Development of a personalized diagnostic model for kidney stone disease tailored to acute care by integrating large clinical, demographics and laboratory data: the diagnostic acute care algorithm - kidney stones (DACA-KS)

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Abstract

Background: Kidney stone (KS) disease has high, increasing prevalence in the United States and poses a massive economic burden. Diagnostics algorithms of KS only use a few variables with a limited sensitivity and specificity. In this study, we tested a big data approach to infer and validate a ‘multi-domain’ personalized diagnostic acute care algorithm for KS (DACA-KS), merging demographic, vital signs, clinical, and laboratory information.

Methods: We utilized a large, single-center database of patients admitted to acute care units in a large tertiary care hospital. Patients diagnosed with KS were compared to groups of patients with acute abdominal/flank/groin pain, genitourinary diseases, and other conditions. We analyzed multiple information domains (several thousands of variables) using a collection of statistical and machine learning models with feature selectors. We compared sensitivity, specificity and area under the receiver operating characteristic (AUROC) of our approach with the STONE score, using cross-validation.

Results: Thirty eight thousand five hundred and ninety-seven distinct adult patients were admitted to critical care between 2001 and 2012, of which 217 were diagnosed with KS, and 744 6 with acute pain (non-KS). The multi-domain approach using logistic regression yielded an AUROC of 0.86 and a sensitivity/specificity of 0.81/0.82 in cross-validation. Increase in performance was obtained by fitting a super-learner, at the price of lower interpretability. We discussed in detail comorbidity and lab marker variables independently associated with KS (e.g. blood chloride, candidiasis, sleep disorders).

Conclusions: Although external validation is warranted, DACA-KS could be integrated into electronic health systems; the algorithm has the potential used as an effective tool to help nurses and healthcare personnel during triage or clinicians making a diagnosis, streamlining patients’ management in acute care.

Keywords: Diagnostic algorithm, Kidney stones, Big data analysis
Background

Kidney stone (KS) disease prevalence has increased in the United States from 5.2% (6.3% males and 4.1% females) in 1994 to 8.8% (10.6% males and 7.1% females) in 2012 [1]. Since it is one of the costliest urologic diseases in the United States, an increase in prevalence poses a huge economic burden on society. The cost of diagnosis, treatment and prevention of KS disease in 2007 was estimated to be ~$4 billion and, due to population growth alone, is projected to increase by more than $780 million by 2030 [2, 3]. The presence of KS also places the individuals at increased risk of development of chronic kidney disease. In a prospective cohort study, those who had KS was associated with a 50–67% higher risk of developing chronic kidney disease as compared to those who did not have, KS group also had twice the risk of developing end-stage renal disease [4].

The emergency department (ED) is a common place where patient with KS are evaluated and diagnosed. During the past two decades, a significant increase in ED visits with stone-related symptoms has been observed [5], with over 1.3 million individuals per year presenting to the ED with KS in the United States. The clinical presentation to the ED with KS commonly involves acute back, flank or groin pain, nausea, vomiting and sometimes blood in urine. The workup may include initial lab tests such as complete blood count with differential, comprehensive metabolic panel, and urine analysis; but often these tests are not promptly measured or are inappropriately interpreted [5].

A cross-sectional analysis of the 2007–2010 National Health and Nutrition Examination Survey (NHANES) dataset suggests that obesity, diabetes, and gout all have a significant positive association with kidney stone history [1]. Results from the Nurses’ Health Study, a large population-based longitudinal study (years 2001–2012) demonstrated that high body-mass index (BMI), cholecystitis, diabetes and specific dietary factors are associated with a higher risk of KS formation in females [6]. In 2014, a clinical prediction score -named STONE- was derived and validated in retrospective and prospective cohorts [7]. The STONE score includes five variables: male sex, short duration of pain, non-black race, presence of nausea or vomiting, and microscopic hematuria. The STONE score was also externally validated and showed good validity in patients with flank pain [8]. An updated STONE-PLUS score, augmented by point-of-care limited ultrasonography assessing hydronephrosis, was recently released and tested prospectively on an ED population sample, with only a moderate improvement in risk stratification [9]. As KS disease is multifactorial in nature, we hypothesized that an approach incorporating laboratory data and additional clinical characteristics would dramatically improve a KS diagnostic model, leading to earlier diagnosis and a better understanding of its complex etiology. In addition, this approach could reduce the number of unnecessary radiographic testing i.e. CT scans, in the acute care setting.

