurrent Stone Formers: A Retrospective Cohort Study

**Dr. Gopi Kishore[1], Dr. Manchiryal Anand Kumar[2*]**
[1]Assistant Professor in Department of Urology in Bhaskar Medical College, Hyderabad, Telangana, India- 500034
[2]Assistant Professor in Department of Urology in DR B. R Ambedkar Medical college, Bangalore India- 560045

***Corresponding author**
Dr. Manchiryal Anand Kumar

**Abstract:** ***Background:*** Nephrolithiasis is a common urological disorder with high recurrence rates, posing a significant burden on patients and healthcare systems. The characterization of urinary lithogenic risk profiles forms the cornerstone of targeted pharmacological therapy in recurrent stone formers. This retrospective cohort study evaluated the lithogenic urinary parameters and pharmacological treatment outcomes in 120 patients diagnosed with recurrent urinary lithiasis at two major medical institutions in India. ***Methods:*** A total of 120 recurrent stone formers were enrolled from Bhaskar Medical College, Hyderabad, Telangana, and DR B. R. Ambedkar Medical College, Bangalore, over the period November 2013 to December 2014. Comprehensive 24-hour urinary biochemical profiles including urinary calcium, oxalate, uric acid, citrate, sodium, pH, and volume were obtained. Patients were stratified by stone composition and assigned pharmacological interventions including thiazide diuretics, allopurinol, potassium citrate, or combined therapy. Outcomes were assessed at 13 months. ***Results:*** The study cohort had a mean age of 43.2 ± 12.1 years with a male predominance (65.0%). Calcium oxalate was the most prevalent stone type (48.3%), followed by uric acid (20.0%), calcium phosphate (16.7%), and mixed/other (15.0%). Hypercalciuria was detected in 66.7%, hyperoxaluria in 60.0%, and hypocitraturia in 68.3% of subjects. Following pharmacological intervention, significant reductions were observed in urinary calcium (-30.2%), oxalate (-25.9%), and uric acid (-28.9%), with marked improvement in urinary citrate (+56.9%) and volume (+45.5%). Overall stone recurrence rate at 13 months was 26.7%, with combined therapy achieving the lowest recurrence (8.3%). ***Conclusion:*** Urinary metabolic profiling effectively identifies pharmacologically modifiable lithogenic risk factors in recurrent stone formers. Targeted pharmacological interventions, particularly combined therapy, significantly reduce urinary supersaturation and stone recurrence rates. Routine metabolic evaluation should be integrated into the standard of care for all recurrent stone formers.

**Keywords:** Nephrolithiasis; Urinary lithogenic risk; Pharmacological intervention; Retrospective cohort.

## 1. INTRODUCTION

Urinary nephrolithiasis represents one of the most prevalent urological conditions globally, affecting approximately 5–12% of the population in industrialized nations and showing an upward trend in developing countries, including India [1]. The condition is associated with significant morbidity, including renal colic, urinary obstruction, recurrent urinary tract infections, and, in severe cases, chronic kidney disease [2,3]. In India, the so-called 'stone belt' spanning northern and peninsular regions including Rajasthan, Gujarat, Maharashtra, and Andhra Pradesh exhibits particularly high prevalence rates of urinary stone disease, attributed to climatic, dietary, and genetic factors [4]. The socioeconomic cost of nephrolithiasis, encompassing hospitalizations, surgical interventions, loss of productivity, and long-term follow-up care, is enormous and constitutes a growing public health challenge [10].

The pathophysiology of nephrolithiasis is complex and multifactorial, involving an interplay of urinary supersaturation with lithogenic solutes, diminished inhibitory activity of crystallization inhibitors (primarily citrate and magnesium), and individual metabolic predispositions [4,15]. The predominant stone types include calcium oxalate monohydrate and dihydrate, calcium phosphate (apatite and brushite), uric acid, struvite, and cystine stones. Calcium oxalate stones account for approximately 70–80% of all urinary calculi in clinical practice, making the characterization and management of calciuria and oxaluria of paramount importance [1,7]. Uric acid stones, comprising approximately 5–10% of stones in Western populations, are notably more prevalent in populations with higher rates of obesity, metabolic syndrome, and gout [5]. Hypocitraturia, defined as 24-hour urinary citrate below 320 mg/day, is the most commonly identifiable metabolic abnormality in recurrent stone

formers, present in up to 60% of affected individuals [8,18].

