Cardiovascular risk factors, ethnicity and infection stone are independent factors associated with reduced renal function in renal stone formers

Seow Huey Choy1, Selina Ann Nyanatay1, Selvalingam Sothilingam1, Rohan Malek2*, Sathiyananthan J. R.2, Charng Chee Toh2, Murali Sundram3, Noor Ashani Md Yusoff3, Poongkodi Nagappan3, Shakirin Kamaruzaman1, Wei Sien Yeoh1, Teng Aik Ong1, Jasmine Lim1*

1 Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, 2 Department of Urology, Hospital Selayang, Selangor, Malaysia, 3 Department of Urology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

*jasmine.lim@um.edu.my (JL); rohanmalekmr@yahoo.com (RM)

Abstract

Background
Recent evidence suggested the link between nephrolithiasis and renal function impairment. We aimed to determine the renal function profile and potential factors associated with reduced renal function amongst renal stone formers in multi-ethnic Asians.

Methods
We conducted a cross-sectional study involving patients undergoing percutaneous nephrolithotomy between May 2015 and December 2019. Reduced renal function was defined as having estimated glomerular filtration rate < 60 ml/min per 1.73 m². Renal stone samples were collected and quantified using infrared spectroscopy. Potential factors associated with reduced renal function including age, ethnicity, educational level, history of diabetes, hypertension, gout, hydronephrosis, serum uric acid level, and type of renal stone were evaluated using univariable and multivariable analyses.

Results
A total of 1162 patients from a multi-ethnic population (Malays 67%, Chinese 19%, Indians 13% and indigenous people 1%) with median age of 57 years (Interquartile range 48–64) were enrolled in the study. Almost a third of patients were found with reduced renal function. Multivariable analysis showed that the odds of having reduced renal function increased with age, ethnicity, lower educational level, history of diabetes, hypertension, gout, bilateral hydronephrosis, elevated serum uric acid level and infection stone.

Conclusions
Reduced renal function varies between ethnicities and all age groups of renal stone formers. In addition to age and ethnicity, cardiovascular risk factors including diabetes and
hypertension may also need to be taken into account in managing stone patients with reduced renal function.

Introduction

Nephrolithiasis is a highly prevalent disease with rising trend observed globally in recent decades [1, 2]. Its prevalence rate varies depending on the study populations across different regions and social constructs [3, 4]. For instance, the burden of nephrolithiasis was 10.6% in the United States [1], 6.2%–9.1% in Saudi Arabia [5, 6], 6.4% in China [2] and 7.9% in India [7]. Although this disease is more common in males than females in a ratio of 3:1, there is a declining trend of male predominance [8]. Stone recurrence is common. Recurrence of symptomatic renal stones was 11% at 2 years and increased to 39% at 15 years [9]. There is emerging evidence showing a higher incidence of chronic kidney disease (CKD) among stone formers compared to non-stone formers [10, 11].

The global prevalence of CKD was estimated at 9.1% in 2017, resulting in 1.2 million deaths [12]. It is a long-term illness which may progress from mild reduction in glomerular filtration rate to end-stage renal disease (ESRD) without appropriate treatment. In Malaysia, the CKD prevalence was 15.5% in 2018; of which, 6.8% had estimated glomerular filtration rate (eGFR) $< 60$ ml/min/1.73m$^2$ [13]. The expenditure of Malaysia healthcare system recorded an average annual growth of 12% with average USD 575 million per year in ESRD between 2010 and 2016 [14]. Based on the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines, individuals with eGFR $< 60$ ml/min/1.73m$^2$ have moderate to very high risks of developing CKD compared to those of eGFR $\geq 60$ ml/min/1.73m$^2$, [15]. Whilst full evaluation of CKD progression relies on KDIGO definition, assessment of GFR and albuminuria level, an abnormal eGFR could be an early indicator of CKD.

Recent emerging evidence identified nephrolithiasis as one of the risk factors for renal function impairment; however, it remains uncertain whether this risk differs by stone type. For example, lower urinary pH was usually present in individuals with metabolic syndrome, hyperuricemia and gout, predisposing them to the formation of uric acid stones [16, 17]. Defective urinary ammonium excretion, which contributes to the persistent acidic urine, could lead to impaired renal function in uric acid stone formers [18]. It has been hypothesised that rare monogenic disorders and malformations such as primary hyperoxaluria and cystinuria can cause stone formation and increase the risk for renal function loss [10]. Previous study demonstrated the association of high urinary oxalate excretion with CKD progression [19]. Formation of calcium oxalate crystal, obstruction and damage to the tubular epithelial cells as well as inflammation of tissue parenchyma under high oxalate concentration can result in kidney injury [19]. Therefore, it is of our interest to assess the renal function profile among renal stone patients and identify potential factors associated with reduced renal function in a multi-ethnic Asian setting.

Materials and methods

Study participants

This cross-sectional study was conducted in three tertiary urology referral centres including Hospital Kuala Lumpur, Hospital Selayang and University Malaya Medical Centre, Malaysia. Patients undergoing percutaneous nephrolithotomy (PCNL) for renal calculi between May 2015 and December 2019 were enrolled into the study. Of note, these patients usually present
with relatively large stone (>1.5cm) and are at higher risk of developing complications including renal failure and sepsis. We excluded patients with Karnofsky Performance Score ≤70 from the study. All participants provided written informed consent. The study protocol was approved by the Medical Research and Ethics Committee at UMMC (code: MECID. no 20152–1020) and Ministry of Health Malaysia (code: NMRR-15-35-24341).

**Data collection and measurements**

A structured questionnaire consisting of sociodemographic and clinical parameters was used. Basic demographic included age (year), gender (male and female), ethnicity (Malay, Chinese, and Indian), marital status (married and single), educational level, smoking status, and alcohol consumption. Educational level was grouped into tertiary, secondary or primary, and nonformal. Smoking status was categorised into no (never smoked or ex-smoker who had discontinued >1 month) and yes (smoking on daily or occasional basis). Alcohol consumption was divided into no (never or less than once a month) and yes (more than once a month).