In this study, we tested a big data approach, merging demographic, vital signs, clinical, and laboratory information, to infer and validate a ‘multi-domain’ personalized diagnostic score for KS. We utilized a large, single-center database of patients admitted to ED and other intensive/acute care units in a large tertiary care hospital (over 58,000 admissions with majority admitted through ED). We analyzed the information domains individually (e.g. only comorbidities, or only lab tests), together, and compared our approach with the STONE score. A number of statistical and machine learning models were fit and compared to optimize performance. Using this multi-domain integration approach our goal was to significantly improve the sensitivity and specificity of KS diagnosis in acute settings.

Methods

Study population

The study population comprised individuals admitted to critical care units at the Beth Israel Deaconess Medical Center in Boston, Massachusetts, United States, between 2001 and 2012. Data are stored electronically in the Medical Information Mart for Intensive Care (MIMIC-III) database, which is available to the public upon request, upon Collaborative Institutional Training Initiative (CITI) training, and license agreement for full download and research [10]. MIMIC-III includes information on: demographics; clinical diagnoses and procedures encoded with the International Classification of Diseases ver. 9 (ICD-9) ontology; vital sign measurements made at the bedside (~ 1 data point per hour); laboratory test results; medications; caregiver notes; imaging reports; mortality (both in- and out-of-hospital).

This is a secondary data analysis. We used the MIMIC-III ver. 1.4, released on September 2nd, 2016. Our study included patients aged 18 years and older, divided into four groups based on the ICD-9 diagnoses during hospitalization: (a) KS cases (ICD-9592, including sub-codes 592.0, 592.1, 592.9); (b) patients diagnosed with genitourinary diseases (GUD) except KS (any ICD-9 code in the intervals 580–591 or 593–599), e.g. patients with nephritis, nephrotic syndrome, nephrosis; (c) patients admitted to acute care with other conditions (OTH) who did not have any KS or GUD diagnosed (any ICD-9 code not including 580–599) to represent a general patient population; (d) patients admitted with acute localized pain (ALP) of abdominal (ICD-9 code: 789.0), back (ICD-9 code: 724.2), flank, or groin (identified through patients’ electronic chart record). In addition to ICD-9 codes, we also examined recorded
charted events on ALP from the dataset. Patients with both KS and GUD codes were put into the KS group. Each patient was associated to a covariate vector of demographic info, vital signs, clinical diagnoses, procedures, medicaments, and laboratory tests performed during hospitalization.

**Statistical analysis**

Descriptive analysis was used to assess demographic characteristics (e.g. gender, age, insurance status, and religion), vital signs (e.g. BMI, blood pressure), laboratory tests (e.g. creatinine), and distribution of ICD-9 diagnoses at admission and during hospitalization. We also calculated the Charlson Comorbidity Index (CCI) using Deyo’s algorithm [11], and the estimated glomerular filtration rate (eGFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation equation [12].

Due to a low frequency of KS, we included only ICD-9 diagnostic codes that were occurred in less than 5 counts of the KS group, and lab tests that performed in at least 50% of the KS formers. Missing values were imputed via population median/mode. Univariate analysis was conducted to assess differences between KS and GUD/OTH/ALP groups on demographics, ICD-9 diagnoses, and lab tests, using Student’s t-test, Wilcoxon rank test, or chi-square test, where appropriate. Significance p-values were adjusted using False Discover Rate (FDR) correction [13].

In order to infer a KS diagnostic score, we fitted a collection of multivariable logistic regression models with the GUD, OTH or ALP as negative examples, using different input covariate domains. Specifically, we evaluated seven models: (a) demographic variables and vital signs (including blood pressure, heart rate and body temperature) (b) CCI, plus demographic variables; (c) eGFR alone; (d) ICD-9 diagnosis (top-25 as selected by the univariate filter, i.e. the top-25 variables that were differently distributed between KS and other groups), plus demographic variables; (e) laboratory tests (top-25 as selected by the univariate filter), plus demographic variables; (f) ICD-9 diagnosis and laboratory tests (top-50 as selected by the univariate filter), plus all other variables included in models (a) to (e); (g) stepwise (forward-backward) selection of model (f); (h) STONE model. Note that ICD-9 codes used to define the GUD were not used as input covariates to any of the models, except for the STONE model where hematuria (ICD-9 code 599.7) is a covariate. Also, the duration of pain to presentation in the STONE score could not be precisely ascertained from our data; we used ICD-9 codes in the 338 s family plus codes 780.96 and 789.0, excluding chronic pain entries, using a weight of 2 (the STONE score a < 6 h pain is weighted 3 and 6–24 h pain is weighted 1, but duration of pain was not available in our data set). In addition to ICD-9 codes, we also used charted events to identify pain events. For nausea/vomiting we used ICD-9797.0 codes. In a sensitivity analysis, we also evaluated the contribution of GUD codes to overall performance of models (d) to (g).