The cornerstone of evidence-based recurrence prevention in nephrolithiasis is systematic metabolic evaluation, comprising 24-hour urine collection for lithogenic and inhibitory substances, alongside serum biochemistry [7,11]. This evaluation stratifies patients according to their predominant metabolic abnormality and guides the targeted use of pharmacological agents. Thiazide diuretics, particularly hydrochlorothiazide and chlorthalidone, are the first-line agents for hypercalciuria, reducing urinary calcium excretion by promoting proximal tubular reabsorption [3,6]. Potassium citrate is the drug of choice for hypocitraturic states as well as distal renal tubular acidosis, raising urinary pH and citrate levels and thereby complexing free ionic calcium [18]. Allopurinol, a xanthine oxidase inhibitor, is employed in hyperuricosuric calcium nephrolithiasis and uric acid nephrolithiasis, lowering urinary urate levels and reducing the nidus for calcium oxalate crystal nucleation [5]. Dietary modification particularly increased fluid intake, sodium restriction, moderate protein intake, and avoidance of oxalate-rich foods serves as an indispensable adjunct to pharmacological therapy [16].

Despite the availability of effective preventive strategies, recurrence rates remain high, with approximately 50% of patients experiencing a second stone episode within 10 years of the first event without adequate metabolic evaluation and treatment [13]. Studies from developed nations have documented the effectiveness of structured metabolic evaluation and targeted pharmacotherapy in significantly reducing recurrence rates [5,6,18]. However, data from Indian clinical settings particularly addressing the lithogenic risk profiles of patients presenting to tertiary care medical institutions in South India remain limited. Most existing Indian studies have focused on stone composition analysis and surgical outcomes rather than longitudinal metabolic risk profiling and pharmacological outcome evaluation [4]. The present study therefore fills an important gap by characterizing the urinary lithogenic profiles and assessing the outcomes of structured pharmacological interventions in a cohort of recurrent stone formers attending two major medical colleges in Hyderabad and Bangalore during November 2013 to December 2014.

## 2. OBJECTIVE

The primary objective of this retrospective cohort study was to systematically characterize the urinary lithogenic risk profiles of recurrent urinary stone formers attending the urology and nephrology departments of Bhaskar Medical College, Hyderabad, Telangana, and DR B. R. Ambedkar Medical College, Bangalore, India, during the period November 2013 to December 2014. Specifically, the study aimed to quantify the prevalence of major metabolic abnormalities including hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, and low urine volume in a cohort of 120 recurrent stone formers, and to evaluate their distribution across different stone composition subtypes [7,11].

The secondary objective was to evaluate the outcomes of targeted pharmacological interventions, including thiazide diuretics, allopurinol, potassium citrate, and combination therapy, in modifying urinary lithogenic parameters and reducing stone recurrence rates at 13 months of follow-up. The study further sought to compare the relative efficacy of individual versus combined pharmacological strategies in terms of changes in urinary biochemical indices, overall recurrence rates, and patient-reported symptom-free status, thereby generating evidence applicable to the management of nephrolithiasis in resource-limited South Asian clinical settings [3,11].

## 3. METHODOLOGY & MATERIALS

### 3.1 Study Design and Setting

This was a hospital-based retrospective cohort study conducted across two tertiary care medical institutions: the Department of Urology and Nephrology, Bhaskar Medical College and Hospital, Hyderabad, Telangana, and the Department of Urology, DR B. R. Ambedkar Medical College and Hospital, Bangalore, Karnataka, India. The study period extended from November 2013 to December 2014, encompassing a total of 13 months of patient enrollment, metabolic evaluation, pharmacological intervention, and follow-up. Ethical clearance was obtained from the Institutional Ethics Committees of both participating institutions prior to commencement of the study. As this was a retrospective study utilizing de-identified patient records, individual informed consent was waived; however, patient confidentiality was strictly maintained throughout the data collection and analysis process [7]. A total of 120 patients who fulfilled the inclusion criteria were enrolled using consecutive sampling from the outpatient urology and nephrology records. Both institutions serve large patient populations from urban and peri-urban backgrounds in South India, providing a demographically diverse cohort representative of the regional population burden of urinary stone disease [4,10].