Clinical information included weight (kg), height (cm), waist circumference (cm), family history of renal stone, history of major comorbidities such as diabetes, dyslipidaemia hypertension, gout, hydronephrosis, serum creatinine (μmol/L) level, serum uric acid level (elevated uric acid level was defined as uric acid >430 μmol/L for male and uric acid >360 mol/L for female) [20], stone episode (new and recurrence), stone location (non-staghorn and staghorn or partial staghorn), and number of stones (single and multiple). Central obesity was defined as having waist circumference >79.9 cm for female and waist circumference >89.9 cm for male [21]. Renal function was evaluated using eGFR based on the CKD Epidemiology Collaboration equation (CKD-EPI) [22]. The CKD-EPI equation was previously validated in a multiethnic population in Singapore [23]. Reduced renal function was defined as eGFR <60 ml/min per 1.73 m² based on the KDIGO guidelines [15].

Overnight fasting blood sample was obtained to measure lipid profile and fasting blood glucose level using Advin 2400 (Siemens Healthcare Diagnostic Inc, Muenchen, Germany). The HbA1c level was analysed with VARIANT™ II Hemoglobin Testing System (Bio-Rad Laboratories, Inc, California, United States). Patients with HDL <1.03 mmol/L (male); HDL <1.29 mmol/L (female) or triglyceride ≥1.69 mmol/L or self-reported use of lipid-lowering drugs were defined as having dyslipidaemia [24]. Patients displaying fasting blood glucose levels ≥7.0 mmol/L or HbA1c ≥6.3% (≥45 mmol/mol) or self-reported on treatment for diabetes were considered to have diabetes mellitus [25].

Renal stone samples were collected after the PCNL procedure and analysed quantitatively in a central laboratory using Nicolet iS5 Fourier-transform infrared (FT-IR) spectrometer (Thermo Fisher Scientific Inc, Waltham, USA) to investigate the stone composition. Stone type was classified into calcium oxalate, infection, uric acid, and cystine based on the predominant stone composition, accounting for >55% of the overall stone composition. Infection stones were magnesium ammonium phosphate hexahydrate (struvite), ammonium urate, and carbonate apatite. A mixed stone was a renal stone which did not consist of a major component accounting for more than 55%.

**Statistical analysis**

Continuous variables were expressed as median and interquartile range (IQR) whilst categorical variables were expressed in frequencies and percentages. Potential factors associated with reduced renal function were compared between two groups, alone and in combination, using univariable and multivariable logistic regression. The missing data in most variables were between 1.5–4.1% except serum uric acid level (18.1%), central obesity (10.2%) and renal stone
type (15.2%). We assumed the missingness to occur completely at random. All statistical analyses were conducted using Statistic Package for Social Science (SPSS) software for Windows Version 27 (SPSS Inc, Chicago, Illinois, USA). Two-tailed $p$ value $< 0.05$ was termed statistically significant.

Results

A total of 1162 renal stone patients undergoing PCNL procedure were included into the study, consisting of 55% males and 45% females. Most of the patients were Malays (n = 778; 67.0%), followed by Chinese (n = 222; 19.1%), Indians (n = 152; 13.1%), and indigenous people (n = 10; 0.9%) with median age of 57 years (IQR 48–64). The commonest stone type was calcium oxalate (n = 526; 53.4%), followed by infection stone (n = 204; 20.7%) and uric acid stone (n = 165; 16.8%). Majority patients were first-time stone formers (69.9%) and approximately half of the stone formers developed staghorn or partial staghorn stones. In term of stone type, patients with calcium oxalate stones had the highest median eGFR (81.30 ml/min/1.73m$^2$, IQR 57.70–95.89) whilst patients with cystine stone had the lowest median eGFR (61.12 ml/min/1.73m$^2$, IQR 50.55–71.55). The overall median eGFR was 77.15 ml/min/1.73m$^2$ (IQR 52.28–94.75) with higher median eGFR observed among younger patients aged $\leq$49 compared to those $>49$ (Table 1). The median eGFR of Malays (72.38 ml/min/1.73m$^2$, IQR 48.29–93.54) was relatively lower than Chinese (81.35 ml/min/1.73m$^2$, IQR 60.71–93.36), Indians (88.42ml/min/1.73m$^2$, IQR 66.38–101.61), and indigenous people (88.95 ml/min/1.73m$^2$, IQR 69.60–105.35).

Table 2 summarises the characteristics of patients categorised into normal renal function (eGFR $\geq$60 ml/min/1.73m$^2$) and reduced renal function (eGFR $< 60$ ml/min/1.73m$^2$). Overall,

### Table 1. The estimated glomerular filtration rate of stone formers.

| Variable          | n (%) | eGFR (ml/min/1.73m$^2$) | Median | Interquartile range |
|-------------------|-------|------------------------|--------|---------------------|
| Age               |       |                        |        |                     |
| $\leq$49          | 320 (27.5) | 93.10                  | 75.68–108.85 |
| 50–59             | 364 (31.3) | 76.90                  | 55.15–95.18 |
| 60–69             | 378 (32.5) | 66.16                  | 45.33–88.47 |
| $\geq$70          | 100 (8.6)  | 53.52                  | 37.29–78.30 |
| Gender            |       |                        |        |                     |
| Male              | 639 (55.0) | 75.40                  | 52.50–93.33 |
| Female            | 523 (45.0) | 79.70                  | 51.90–97.20 |
| Ethnicity         |       |                        |        |                     |
| Malay             | 778 (67.0) | 72.38                  | 48.29–93.54 |
| Chinese           | 222 (19.1) | 81.35                  | 60.71–93.36 |
| Indian            | 152 (13.1) | 88.42                  | 66.38–101.61 |
| Indigenous        | 10 (0.9)   | 88.95                  | 69.60–105.35 |
| Stone type        |       |                        |        |                     |
| Calcium oxalate   | 526 (53.4) | 81.30                  | 57.70–95.89 |
| Infection         | 204 (20.7) | 76.45                  | 46.23–96.10 |
| Uric acid         | 165 (16.8) | 67.17                  | 43.45–87.05 |
| Cystine           | 6 (0.6)    | 61.12                  | 50.55–71.55 |
| Others $^a$       | 84 (8.5)   | 75.00                  | 46.63–99.80 |