Model comparison, evaluation, and selection were carried out using a 10-fold cross-validation framework [14], comparing performance index (see below) distributions from the repeated sampling folds using Bengio and Nadeau’s correction to the Student’s t-test [15], however, th.

In addition to logistic regression, we also fit a number of machine learning techniques on the full variable set as in model (f). In details: (i) a decision tree by means of the C4.5 algorithms [16]; (ii) LogitBoost algorithm in conjunction to logistic regression [17]; (iii) a random forest (optimizing number of trees up to 1000) [18]; (iv) a super learner stacking all the above methods plus a single-rule linear model, internally optimized via 5-fold cross-validation [19]. Given the high class imbalance, in addition to the standard model fit, we also used the synthetic minority over-sampling technique (SMOTE) internally to the cross-validation [20]. The univariate feature selection for these machine learning algorithms was done internally within the cross-validation setting.

The performance and discriminative ability of models was assessed using sensitivity (true positive rate), specificity (true negative rate), and the area under the receiver operating characteristic (AUROC), which is the expectation that a uniformly drawn random positive case is ranked before a uniformly drawn random negative (an area of 100% represents a perfect test; an area of 50% represents a worthless test) [21]. The optimal sensitivity/specificity cutoff was chosen based on the maximal of the Youden’s J statistic [22]. All statistical analyses were conducted using SAS software ver. 9.4 (SAS Institute Inc., Cary, NC, USA) and Weka ver. 3.9 [23].

**Results**

There were 38,597 distinct adult patients (> 18-year-old) in the MIMIC-III database admitted to critical care units between June 2001 to October 2012 (90% from emergency room admission, 8% elective surgery, and 2% urgent care services), of which 217 were diagnosed with KS, 14,391 with GUD, 23,931 as OTH who did not have any GUD nor KS, and 7,446 as ALP with abdominal, back, flank, groin pain.

Table 1 summarizes population characteristics among the three groups. There was an excess of females in the KS group as compared to other three groups (45.2% vs. 54.3%, 58.1% and 52.4%, respectively, p < 0.05). Most sample population were admitted through emergency or urgent (84.2%). The distribution of race was similar between KS and GUD, but comparing to OTH and ALP, KS had a higher proportion of white (76.5% vs. 71.1%...
and 72.7%) and black African American (10.6% vs 6.0% and 7.4%, \( p = 0.008 \)). The median eGFR in KS was 65.3, lower than in OTH (93.1, \( p = 0.0013 \)) and ALP (77.3, \( p < 0.0001 \)), but higher than GUD (49.3, \( p < 0.0001 \)).

The median (IQR) STONE score in KS formers was 4, higher than in GUD (2, \( p < 0.0001 \)) or in OTH (2, \( p < 0.0001 \)), but not different from ALP (4, \( p = 0.46 \)).

Figure 1 shows the comparison of the distributions of age categories by gender, CCI and BMI in the three groups of KS, GUD and OTH. The highest rates of KS were seen in the age group 71–80 for both males (30%) and females (23%), and the rates of KS increased significantly after 50 years-of-age in males, while in females a steady increase was observed after 30 years-of-age with a leveling off after 70 years. As for BMI, KS had the highest overall distribution (median 29.1) among all four groups (median of GUD, OTH and ALP: 27.5, 27.2, 27.0), it also had the highest proportion of obese (17% vs 11% in GUD, 9% in OTH and 2% in ALP, all \( p \)-values < 0.05).

Figure 2 shows the most frequent ICD-9 diagnoses in all four groups of KS, GUD, OTH and ALP, collating the top-10 frequencies of each group. Essential hypertension (45.8%), disorders of fluid, electrolyte, and acid-base balance (44%), and septicemia (41.7%) were most frequently diagnosed conditions among KS patients. Some of these high frequency comorbidities also had different distribution in KS compared to other groups. For example, rates of septicemia and certain adverse effects (including anaphylaxis, unspecified medication adverse effects, unspecified allergy, etc.) in KS were higher than in GUD, OTH or ALP (18%, 36% and 23% higher respectively). The proportion of essential hypertension was 10% higher in KS than GUD or ALP but was similar to the rate in OTH; heart failure and hypertensive renal disease had much lower rates (14% and 16% less respectively) in KS than in GUD, but the rates were higher in KSF comparing to OTH (8% and 10% higher).