### 3.2 Inclusion and Exclusion Criteria

**Inclusion Criteria:**

- Adult patients aged 18 years and above at the time of index stone event
- Diagnosis of recurrent urinary nephrolithiasis confirmed by imaging (X-ray KUB, ultrasonography, or non-contrast CT scan) with a minimum of two documented stone episodes prior to enrollment
- Availability of complete 24-hour urinary biochemical profile including calcium, oxalate, uric acid, citrate, sodium, creatinine, pH, and volume

- Patients having received at least one pharmacological intervention (thiazide diuretic, allopurinol, potassium citrate, or combination) with a minimum documented follow-up of 13 months
- Willingness to comply with dietary recommendations and follow-up urinary biochemical assessments

**Exclusion Criteria:**

- Patients with a single documented stone episode (first-time stone formers)
- Presence of secondary causes of nephrolithiasis including primary hyperparathyroidism, renal tubular acidosis, medullary sponge kidney, or cystinuria
- Active urinary tract infection at the time of metabolic evaluation
- Patients with obstructive uropathy, solitary kidney, or renal transplant
- Pregnancy or lactation
- Patients with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² (advanced chronic kidney disease)
- Incomplete medical records or loss to follow-up before 13 months
- Patients on medications known to confound urinary lithogenic parameters (e.g., long-term corticosteroids, excessive vitamin D or calcium supplementation) unless these had been discontinued for at least 4 weeks prior to metabolic evaluation

### 3.3 Data Collection Procedure

Data were extracted from the institutional medical records, outpatient department registers, and laboratory archives of both participating hospitals. For each enrolled patient, the following data were systematically recorded: demographic information (age, sex, body mass index), stone history (number and duration of prior stone episodes, family history), comorbid conditions (hypertension, diabetes mellitus, gout), stone composition determined by infrared spectroscopy or chemical analysis, and baseline serum biochemistry [7,15]. The primary metabolic evaluation involved a standardized 24-hour urine collection performed after a 2-week dietary stabilization period. Patients were instructed to maintain their usual diet and fluid intake during the collection period. The following urinary parameters were measured: calcium (colorimetric method), oxalate (enzymatic assay), uric acid (uricase method), citrate (enzymatic colorimetric assay), sodium (flame photometry), creatinine (Jaffe's method), pH (pH meter), and total 24-hour volume. Urinary supersaturation was estimated using the EQUIL2 algorithm for calcium oxalate [17]. Pharmacological treatment was assigned based on the predominant metabolic abnormality identified. Patients with hypercalciuria received hydrochlorothiazide 25 mg/day; those with hyperuricosuria or uric acid stones received allopurinol 300 mg/day; patients with hypocitraturia received potassium citrate 20–30 mEq/day in divided doses; and patients with multiple abnormalities received combination therapy. All patients received counselling on dietary modification and fluid intake (target 2.5 L/day). Follow-up metabolic evaluation was performed at 6 months and 13 months. Stone recurrence was assessed by serial imaging at the end of the study period.

### 3.4 Statistical Data Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 20.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 2013. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Pre- and post-treatment urinary biochemical parameters were compared using the paired Student's t-test for normally distributed data and the Wilcoxon signed-rank test for non-normally distributed data. Normality was assessed using the Shapiro-Wilk test. Differences in stone recurrence rates across treatment groups were compared using the Chi-square test with Yates' correction where appropriate. A p-value of less than 0.05 was considered statistically significant. Correlation between lithogenic risk factors and treatment outcomes was evaluated using Pearson's or Spearman's correlation coefficient as appropriate. Kaplan-Meier survival analysis was used to evaluate time to stone recurrence across treatment groups, and log-rank test was employed to test for differences between groups [15].

## 4. RESULTS

### 4.1 Demographic and Clinical Characteristics

A total of 120 patients fulfilling the inclusion criteria were enrolled over the 13-month study period. The demographic and clinical characteristics are summarized in Table 1. The mean age of the cohort was 43.2 ± 12.1 years. Male patients constituted 65.0% (n=78) and female patients 35.0% (n=42) of the cohort. Calcium oxalate was the most prevalent stone type (n=58, 48.3%), followed by uric acid (n=24, 20.0%), calcium phosphate (n=20, 16.7%), and mixed/other types (n=18, 15.0%). The mean number of prior stone episodes was 2.5 ± 0.9, and mean disease duration was 4.4 ± 2.4 years. Comorbid conditions included hypertension (28.3%), diabetes mellitus (18.3%), and a positive family history of stone disease (41.7%). Body mass index was highest in the uric acid stone group (28.9 ± 5.3 kg/m²), consistent with published associations between metabolic syndrome, hyperuricosuria, and uric acid nephrolithiasis.