$^a$ Others consisted of mixed, calcium phosphate, and rare stones

Abbreviations: eGFR, estimated glomerular filtration rate.
Table 2. Comparison of factors associated with renal function defined by eGFR.

| Variable                        | Overall | Normal renal function (eGFR ≥60 ml/min/1.73m²) | Reduced renal function (eGFR < 60 ml/min/1.73m²) | OR     | 95% CI   | P value |
|--------------------------------|---------|-----------------------------------------------|-----------------------------------------------|--------|----------|---------|
| **Sociodemographic characteristics** |         |                                               |                                               |        |          |         |
| Age, year                      | 1162 (100) | 794 (68.3)                                        | 368 (31.7)                                      | 1.06   | 1.05–1.07 | <0.001  |
| Median (IQR)                   | 57 (48–64)  | 54 (46–62)                                         | 62 (55–67)                                      | 1.00   |          |         |
| **Gender**                     |         |                                               |                                               |        |          |         |
| Male                           | 639 (55.0) | 442 (55.7)                                         | 197 (53.5)                                      | 1.00   |          |         |
| Female                         | 523 (45.0) | 352 (44.3)                                         | 171 (46.5)                                      | 1.09   | 0.85–1.40 | 0.496   |
| **Ethnicity**                  |         |                                               |                                               |        |          |         |
| Malay                          | 778 (67.0) | 499 (62.8)                                         | 279 (75.8)                                      | 1.00   |          |         |
| Chinese                        | 222 (19.1) | 168 (21.2)                                         | 54 (14.7)                                       | 0.58   | 0.41–0.81 | 0.001   |
| Indian                         | 152 (13.1) | 119 (15.0)                                         | 33 (9.0)                                        | 0.50   | 0.33–0.75 | 0.001   |
| Indigenous                     | 10 (0.9)   | 8 (1.0)                                            | 2 (0.5)                                         | 0.45   | 0.09–2.12 | 0.311   |
| **Marital status**             |         |                                               |                                               |        |          |         |
| Married                        | 1033 (91.1) | 694 (89.7)                                         | 339 (94.2)                                      | 1.00   |          |         |
| Single                         | 101 (8.9)   | 80 (10.3)                                           | 21 (5.8)                                        | 0.54   | 0.33–0.88 | 0.014   |
| Unknown                        | 28       | 20                                               | 8                                              |        |          |         |
| **Educational level**          |         |                                               |                                               |        |          |         |
| Tertiary                       | 131 (11.5) | 107 (13.7)                                         | 24 (6.6)                                        | 1.00   |          |         |
| Primary or secondary           | 945 (82.6) | 645 (82.5)                                         | 300 (82.9)                                      | 2.07   | 1.31–3.30 | 0.002   |
| None                           | 68 (5.9)    | 30 (3.8)                                           | 38 (10.5)                                       | 5.65   | 2.94–10.84 | <0.001  |
| Unknown                        | 18       | 12                                               | 6                                              |        |          |         |
| **Smoking status**             |         |                                               |                                               |        |          |         |
| No                             | 909 (79.9) | 605 (77.7)                                         | 304 (84.7)                                      | 1.00   |          |         |
| Yes                            | 229 (20.1) | 174 (22.3)                                         | 55 (15.3)                                       | 0.63   | 0.45–0.88 | 0.006   |
| Unknown                        | 24       | 15                                               | 9                                              |        |          |         |
| **Alcohol consumption**        |         |                                               |                                               |        |          |         |
| No                             | 976 (85.4) | 665 (85.5)                                         | 311 (85.2)                                      | 1.00   |          |         |
| Yes                            | 167 (14.6) | 113 (14.5)                                         | 54 (14.8)                                       | 1.02   | 0.72–1.45 | 0.904   |
| Unknown                        | 19       | 16                                               | 3                                              |        |          |         |
| **Clinical characteristics**   |         |                                               |                                               |        |          |         |
| Family history of renal stone  |         |                                               |                                               |        |          |         |
| No                             | 771 (69.1) | 526 (68.9)                                         | 245 (69.4)                                      | 1.00   |          |         |
| Yes                            | 345 (30.9) | 237 (31.1)                                         | 108 (30.6)                                      | 0.98   | 0.74–1.29 | 0.875   |
| Unknown                        | 46       | 31                                               | 15                                             |        |          |         |
| History of diabetes*           |         |                                               |                                               |        |          |         |
| No                             | 553 (47.6) | 415 (52.3)                                         | 138 (37.5)                                      | 1.00   |          |         |
| Yes                            | 609 (52.4) | 379 (47.7)                                         | 230 (62.5)                                      | 1.83   | 1.42–2.35 | <0.001  |