When looking at the STONE variables, we found that hematuria was positively associated with KS (7.4% vs. 4.6% in GUD, \( p = 0.051 \), and vs. 1.1% in OTH, \( p < 0.0001 \), and vs. 1.5% in ALP, \( p < 0.0001 \)); 98.6% of KS formers had experienced pain while 53.1% of GUD and 57.6% of OTH had pain events (both \( p < 0.0001 \)); 0.92% of KS formers had vomiting

| Table 1 Characteristics of the study population (n = 38,597), stratified by outcome group | kidney stones (KS) | other genitourinary diseases (GUD) | other conditions (OTH) | acute localized pain (ALP) |
| --- | --- | --- | --- | --- |
| Total | 217 | 14,391 | 23,931 | 7446 |
| Gender |  |  |  |  |
| Male | 45.2% (98) | 54.3% (7816) | 58.1% (13895) | 52.4% (3902) |
| Female | 54.8% (116) | 45.7% (6430) | 41.9% (10072) | 47.6% (3544) |
| Ethnicity |  |  |  |  |
| White | 76.5% (166) | 72.0% (10359) | 71.1% (17007) | 72.7% (5413) |
| Black | 10.6% (23) | 10.4% (1493) | 6.0% (1445) | 7.4% (549) |
| Hispanic | 3.2% (7) | 2.9% (416) | 3.5% (833) | 3.1% (231) |
| Asian | 1.4% (3) | 2.5% (358) | 2.3% (555) | 1.7% (124) |
| Other | 8.3% (18) | 12.2% (1765) | 17.1% (4091) | 15.2% (1129) |
| Insurance |  |  |  |  |
| Medicare/Medicaid/Government | 67.3% (146) | 77.6% (11164) | 57.8% (13837) | 64.7% (4814) |
| Self pay/Private | 32.3% (70) | 21.7% (3130) | 40.4% (9671) | 34.4% (2560) |
| Missing | 0.5% (1) | 0.7% (97) | 1.8% (423) | 1.0% (72) |
| Admission type |  |  |  |  |
| Elective | 9.2% (20) | 8.2% (1176) | 20.2% (4841) | 16.0% (1193) |
| Emergency | 89.4% (194) | 89.6% (12895) | 76.9% (18406) | 80.7% (6005) |
| Urgent | 1.4% (3) | 2.2% (320) | 2.9% (684) | 3.3% (248) |
| Median (IQR) |  |  |  |  |
| Age | 67 (56–77) | 72 (59–82) | 62 (50–75) | 64 (51–77) |
| BMI | 29.1 (28.3–30.5) | 27.5 (26.9–27.6) | 27.2 (27.2–27.2) | 27.0 (26.9–27.1) |
| Charlson Index | 1 (0–2) | 2 (1–4) | 1 (0–2) | 1 (0–3) |
| eGFR | 50.8 (33.4, 81.9) | 38.9 (22.5, 62.3) | 82.5 (59.1, 98.7) | 65.1 (37.3, 93.9) |
| STONE | 4 (2–4) | 2 (2–4) | 2 (2–4) | 4 (2–4) |
and 0.46% had nausea recorded, and the percentages of vomiting and nausea in KS were slightly higher than in other three groups. Hydronephrosis (variable from STONE-PLUS) was also positively associated with KS (35.94% vs. 1.54% in GUD, \( p < 0.0001 \) and vs. 0% in OTH, \( p < 0.0001 \)).

Next, we performed univariate analysis of ICD-9 diagnosis and lab tests comparing KS with GUD/OTH/ALP. A total of 940 distinct three-letter ICD-9 codes were identified in the whole study population; after code filtering based on low frequency (<5 cases in KS), 83 variables remained. For laboratory tests, a total of 754 entries were found, further condensed to 637 by manual inspection of physicians, and reduced to 69 after frequency filtering. The frequencies of missing values of these included lab tests ranges from 0 to 45%, 66.0% and 45.2% in GUD, OTH and ALP respectively, with the majority of them have less than 50% of missing.