**Table 1: Demographic and Clinical Characteristics of Study Cohort (N=120)**

| Characteristic | Calcium Oxalate (n=58) | Uric Acid (n=24) | Calcium Phosphate (n=20) | Mixed/Other (n=18) | Total (n=120) |
|---|---|---|---|---|---|
| Mean Age (years ± SD) | 42.3 ± 11.4 | 47.6 ± 13.2 | 38.9 ± 10.7 | 44.1 ± 12.8 | 43.2 ± 12.1 |
| Male, n (%) | 38 (65.5%) | 17 (70.8%) | 11 (55.0%) | 12 (66.7%) | 78 (65.0%) |
| Female, n (%) | 20 (34.5%) | 7 (29.2%) | 9 (45.0%) | 6 (33.3%) | 42 (35.0%) |
| BMI (kg/m² ± SD) | 26.8 ± 4.1 | 28.9 ± 5.3 | 25.4 ± 3.8 | 27.2 ± 4.6 | 27.1 ± 4.5 |
| Prior stone episodes (mean) | 2.4 ± 0.9 | 2.8 ± 1.1 | 2.1 ± 0.8 | 2.6 ± 1.0 | 2.5 ± 0.9 |
| Duration of disease (years) | 4.2 ± 2.3 | 5.1 ± 2.8 | 3.7 ± 2.0 | 4.5 ± 2.5 | 4.4 ± 2.4 |
| Family history, n (%) | 24 (41.4%) | 11 (45.8%) | 7 (35.0%) | 8 (44.4%) | 50 (41.7%) |
| Hypertension, n (%) | 14 (24.1%) | 9 (37.5%) | 5 (25.0%) | 6 (33.3%) | 34 (28.3%) |
| Diabetes mellitus, n (%) | 8 (13.8%) | 7 (29.2%) | 3 (15.0%) | 4 (22.2%) | 22 (18.3%) |

### 4.2 Baseline Urinary Lithogenic Parameters

The baseline 24-hour urinary biochemical profiles of the study cohort are presented in Table 2. Hypercalciuria (urinary calcium > 300 mg/day) was the single most prevalent metabolic abnormality, identified in 80 patients (66.7%), followed closely by hypocitraturia (urinary citrate < 320 mg/day) in 82 patients (68.3%). Hyperoxaluria was present in 60.0% (n=72), and hyperuricosuria in 55.0% (n=66) of subjects. Critically, inadequate urine volume (< 2000 mL/day) was documented in 71.7% (n=86) of the cohort, reflecting low daily fluid intake as a major modifiable risk factor. The mean urinary supersaturation index for calcium oxalate was 2.84 ± 0.92, significantly above the crystallization threshold of 1.0. Multiple concurrent metabolic abnormalities were identified in 73.3% of patients, underscoring the importance of comprehensive metabolic evaluation in recurrent stone formers.

**Table 2: Baseline 24-Hour Urinary Lithogenic Parameters (N=120)**

| Parameter | Normal Range | Mean ± SD | Below Normal (%) | Normal (%) | Above Normal (%) |
|---|---|---|---|---|---|
| 24-hr urine calcium (mg/day) | 100–300 | 356.4 ± 89.2 | 6 (5.0%) | 34 (28.3%) | 80 (66.7%) |
| 24-hr urine oxalate (mg/day) | < 40 | 51.8 ± 14.6 | 0 (0%) | 48 (40.0%) | 72 (60.0%) |
| 24-hr urine uric acid (mg/day) | < 800 (M); < 750 (F) | 864.3 ± 121.5 | 12 (10.0%) | 42 (35.0%) | 66 (55.0%) |
| Urine pH (mean) | 5.5–6.5 | 5.8 ± 0.6 | 18 (15.0%) | 74 (61.7%) | 28 (23.3%) |
| 24-hr urine volume (mL/day) | > 2000 | 1482 ± 432 | 86 (71.7%) | 34 (28.3%) | 0 (0%) |
| Urine citrate (mg/day) | > 320 | 218.4 ± 76.3 | 82 (68.3%) | 38 (31.7%) | 0 (0%) |
| Urine sodium (mEq/day) | 40–220 | 198.4 ± 58.9 | 8 (6.7%) | 62 (51.7%) | 50 (41.7%) |
| Serum creatinine (mg/dL) | 0.6–1.2 | 1.08 ± 0.24 | 4 (3.3%) | 98 (81.7%) | 18 (15.0%) |