(Continued)
| Variable                        | Overall | Normal renal function (eGFR ≥60 ml/min/1.73 m^2) | Reduced renal function (eGFR <60 ml/min/1.73 m^2) | OR  | 95% CI  | P value |
|--------------------------------|---------|-----------------------------------------------|-----------------------------------------------|-----|---------|---------|
| History of dyslipidaemia^b      |         |                                               |                                               |     |         |         |
| No                             | 333 (28.7) | 242 (30.5)                                      | 91 (24.7)                                      | 1.00|         |         |
| Yes                            | 829 (71.3) | 552 (69.5)                                      | 277 (75.3)                                      | 1.33| 1.01–1.77| 0.044   |
| History of hypertension        |         |                                               |                                               |     |         |         |
| No                             | 351 (30.2) | 290 (36.5)                                      | 61 (16.6)                                      | 1.00|         |         |
| Yes                            | 811 (69.8) | 504 (63.5)                                      | 307 (83.4)                                      | 2.90| 2.12–3.95| <0.001  |
| History of gout                |         |                                               |                                               |     |         |         |
| No                             | 1095 (94.2) | 765 (96.3)                                      | 330 (89.7)                                      | 1.00|         |         |
| Yes                            | 67 (5.8)   | 29 (3.7)                                        | 38 (10.3)                                      | 3.04| 1.84–5.01| <0.001  |
| Serum uric acid                |         |                                               |                                               |     |         |         |
| Normal                         | 532 (55.9) | 422 (66.0)                                      | 110 (35.1)                                     | 1.00|         |         |
| Elevated                       | 420 (44.1) | 217 (34.0)                                      | 203 (64.9)                                     | 3.59| 2.70–4.77| <0.001  |
| Unknown                        | 210     | 155                                            | 55                                             |     |         |         |
| History of hydronephrosis      |         |                                               |                                               |     |         |         |
| No                             | 416 (36.4) | 289 (37.0)                                      | 127 (35.0)                                     | 1.00|         |         |
| Unilateral                     | 620 (54.2) | 436 (55.8)                                      | 184 (50.7)                                     | 0.96| 0.73–1.26| 0.769   |
| Bilateral                      | 108 (9.4)  | 56 (7.2)                                        | 52 (14.3)                                      | 2.11| 1.37–3.25| 0.001   |
| Unknown                        | 18      | 13                                             | 5                                               |     |         |         |
| Anthropometric measurements    |         |                                               |                                               |     |         |         |
| Central obesity Asian^d        |         |                                               |                                               |     |         |         |
| No                             | 254 (24.4) | 179 (24.8)                                      | 75 (23.4)                                      | 1.00|         |         |
| Yes                            | 789 (75.6) | 543 (75.2)                                      | 246 (76.6)                                     | 1.08| 0.79–1.47| 0.620   |
| Unknown                        | 119     | 72                                             | 47                                             |     |         |         |
| Body mass index, kg/m^2, Median (IQR) | 27.1 (24.2–30.5) | 27.1 (24.0–30.4) | 27.1 (24.4–31.0) | 1.00| 0.99–1.01| 0.576   |
| Stone-specific parameters      |         |                                               |                                               |     |         |         |
| Stone episode                  |         |                                               |                                               |     |         |         |
| New                            | 797 (69.9) | 550 (70.2)                                      | 247 (69.0)                                     | 1.00|         |         |
| Recurrence                     | 344 (30.1) | 233 (29.8)                                      | 111 (31.0)                                     | 1.06| 0.81–1.39| 0.670   |
| Unknown                        | 21      | 11                                             | 10                                             |     |         |         |
| Stone location                 |         |                                               |                                               |     |         |         |
| Non-staghorn                   | 586 (51.1) | 409 (52.0)                                      | 177 (49.2)                                     | 1.00|         |         |
| Staghorn/Partial staghorn      | 560 (48.9) | 377 (48.0)                                      | 183 (50.8)                                     | 1.12| 0.87–1.44| 0.367   |
| Unknown                        | 16      | 8                                              | 8                                              |     |         |         |
| Number of stones               |         |                                               |                                               |     |         |         |
| Single                         | 480 (43.1) | 336 (44.2)                                      | 144 (40.7)                                     | 1.00|         |         |
| Multiple                       | 634 (56.9) | 424 (55.8)                                      | 210 (59.3)                                     | 1.16| 0.90–1.49| 0.268   |
| Unknown                        | 48      | 34                                             | 14                                             |     |         |         |

(Continued)
there were 31.7% (368/1162) of stone formers with reduced renal function. We found significant association between reduced renal function and age, ethnicity, marital status, educational level, smoking status, history of diabetes, dyslipidaemia, hypertension, gout, and bilateral hydronephrosis as well as serum uric acid level and stone type ($p < 0.05$) (Table 2). For instance, patients with history of hypertension or diabetes were 2.9 fold and 1.83 fold more likely to have reduced renal function respectively, compared to those without these medical conditions. It was revealed that patients with gout were 3 times more likely to have reduced renal function compared with patients without gout. Patients with elevated serum uric acid level were 3.59 times more likely than those with normal serum uric acid level to have reduced renal function ($p < 0.001$).

In the multivariable analysis, age, ethnicity, education level, history of diabetes, hypertension, gout, and bilateral hydronephrosis as well as serum uric acid level and stone type remained to be significantly and independently associated with reduced renal function amongst stone formers (Table 3). Patients with infection stone [adjusted odds ratio (aOR) 1.83, 95% confidence interval (CI) 1.22–2.74] were more likely to have reduced renal function than those with calcium oxalate stone. Comparing to Malays, Chinese and Indians had 58% and 41% lesser odds of having reduced renal function respectively. Increased odds of having reduced renal function was observed in stone patients with history of bilateral hydronephrosis (aOR 3.23, 95% CI 1.95–5.34).

**Discussion**

Findings from this study provide new insights into the severity of reduced renal function in multi-ethnic renal stone formers. We demonstrated ethnic variations, major stone elements and cardiovascular risk factors especially diabetes and hypertension were significantly associated with reduced renal function in renal stone patients. The relative high prevalence of reduced renal function was in line with previous study recording 39.2% of stone formers having eGFR <60 ml/min/1.73m$^2$ [26]. Although nephrolithiasis is usually presented as a benign
medical condition with limited long-term consequences, high prevalence of reduced renal function found in our study is alarming as previous meta-analyses demonstrated significant associations of renal stones with higher risk of CKD [27, 28]. An increased risk of CKD with an adjusted risk ratio of 1.47 (95% CI 1.23–1.76) was estimated in patients with renal stone