Table 2 shows frequencies of the top ICD-9 diagnosis identified through univariate analysis, selecting those with an FDR-adjusted \( p \)-value below 0.1 (up to the top-25). Overall, 7 ICD-9 were differentially distributed.
between KS and GUD at the 5% FDR level, while 25 of them were found different between KS and OTH or ALP at the same significance level. Out of the 69 lab tests performed in more than half of KS patients, 43, 50, and 25 showed a significant (5% FDR level) mean or distribution location shift between KS vs. GUD, KSF vs. OTH, and KSF vs. ALP, respectively. The top-25 lab tests rank is shown in Table 3.

In order to derive a multi-domain diagnostic model of KS diagnosis, we fitted different logistic models on selected covariate input domains, as specified in the Methods section, and compared against the STONE. Table 4 summarizes the performance indices for models (a) through (h), showing average (st.dev.) AUROC, sensitivity, specificity across 10-fold cross-validation runs (i.e. results obtained on the test data), along with the best Youden’s J. Figure 3 (top panels) shows the ROC curves for each model, also obtained by averaging the 10 tests sets, for the KS vs. GUD, KS vs. OTH, and KS vs. ALP data samples. Overall, model (f), i.e. the top-ranked ICD-9 diagnosis and laboratory tests plus demographic variables, and model (g), i.e. the stepwise selection of features included in model (f), showed the best performance, with AUROCs ~ 80%. All other models were significantly less performant (adjusted \( p < 0.05 \)) than these two. Following cross-validated AUROC ranking, the second best-performing models were those with top-ranked ICD-9 codes (d), laboratory tests (e), CCI (b), eGFR (c), and demographics alone (a).

Notably, models using top-ranked ICD-9 diagnostic codes showed high sensitivity and moderate specificity, while models using top lab tests showed moderate sensitivity and high specificity, while both high sensitivity and high specificity were achieved in the multi-domain models. The STONE model (h) yielded relatively low AUROC (62% for KS vs. GUD, 64% for KS vs. OTH, and 61% for KS vs. ALP).

When we added the ICD-9 code for hematuria and other GUD codes to the set of input variables for models (f) and (g), performance increased significantly: For KS

| ICD-9 code | Condition | frequency in kidney stones (KS) | other genitourinary diseases (GUD) frequency | other conditions (OTH) frequency | acute localized pain (ALP) frequency |
|-----------|-----------|-------------------------------|------------------------------------------|-------------------------------|---------------------------------|
| 401       | Essential hypertension        | 45.6% (99)                     | 35.4% (5101)                             | 48.5% (11447)                 | 37.6% (2797)                    |
| 276       | Disorders of fluid, electrolyte, and acid-base balance | 43.8% (95) | 45.6% (6565) | 18.3% (4375) | 0.02 | 27.9% (2047) | 0.0001 |
| 38        | Septicaemia                     | 41.5% (90)                      | 23.4% (3361)                             | < 0.0001                     | 5.4% (1297)                     | < 0.0001 |
| 995       | Certain adverse effects         | 39.6% (86)                      | 21.4% (3078)                             | < 0.0001                     | 4.8% (1159)                     | < 0.0001 |
| 785       | Symptoms involving cardiovascular system | 24.9% (54) | 18.5% (2664) | 0.09 | 5.7% (1353) | < 0.0001 |
| 428       | Heart failure                   | 24.9% (54)                      | 38.3% (5508)                             | 0.00                          | 16.2% (3867)                    | 0.002 |
| 41        | Other bacteria infections       | 21.2% (46)                      | 16.3% (2350)                             | 0.14                          | 3.1% (752)                      | < 0.0001 |
| 287       | Purpura and other hemorrhagic conditions | 12.9% (28) | 11.7% (1680) | 0.76 | 5.1% (1211) | < 0.0001 |
| 790       | Nonspecific findings on examination of blood | 12.0% (26) | 9.8% (1413) | 0.54 | 5.2% (1243) | < 0.0001 |
| 403       | Hypertensive renal disease      | 11.1% (24)                      | 27.0% (3892)                             | < 0.0001                     | 1.2% (278)                      | < 0.0001 |
| 278       | Obesity and other hyperalimentation | 10.1% (22) | 6.0% (863) | 0.08 | 4.7% (1121) | 0.001 |
| 311       | Depressive disorder, not elsewhere classified | 10.1% (22) | 7.7% (1104) | 0.77 | 5.9% (1403) | 0.01 |
| 300       | Neurotic disorders              | 9.2% (20)                       | 5.68% (817)                              | 0.08                          | 5.71% (1366)                    | 0.03 |
| 327       | Sleep disorders                 | 9.2% (20)                       | 5.4% (778)                               | 0.09                          | 3.5% (843)                      | < 0.0001 |
| 112       | Candidiasis                     | 8.8% (19)                       | 4.3% (619)                               | 0.02                          | 2.0% (479)                      | < 0.0001 |
| 416       | Chronic pulmonary heart disease | 7.8% (17)                       | 6.9% (989)                               | 0.77                          | 3.4% (809)                      | 0.001 |
| 799       | Decreased libido and other ill-defined conditions | 7.4% (16) | 4.7% (668) | 0.19 | 2.4% (569) | < 0.0001 |
| 788       | Symptoms involving urinary system | 7.4% (16) | 5.7% (820) | 0.77 | 3.0% (712) | 0.001 |
| 288       | Diseases of white blood cells   | 6.0% (13)                       | 4.7% (674)                               | 0.77                          | 2.6% (629)                      | 0.001 |
| 574       | Cholelithiasis                  | 5.5% (12)                       | 2.9% (419)                               | 0.11                          | 1.6% (392)                      | < 0.0001 |
| 570       | Acute and subacute necrosis of liver | 4.1% (9) | 5.0% (717) | 0.76 | 0.8% (184) | < 0.0001 |
| 345       | Epilepsy                        | 3.7% (8)                        | 3.4% (491)                               | 0.87                          | 2.9% (688)                      | 0.48 |
| 346       | Migraine                        | 2.8% (6)                        | 0.79% (113)                              | 0.02                          | 1.32% (316)                     | 0.11 |