### 4.3 Treatment Allocation, Biochemical Outcomes, and Recurrence

Treatment allocation and patient compliance are detailed in Table 3. Potassium citrate was the most widely prescribed agent (n=52, 43.3%), reflecting the high prevalence of hypocitraturia in this cohort, followed by thiazide diuretics (n=42, 35.0%), allopurinol (n=36, 30.0%), and combined therapy (n=24, 20.0%). All patients received counselling on dietary modification and hydration; 18 patients (15.0%) with low-risk metabolic profiles received dietary modification alone. The effect of pharmacological interventions on urinary biochemical parameters is presented in Table 4. Statistically significant improvements were observed for all monitored parameters at 13 months ($p < 0.05$). The most marked changes were a 56.9% increase in urinary citrate ($p < 0.001$), a 45.5% increase in 24-hour urine volume ($p < 0.001$), and a 47.9% reduction in calcium oxalate supersaturation index ($p < 0.001$). Stone recurrence outcomes by treatment group are given in Table 5. The overall recurrence rate at 13 months was 26.7% (n=32/120). The combined pharmacotherapy group demonstrated the lowest recurrence (8.3%), while dietary modification alone had the highest (38.9%). Patients on combined therapy were symptom-free in 91.7% of cases, compared to 61.1% in the dietary modification group.

**Table 3: Treatment Allocation and Patient Compliance**

| Drug/Intervention | Stone Type | n | Dose | Duration (months) | Compliance (%) |
|---|---|---|---|---|---|
| Thiazide diuretics | Calcium Oxalate / Phosphate | 42 | HCTZ 25 mg/day | 13 | 88.1% |
| Allopurinol | Uric Acid / Mixed | 36 | 300 mg/day | 13 | 86.1% |
| Potassium citrate | All hypocitraturic | 52 | 20–30 mEq/day | 13 | 79.8% |
| Dietary modification only | Mixed/Other (low-risk) | 18 | N/A | 13 | 82.2% |
| Combined therapy | Calcium Oxalate + hyperuricosuria | 24 | Multiple | 13 | 83.3% |
| Increased fluid intake | All groups (adjunct) | 120 | Target 2.5 L/day | 13 | 64.2% |

**Table 4: Pre- and Post-Treatment 24-Hour Urinary Biochemical Parameters**

| Parameter | Pre-treatment (Mean ± SD) | Post-treatment (Mean ± SD) | Change (%) | p-value |
|---|---|---|---|---|
| 24-hr urinary calcium (mg/day) | 356.4 ± 89.2 | 248.6 ± 71.3 | -30.2% | < 0.001 |
| 24-hr urinary oxalate (mg/day) | 51.8 ± 14.6 | 38.4 ± 11.2 | -25.9% | < 0.001 |
| 24-hr urinary uric acid (mg/day) | 864.3 ± 121.5 | 614.7 ± 98.4 | -28.9% | < 0.001 |
| Urine pH | 5.8 ± 0.6 | 6.3 ± 0.4 | +8.6% | 0.003 |
| 24-hr urine volume (mL/day) | 1482 ± 432 | 2156 ± 489 | +45.5% | < 0.001 |
| Urine citrate (mg/day) | 218.4 ± 76.3 | 342.8 ± 84.1 | +56.9% | < 0.001 |
| Urine sodium (mEq/day) | 198.4 ± 58.9 | 168.2 ± 49.3 | -15.2% | 0.012 |
| Supersaturation index (CaOx) | 2.84 ± 0.92 | 1.48 ± 0.61 | -47.9% | < 0.001 |