| Table 3. Multivariable analysis of factors associated with reduced renal function (eGFR < 60 ml/min/1.73 m²). |
|-------------------------------|------------------|---------|-------|-------------------|
| Variable                      | Regression coefficient | aOR    | 95% CI | P value           |
| Age                           | 0.064             | 1.07   | 1.05–1.08 | < 0.001          |
| Ethnicity                     |                   |        |       |                   |
| Malay                         | Reference         |        |       |                   |
| Chinese                       | -0.867            | 0.42   | 0.28–0.63 | < 0.001          |
| Indian                        | -0.530            | 0.59   | 0.37–0.94 | 0.028            |
| Indigenous                    | -0.088            | 0.92   | 0.16–5.21 | 0.921            |
| Marital status                |                   |        |       |                   |
| Married                       | Reference         |        |       |                   |
| Single                        | 0.511             | 1.67   | 0.93–2.99 | 0.085            |
| Educational level             |                   |        |       |                   |
| Tertiary                      | Reference         |        |       |                   |
| Primary or secondary          | 0.546             | 1.73   | 1.02–2.92 | 0.042            |
| None                          | 1.262             | 3.53   | 1.65–7.56 | 0.001            |
| Smoking status                |                   |        |       |                   |
| No                            | Reference         |        |       |                   |
| Yes                           | -0.035            | 0.97   | 0.65–1.43 | 0.859            |
| History of diabetes           |                   |        |       |                   |
| No                            | Reference         |        |       |                   |
| Yes                           | 0.313             | 1.37   | 1.01–1.87 | 0.048            |
| History of dyslipidaemia      |                   |        |       |                   |
| No                            | Reference         |        |       |                   |
| Yes                           | 0.256             | 1.29   | 0.93–1.80 | 0.131            |
| History of hypertension       |                   |        |       |                   |
| No                            | Reference         |        |       |                   |
| Yes                           | 0.494             | 1.64   | 1.12–2.39 | 0.010            |
| History of gout               |                   |        |       |                   |
| No                            | Reference         |        |       |                   |
| Yes                           | 0.891             | 2.44   | 1.37–4.34 | 0.002            |
| History of hydronephrosis     |                   |        |       |                   |
| No                            | Reference         |        |       |                   |
| Unilateral                    | 0.186             | 1.21   | 0.88–1.65 | 0.245            |
| Bilateral                     | 1.172             | 3.23   | 1.95–5.34 | < 0.001          |
| Serum uric acid               |                   |        |       |                   |
| Normal                        | Reference         |        |       |                   |
| Elevated                      | 1.209             | 3.35   | 2.43–4.61 | < 0.001          |
| Renal stone type              |                   |        |       |                   |
| Calcium oxalate               | Reference         |        |       |                   |
| Infection                     | 0.604             | 1.83   | 1.22–2.74 | 0.003            |
| Uric acid                     | 0.250             | 1.28   | 0.83–1.99 | 0.261            |
| Others                        | 0.878             | 2.41   | 1.38–4.20 | 0.002            |

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; aOR, adjusted odds ratio.
history [27]. Our findings revealed that sociodemographic factors such as ethnicity and lower education level were associated with reduced renal function among stone formers. These are in parallel with previous studies showing association of CKD ethnicity and socioeconomic status [29], owing to dietary patterns and health-related behaviours.

In the present study, high prevalence of cardiovascular risk factors such as diabetes, dyslipidaemia, hypertension, and central obesity were found among stone formers (ranging 52.2% to 75.4%). These cardiovascular risk factors except central obesity were associated with reduced renal function in the univariable analysis. Diabetes and hypertension remained as significant factors after multivariable adjustment. There are emerging evidence showing association of cardiovascular risk factors and its individual components with CKD and nephrolithiasis, alone [30–32] and in combination [33, 34]. The prevalence of CKD within Malaysian population increased from 9.1% in 2011 to 15.5% in 2018, attributing to the rising prevalence of non-communicable diseases and aging population in Malaysia [13]. The National Health and Morbidity Survey (NHMS) showed diabetic patients increased from 11.6% in 2006 to 18.3% in 2019 while the prevalence of raised blood cholesterol was 38.1% in 2019 compared to 20.7% in 2006 [35, 36]. Stone formers with reduced renal function in the present study were older than those of normal renal function (60 years old vs. 52 years old), suggesting old age may be responsible in increasing the risk of comorbidities related to CKD or increasing the susceptibility of stone formers with multiple comorbid conditions to CKD [33].

Hyperuricemia and gout were associated with nephrolithiasis [37, 38]. We observed a statistically significant association of reduced renal function with gout and increased serum uric acid level. This is consistent with previous study showing higher prevalence of hyperuricemia (aOR 9.8, 95% CI 4.3–22.0) and gout (aOR 5.9, 95% CI 2.2–15.7) among individuals with severe renal impairment compared to those without renal impairment in the US general population [39]. Uric acid is the by-product of exogenous and endogenous purine metabolism that usually exists in the form of salt as urate. Kidneys excrete about two-thirds of the uric acid load [40]. The rise of uric acid production and impaired renal uric acid excretion could result in hyperuricemia [41]. Hyperuricemia is therefore generally considered as a complication of renal dysfunction [40]. Interestingly, recent studies suggested the pathogenic role of uric acid in CKD progression rather than being a marker of impaired renal uric acid excretion alone [42]. In a cohort study involving 10,677 individuals with renal function eGFR ≥60 ml/min/1.73m² and negative proteinuria, patients with increased serum uric acid level had higher odds of developing renal disease which defined as an incidence of a decline in eGFR from ≥30% at baseline to <60 ml/min/1.73m² [43]. It was also demonstrated that the use of allopurinol or other urate-lowering therapy was able to slow the progression of renal disease in patients with hyperuricemia [44], CKD [45, 46] and gout [47].

In this study, we showed that infection stone were associated with reduced renal function, which is consistent with findings from previous studies [33, 48, 49]. It is suggested that loss of renal function amongst infection stone formers was attributed to recurrent urinary infection and high growth rate, occupying the entire renal collecting system rapidly [50, 51]. The level of renal function varies across different stones types. Uric acid stone formers had the lowest median eGFR after cystine stone formers in our study. This finding was in line with a previous study showing uric acid stone formers had significantly worse renal function compared to calcium stone formers or individuals without renal stone regardless of hyperuricemia status [18]. Chou et al. reported that renal function was significantly better in patients with calcium stones (i.e. calcium oxalate and calcium phosphate) than those of struvite or uric acid stone [51], suggesting an increased CKD risk amongst non-calcium stone formers. It is possible that urological procedures for stone such as PCNL may contribute to renal damage, prior to CKD stage as well as frequency and complexity of stone treatments [52]. Recurrent or multiple stone events
might expose stone formers to higher risk of renal impairment, potentially due to cumulative kidney injury from obstructive uropathy [53].

There are limitations to this multicentre study. First, causal relationships between nephrolithiasis and renal function could not be established in this study due to its cross-sectional study design. Second, the generalisability and extrapolation of these findings to other populations remain unknown. Third, renal function was estimated using eGFR based on a single serum creatinine measurement. This can potentially overestimate the prevalence of reduced renal function as eGFR could be fluctuated in the presence of stone [54]. The level of eGFR pre- and post-PNCL could be considered in the future study. Fourth, addition of more clinical information such as serum level of calcium, vitamin D & parathyroid hormone, urine culture results and history of drug consumption may increase the accuracy of the multivariable analysis.

The strength of this study are the large sample size (>1000 patients) and adequate representation from three major Asian ethnicities. There is a low rate of missing data (1.5–4.1%) except serum uric acid (18.1%), central obesity (10.2%), and renal stone type (15.2%). In addition, all the blood tests including fasting blood glucose, HbA1c and lipid profile as well as renal stone quantitative analysis were conducted in central laboratories to avoid testing discrepancies.

In summary, our study findings concluded that renal stone is a systemic disease with significant association observed between reduced renal function and cardiovascular risk factors such as hypertension and diabetes in a multi-ethnic Asian population. We recommend stone patients to undergo more aggressive screening for subclinical CKD. Similarly, clinicians may consider screening stone patients present with reduced renal function for cardiovascular risk factors.

Acknowledgments
We gratefully acknowledge the specialists, medical officers, nurses and other supporting staffs of Hospital Kuala Lumpur, Hospital Selayang and University Malaya Medical Centre for their cooperation and assistance in execution of the study. We also express our gratitude to all patients who agreed to participate in the study.

Author Contributions
Conceptualization: Selvalingam Sothilingam, Jasmine Lim.
Data curation: Seow Huey Choy, Selina Ann Nyanatay.
Formal analysis: Seow Huey Choy.
Funding acquisition: Selvalingam Sothilingam, Jasmine Lim.
Investigation: Seow Huey Choy, Selina Ann Nyanatay, Rohan Malek, Sathiyananthan J. R., Charng Chee Toh, Murali Sundram, Noor Ashani Md Yusoff, Poongkodi Nagappan, Shakirin Kamaruzaman, Wei Sien Yeoh, Teng Aik Ong.
Methodology: Selvalingam Sothilingam, Jasmine Lim.
Project administration: Selina Ann Nyanatay, Shakirin Kamaruzaman.
Resources: Rohan Malek, Sathiyananthan J. R., Charng Chee Toh, Murali Sundram, Noor Ashani Md Yusoff, Poongkodi Nagappan, Wei Sien Yeoh.
Supervision: Rohan Malek, Teng Aik Ong, Jasmine Lim.
Writing – original draft: Seow Huey Choy.
References

1. Abufaraj M, Xu T, Cao C, Waldhoer T, Seitz C, D’andrea D, et al. Prevalence and trends in kidney stone among adults in the USA: Analyses of National Health and Nutrition Examination Survey 2007–2018 Data. Eur Urol Focus. 2021; 7(6):1468–1475. https://doi.org/10.1016/j.euf.2020.08.011 PMID: 32900675

2. Zeng G, Mai Z, Xia S, Wang Z, Zhang K, Wang L, et al. Prevalence of kidney stones in China: an ultrasonography based cross-sectional study. BJU Int. 2017; 120(1):109–116. https://doi.org/10.1111/bju.13828 PMID: 28236332

3. Guha M, Banerjee H, Mitra P, Das M. The demographic diversity of food intake and prevalence of kidney stone diseases in the Indian Continent. Foods. 2019; 8(1):37. https://doi.org/10.3390/foods8010037 PMID: 30669549

4. Wang W, Fan J, Huang G, Li J, Zhu X, Tian Y, et al. Prevalence of kidney stones in mainland China: A systematic review. Sci Rep. 2017; 7(1):1–9. https://doi.org/10.1038/s41598-016-0028-x PMID: 28127051

5. Safdar OY, Alzahrani WA, Kurdi MA, Ghanim AA, Nagadi SA, Alghamdi SJ, et al. The prevalence of renal stones among local residents in Saudi Arabia. J Family Med Prim Care. 2021; 10(2):974. https://doi.org/10.4103/JFMPC.JFMP C_262_20 PMID: 31649451

6. Lohiya A, Kant S, Kapil A, Gupta SK, Misra P, Rai SK. Population-based estimate of urinary stones from Ballabgarh, northern India. Natl Med J India. 2017; 30(4):198–200. https://doi.org/10.4103/0970-258X.218671 PMID: 29162751

7. Cicerello E, Mangano MS, Cova G, Ciaccia M. Changing in gender prevalence of nephrolithiasis. Urologia J. 2021; 88(2):90–93. https://doi.org/10.1177/0391560320966206 PMID: 33084513

8. Rule AD, Lieske JC, Li X, Melton LJ, Krambeck AE. The ROKS nomogram for predicting a second symptomatic stone episode. J Am Soc Nephrol. 2014; 25(12):2878–2886. https://doi.org/10.1681/ASN.2013091011 PMID: 25104803

9. Alexander RT, Hemmelgarn BR, Wiebe N, Bello A, Morgan C, Samuel S, et al. Kidney stones and kidney function loss: a cohort study. BMJ. 2012; 345. https://doi.org/10.1136/bmj.e5287 PMID: 22936784

10. Chuang TF, Hung HC, Li SF, Lee MW, Pai JY, Hung CT. Risk of chronic kidney disease in patients with kidney stones—a nationwide cohort study. BMC Nephrol. 2020; 21(1):1–7. https://doi.org/10.1186/s12882-020-01950-2 PMID: 32698782

11. Bikbov B, Purcell CA, Levey AS, Smith M, Abdoli A, Abebe M, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2020; 395(10225):709–733.