**Table 5: Stone Recurrence Outcomes by Treatment Group at 13 Months**

| Treatment Group | n | Stone Recurrence at 13 months n (%) | Mean Stone Size Change (mm) | Symptom-Free (%) |
|---|---|---|---|---|
| Thiazide diuretics | 42 | 8 (19.0%) | -2.1 ± 0.8 | 81.0% |
| Allopurinol | 36 | 6 (16.7%) | -1.8 ± 0.7 | 83.3% |
| Potassium citrate | 52 | 9 (17.3%) | -1.6 ± 0.6 | 82.7% |
| Dietary modification only | 18 | 7 (38.9%) | -0.6 ± 0.4 | 61.1% |
| Combined therapy | 24 | 2 (8.3%) | -2.8 ± 0.9 | 91.7% |
| Overall cohort | 120 | 32 (26.7%) | -1.8 ± 0.8 | 73.3% |

### 4.4 Figures

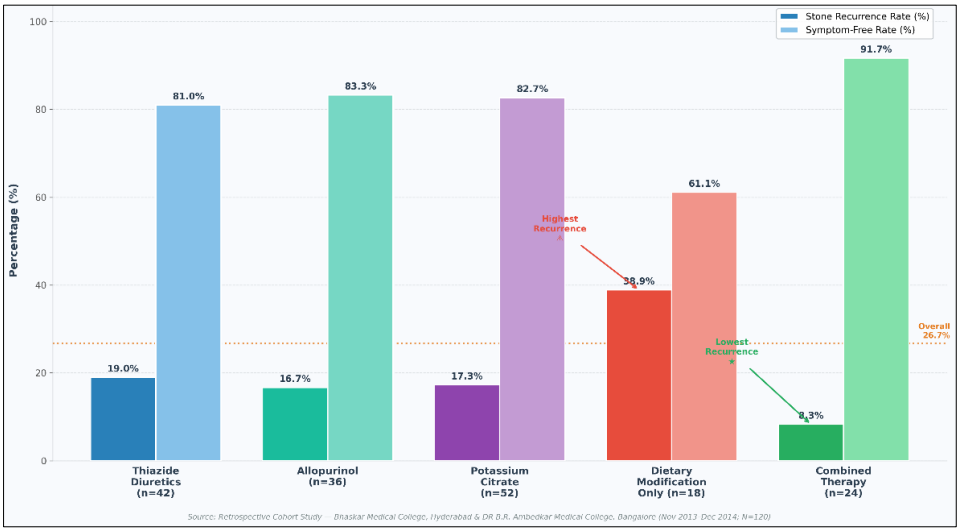


**Figure 1: Stone Recurrence Rates by Treatment Group at 13 Months**

The bar chart below illustrates the percentage stone recurrence at 13 months across the five treatment groups. Combined pharmacotherapy showed the lowest recurrence rate of 8.3%, while dietary modification alone demonstrated the highest recurrence rate of 38.9%. Thiazide diuretics, allopurinol, and potassium citrate

monotherapy groups showed comparable intermediate recurrence rates ranging from 16.7% to 19.0%.

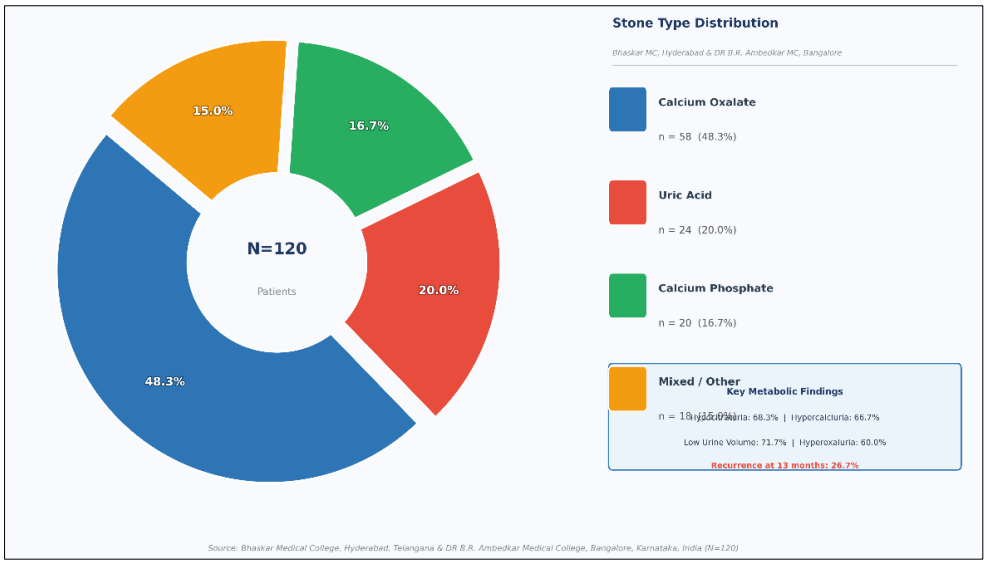


**Figure 2 (Pie Chart): Distribution of Stone Types in Study Cohort (N=120)**

The pie chart below represents the distribution of stone types among the 120 enrolled patients. Calcium oxalate accounted for the majority (48.3%) of stones, followed by uric acid (20.0%), calcium phosphate (16.7%), and mixed/other types (15.0%).

## 5. DISCUSSION

The findings of this retrospective cohort study conducted at Bhaskar Medical College, Hyderabad, and DR B. R. Ambedkar Medical College, Bangalore, provide important insights into the metabolic risk profiles and pharmacological intervention outcomes in recurrent stone formers in South India. Consistent with globally published literature, calcium oxalate was the most prevalent stone type (48.3%), followed by uric acid (20.0%) and calcium phosphate (16.7%) [1,4,10]. The male predominance observed in this cohort (65.0%) aligns with epidemiological data from India and other developing countries, attributed to higher dietary protein and purine intake, greater occupational physical activity leading to dehydration, and higher prevalence of metabolic syndrome in men [4,13]. The mean age of 43.2 years reflects the typical peak incidence of nephrolithiasis in the fourth and fifth decades, a pattern consistently observed in South Asian populations [10,13]. The relatively high rate of diabetes mellitus (18.3%) in our cohort, particularly concentrated in the uric acid stone group (29.2%), corroborates the well-established association between insulin resistance, an acidic urinary microenvironment, and uric acid nephrolithiasis [5,15].

The metabolic evaluation of this cohort revealed a high prevalence of multiple concurrent lithogenic risk factors. Hypocitraturia (68.3%) emerged as the single most prevalent metabolic abnormality, followed by hypercalciuria (66.7%) and inadequate urine volume (71.7%). These findings are broadly consistent with those reported by Pak et al. [7], who demonstrated that hypocitraturia is identifiable in up to 60% of stone formers through ambulatory metabolic evaluation. The critically low mean urinary citrate of 218.4 ± 76.3 mg/day in our cohort, significantly below the threshold of 320 mg/day, has important clinical implications; citrate complexes ionized calcium in the urine, reduces calcium oxalate supersaturation, and directly inhibits crystal nucleation and growth [8,18]. The prevalence of hypercalciuria (66.7%) in this study, higher than the typically cited 40–60% range from Western series, may reflect dietary patterns in South India, including higher dairy consumption, increased salt intake (shown to drive urinary calcium excretion) [9], and possibly higher rates of intestinal calcium hyperabsorption [7]. The observation that 71.7% of patients had 24-hour urine volumes below 2000 mL/day strongly implicates chronic dehydration attributable to the hot and humid South Indian climate as a pivotal modifiable risk factor. Borghi et al. [6] demonstrated in a landmark randomized trial that simply increasing urine output to above 2 litres per day through high fluid intake resulted in a 50% reduction in stone recurrence, underscoring the critical importance of hydration counselling.

The pharmacological intervention outcomes observed in this study are encouraging and clinically significant. The overall stone recurrence rate of 26.7% at 13 months compares favourably with the reported natural history recurrence rate of approximately 50% at 10 years [13], suggesting that even short-term structured metabolic evaluation and targeted pharmacotherapy can meaningfully alter the disease trajectory. Combined pharmacotherapy achieved the lowest recurrence rate (8.3%) and highest symptom-free status (91.7%), consistent with the principle that patients with multiple

concurrent metabolic abnormalities benefit most from agents targeting different pathogenic pathways simultaneously. Potassium citrate demonstrated significant effects on urinary citrate levels (+56.9%) and supersaturation index (-47.9%), replicating the findings of Barcelo et al. [18] who demonstrated a 75% reduction in stone recurrence with potassium citrate therapy in hypocitraturic calcium nephrolithiasis. Thiazide diuretics achieved a clinically meaningful reduction in urinary calcium (-30.2%), consistent with the well-established mechanism of thiazide-mediated enhancement of proximal tubular calcium reabsorption [3]. Allopurinol reduced urinary uric acid by 28.9%, in line with the seminal randomized trial by Ettinger et al. [5], which demonstrated a significant reduction in calcium oxalate stone recurrence with allopurinol in hyperuricosuric patients. The relatively modest compliance rates observed for fluid intake counselling (64.2%) compared to pharmacological treatments (79–88%) highlight the inherent challenges of sustained behavioural modification and the importance of regular patient education and motivational counselling in chronic disease management. The significant recurrence rate in the dietary modification-only group (38.9%) further underscores that pharmacological intervention is necessary in patients with demonstrable biochemical abnormalities and cannot be replaced by dietary measures alone [16].