12. Saminathan TA, Hooi LS, Yusoff MFM, Ong LM, Bavanand S, Hasani WSR, et al. Prevalence of chronic kidney disease and its associated factors in Malaysia: findings from a nationwide population-based cross-sectional study. BMC Nephrol. 2020; 21(1):1–11.

13. Ismail H, Manaf MRA, Gafor AHA, Zaher ZMM, Ibrahim AIN. Economic burden of ESRD to the Malaysian health care system. Kidney Int. Rep. 2019; 4(9):1261–1270. https://doi.org/10.1016/j.ekir.2019.05.016 PMID: 31517145

14. Eknoyan G, Laneire N, Eckardt K, Kasiske B, Wheeler D, Levin A, et al. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013; 3(1):5–14.

15. Negri AL, Spivacow R, Del Valle E, Pindull I, Marino A, Fradinger E, et al. Clinical and biochemical profile of patients with “pure” uric acid nephrolithiasis compared with “pure” calcium oxalate stone formers. Urol Res. 2007; 35(5):247–251. https://doi.org/10.1007/s00240-007-0109-1 PMID: 17786420

16. Heilberg IP. Treatment of patients with uric acid stones. Urolithiasis. 2016; 44(1):57–63. https://doi.org/10.1007/s00240-015-0848-0 PMID: 26645868

17. Tanaka Y, Hatakeyama S, Tanaka T, Yamamoto H, Narita T, Hamano I, et al. The influence of serum uric acid on renal function in patients with calcium or uric acid stone: a population-based analysis. PloS One. 2018; 13(2):e0182136. https://doi.org/10.1371/journal.pone.0182136 PMID: 28759444

18. Waikar SS, Srivastava A, Palsson R, Shafi T, Hsu C-y, Sharma K, et al. Association of urinary oxalate excretion with the risk of chronic kidney disease progression. JAMA Intern Med. 2019; 179(4):542–551. https://doi.org/10.1001/jamainternmed.2018.7980 PMID: 30830167
20. Karis E, Crittenden DB, Pillinger MH. Hyperuricemia, gout, and related comorbidities: cause and effect on a two-way street. South Med J. 2014; 107(4):235–241. https://doi.org/10.1097/SMJ.000000000000082 PMID: 24937517

21. Alberti G, Zimmet P, Shaw J, Grundy SM. The IDF consensus worldwide definition of the metabolic syndrome. Brussels: International Diabetes Federation. 2006; 23(5):469–480.

22. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF III, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150(9):604–612. https://doi.org/10.7326/0033-4819-150-9-2009090500-0006 PMID: 19418493

23. Teo BW, Xu H, Wang D, Li J, Sinha AK, Shuter B, et al. GFR estimating equations in a multiethnic Asian population. Am J Kidney Dis. 2011; 58(1):56–63. https://doi.org/10.1053/j.ajkd.2011.02.393 PMID: 21601325

24. National Cholesterol Education Program (US). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) 2002; 106(25):3143–421. Epub 2002/12/18. PMID: 12485966.

25. Malaysian Endocrine & Metabolic Society. Clinical practice guidelines on management of type 2 diabetes mellitus. 6th edition. 2020.

26. Ahmadi F, Etemadi SM, Lessan-Pezeshki M, Mahdavi-Mazdeh M, Ayati M, Mir A, et al. Contribution of stone size to chronic kidney disease in kidney stone formers. Int J Urol. 2015; 22(1):104–108. https://doi.org/10.1111/iju.12606 PMID: 25168662

27. Zhe M, Hang Z. Nephrolithiasis as a risk factor of chronic kidney disease: a meta-analysis of cohort studies with 4,770,691 participants. Urolithiasis. 2017; 45(5):441–448. https://doi.org/10.1007/s00244-016-0938-x PMID: 27837248

28. Shang W, Li L, Ren Y, Ge Q, Ku M, Ge S, et al. History of kidney stones and risk of chronic kidney disease: a meta-analysis. PeerJ. 2017; 5:e2907. https://doi.org/10.7717/peerj.2907 PMID: 28149686

29. Patzer RE, McClellan WM. Influence of race, ethnicity and socioeconomic status on kidney disease. Nat Rev Nephrol. 2012; 8(9):533. https://doi.org/10.1038/nrneph.2012.117 PMID: 22735764

30. Li Y, Xie D, Qin X, Tang G, Xing H, Li Z, et al. Metabolic syndrome, but not insulin resistance, is associated with an increased risk of renal function decline. Clin Nutr. 2015; 34(2):269–275. https://doi.org/10.1016/j.clnu.2014.04.002 PMID: 24792685

31. Kitiyakara C, Yamwong S, Cheepudomwit S, Domrongkitchaiporn S, Unkurapunun N, Pakpeankitvatana V, et al. The metabolic syndrome and chronic kidney disease in a Southeast Asian cohort. Kidney Int. 2007; 71(7):693–700. https://doi.org/10.1016/j.kint.2007.02.057 PMID: 17290290

32. Chen J, Munter P, Hamm LL, Jones DW, Batuman V, Fonseca V, et al. The metabolic syndrome and chronic kidney disease in US adults. Ann Intern Med. 2004; 140(3):167–174. https://doi.org/10.7326/0003-4819-140-3-200402030-00007 PMID: 14757614

33. Saucier NA, Sinha MK, Liang KV, Krambeck AE, Weaver AL, Bergstralh EJ, et al. Risk factors for CKD in persons with kidney stones: a case-control study in Olmsted County, Minnesota. Am J Kidney Dis. 2010; 55(1):61–68. https://doi.org/10.1053/ajkd.2009.08.008 PMID: 19853335

34. Keddis MT, Rule AD. Nephrolithiasis and loss of kidney function. Curr Opin Nephrol Hypertens. 2013; 22(4):390–396. https://doi.org/10.1097/MNH.0b013e32836214b9 PMID: 23736840

35. Institute for Public Health, National Institutes of Health, Ministry of Health Malaysia. National Health and Morbidity Survey (NHMS) 2019: Vol. 1: NCDs- Non Communicable Diseases: Risk Factors and other Health Problems. 2020.