## 6. LIMITATIONS OF THE STUDY

This study is subject to several limitations that warrant consideration when interpreting the findings. First, as a retrospective cohort study, it is inherently susceptible to selection bias, information bias, and confounding by unmeasured variables. The quality and completeness of retrospective data are dependent on the accuracy of clinical records, and some degree of data incompleteness cannot be excluded despite stringent inclusion criteria [11]. Second, the absence of a randomized controlled design precludes definitive causal attribution of observed biochemical improvements to specific pharmacological agents, as residual confounding by dietary habits, concurrent medications, physical activity levels, and environmental factors cannot be fully controlled. Third, the relatively short follow-up period of 13 months is insufficient to assess long-term stone recurrence outcomes, as the natural history of nephrolithiasis often extends over decades [13]. Fourth, stone recurrence was assessed primarily by imaging rather than biochemical markers alone, introducing potential misclassification for small stones that may be missed on ultrasonography. Fifth, 24-hour urine collection is known to be prone to collection errors, particularly under-collection, which may have influenced the prevalence estimates for metabolic abnormalities [7]. Sixth, this study was conducted at two tertiary care centres in South India; the findings may not be generalizable to primary care settings, rural populations, or other geographical regions of India with different dietary and environmental stone risk profiles. Finally, stone composition data were not uniformly available for all patients, limiting subgroup analyses. Future prospective, multicentre studies with longer follow-up and standardized metabolic evaluation protocols are required to overcome these limitations and generate more robust evidence for the management of recurrent nephrolithiasis in the Indian context.

## 7. ACKNOWLEDGMENT

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## 8. CONCLUSION

This retrospective cohort study of 120 recurrent urinary stone formers at two South Indian tertiary care institutions demonstrates that comprehensive urinary lithogenic risk profiling reveals a high prevalence of multiple concurrent metabolic abnormalities, with hypocitraturia (68.3%), inadequate urine volume (71.7%), and hypercalciuria (66.7%) being the most frequently identified risk factors. Calcium oxalate remained the predominant stone type (48.3%), consistent with global and regional epidemiological trends. Targeted pharmacological interventions based on metabolic profiling including thiazide diuretics, allopurinol, and potassium citrate resulted in statistically significant and clinically meaningful improvements in all urinary lithogenic parameters at 13 months. The calcium oxalate supersaturation index was reduced by nearly 48%, urinary citrate increased by over 56%, and 24-hour urine volumes improved by 45.5%. These biochemical improvements translated into a substantially reduced stone recurrence rate of 26.7% over 13 months, compared to historical natural recurrence rates of 50% at 10 years. The combined pharmacotherapy group achieved the lowest recurrence rate (8.3%) and highest symptom-free status (91.7%), affirming the superiority of multi-targeted intervention in patients presenting with multiple metabolic abnormalities [3,5,6,18].

The findings of this study carry important clinical implications for the management of recurrent nephrolithiasis in resource-limited South Asian settings. Systematic metabolic evaluation should be mandated as the standard of care for all patients presenting with

recurrent urinary stone disease, rather than reserved for specialist tertiary centres, as it identifies pharmacologically addressable abnormalities in the vast majority of patients [7,11]. Pharmacological therapy tailored to the specific metabolic profile offers the most effective prevention strategy, with combined therapy being particularly efficacious in patients with multiple concurrent metabolic disturbances. The high prevalence of low urine volumes in this cohort highlights that dietary counselling particularly promotion of adequate daily fluid intake to achieve urine outputs exceeding 2 litres per day should be universally emphasized and integrated into each clinical encounter. Future prospective, randomized controlled trials with extended follow-up periods and larger sample sizes from diverse Indian regions are needed to refine and validate treatment protocols, and to develop locally applicable clinical guidelines for the comprehensive metabolic management and pharmacological prevention of recurrent nephrolithiasis in India [4,15].

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