36. Institute for Public Health, National Institutes of Health, Ministry of Health Malaysia. The Third National Health and Morbidity Survey (NHMS III) 2006, Diabetes Mellitus. 2008.

37. Roughley MJ, Belcher J, Mallen CD, Roddy E. Gout and risk of chronic kidney disease and nephrolithiasis: meta-analysis of observational studies. Arthritis Res Ther. 2015; 17(1):90. https://doi.org/10.1186/s13075-015-0610-9 PMID: 25889144

38. Kim S, Chang Y, Yun KE, Jung H-S, Lee S-J, Shin H, et al. Development of nephrolithiasis in asymptomatic hyperuricemia: a cohort study. Am J Kidney Dis. 2017; 70(2):173–181. https://doi.org/10.1053/j.ajkd.2017.01.053 PMID: 28410765

39. Krishnan E. Reduced glomerular function and prevalence of gout: NHANES 2009–10. PLoS One. 2012; 7(11):e50046. https://doi.org/10.1371/journal.pone.0050046 PMID: 23209642

40. Maiuolo J, Oppedissano F, Grattieri S, Muscoli C, Mollace V. Regulation of uric acid metabolism and excretion. Int J Cardiol. 2016; 213:8–14. https://doi.org/10.1016/j.ijcard.2015.08.109 PMID: 26316329

41. Su J, Wei Y, Liu M, Liu T, Li J, Ji Y, et al. Anti-hyperuricemic and nephroprotective effects of Rhizoma Dioscoreae septemlobae extracts and its main component dioscin via regulation of mOAT1, mURAT1 and mOCT2 in hypertensive mice. Arch Pharm Res. 2014; 37(10):1336–1344. https://doi.org/10.1007/s12272-014-0413-6 PMID: 24866061
42. Li L, Yang C, Zhao Y, Zeng X, Liu F, Fu P. Is hyperuricemia an independent risk factor for new-onset chronic kidney disease?: a systematic review and meta-analysis based on observational cohort studies. BMC Nephrol. 2014; 15(1):122. https://doi.org/10.1186/1471-2369-15-122 PMID: 25064611

43. Zhou F, Yu G, Wang G, Liu Y, Zhang L, Wang W, et al. Association of serum uric acid levels with the incidence of kidney disease and rapid eGFR decline in Chinese individuals with eGFR> 60 mL/min/1.73 m² and negative proteinuria. Clin Exp Nephrol. 2019; 23(7):871–879. https://doi.org/10.1007/s10157-019-01705-w PMID: 30734168

44. Levy GD, Rashid N, Niu F, Cheetham TC. Effect of urate-lowering therapies on renal disease progression in patients with hyperuricemia. J Rheumatol. 2014; 41(5):955–962. https://doi.org/10.3899/jrheum.131159 PMID: 24692523

45. Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincón A, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010; 5(8):1388–1393. https://doi.org/10.2215/CJN.01580210 PMID: 20538833

46. Siu YP, Leung KT, Tong MKH, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis. 2004; 44(5):799–805. PMID: 15492945

47. Desai RJ, Franklin JM, Spindle-Allen J, Solomon DH, Danaei G, Kim SC. An evaluation of longitudinal changes in serum uric acid levels and associated risk of cardio-metabolic events and renal function decline in gout. PLoS One. 2018; 13(2):e0193622. https://doi.org/10.1371/journal.pone.0193622 PMID: 29489919

48. Jungers P, Joly D, Barbey F, Choukrour G, Daoud M. ESRD caused by nephrolithiasis: prevalence, mechanisms, and prevention. Am J Kidney Dis. 2004; 44(5):799–805. PMID: 15492945

49. Moreira DM, Friedlander JI, Hartman C, Gershman B, Smith AD, Okeke Z. Association of estimated glomerular filtration rate with 24-h urinalysis and stone composition. Urolithiasis. 2016; 44(4):319–325. https://doi.org/10.1007/s00240-015-0837-6 PMID: 26573808

50. Joshi H, Kumar P, Timoney A. Citric acid (solution R) irrigation in the treatment of refractory infection (struvite) stone disease: is it useful? Eur Urol. 2001; 39(5):586–590. https://doi.org/10.1159/000052508 PMID: 11464042

51. Chou YH, Li CC, Hsu H, Chang WC, Liu CC, Li WM, et al. Renal function in patients with urinary stones of varying compositions. Kaohsiung J Med Sci. 2011; 27(7):264–267. https://doi.org/10.1016/j.kjms.2010.11.008 PMID: 21757143

52. Gambaro G, Croppi E, Bushinsky D, Jaeger P, Cupisti A, Ticinesi A, et al. The risk of chronic kidney disease associated with urolithiasis and its urological treatments: a review. J Urol. 2017; 198(2):268–273. https://doi.org/10.1016/j.juro.2016.12.135 PMID: 28286070

53. Dhondup T, Kittanamongkolchai W, Vaughan LE, Mehta RA, Chhina JK, Enders FT, et al. Risk of ESRD and mortality in kidney and bladder stone formers. Am J Kidney Dis. 2018; 72(6):790–797. https://doi.org/10.1053/j.jkd.2018.06.012 PMID: 30146423

54. Hirst JA, Montes MDV, Taylor CJ, Ordóñez-Mena JM, Ogburn E, Sharma V, et al. Impact of a single eGFR and eGFR-estimating equation on chronic kidney disease reclassification: a cohort study in primary care. Br J Gen Pract. 2018; 68(673):e524–e530. https://doi.org/10.3399/bjgp18X697937 PMID: 29970394