* first 25 ICD-9 codes or those with a false discovery rate-adjusted p-value< 0.05 are shown
### Table 3: Top-ranked laboratory tests differentially associated with KS vs. GUD / OTH / ALP

| Lab test item                  | kidney stones (KS) | other genitourinary diseases (GUD) | other conditions (OTH) | acute localized pain (ALP) |
|--------------------------------|-------------------|-----------------------------------|------------------------|---------------------------|
|                                | mean (Median)     | mean (Median)                     | p-value*               | mean (Median)             | p-value*               |
| **Urine**                      |                   |                                   |                        |                           |                        |
| White Blood Cells (WBC) (#/hpf)| 5.5 (3.1, 6.2)    | 3.0 (1.7, 2.9)                    | < 0.0001               | 15 (1.5, 1.5)             | < 0.0001               |
| Red Blood Cells (RBC) (#/hpf)  | 5.8 (3.3, 6.2)    | 3.4 (1.7, 3.3)                    | < 0.0001               | 19 (1.4, 1.4)             | < 0.0001               |
| Creatinine (mg/dL)             | 800 (730, 73.0)   | 84.7 (70, 86)                     | 0.03                   | 779 (75, 75)              | 0.03                   |
| Protein (mg/dL)                | 40 (3.4, 4.2)     | 3.9 (3.4, 3.4)                    | 0.03                   | 35 (3.4, 3.4)             | < 0.0001               |
| pH                             | 60 (5.5, 6.5)     | 5.8 (5.2, 6.2)                    | < 0.0001               | 60 (5.5, 6.5)             | 0.86                   |
| **Blood**                      |                   |                                   |                        |                           |                        |
| Bands                          | 45 (20, 3.8)      | 2.5 (1, 0.9)                      | < 0.0001               | 15 (0.8, 0.8)             | < 0.0001               |
| Potassium (mEq/L)              | 41 (3.9, 4.1)     | 4.3 (4.0, 4.4)                    | < 0.0001               | 41 (3.9, 4.2)             | 0.09                   |
| Lipase (U/L)                   | 67.1 (26.0, 33.0) | 62.6 (30.0, 42.0)                 | 0.03                   | 44.9 (31.0, 31.0)         | < 0.0001               |
| Magnesium (mEq/L)              | 20 (1.8, 2.1)     | 2.1 (1.9, 2.2)                    | < 0.0001               | 20 (1.9, 2.1)             | 0.03                   |
| Glucose (mg/dL)                | 1460 (137, 137.3) | 143.6 (127, 141.0)                | 0.03                   | 1395 (127, 139.7)         | 0.08                   |
| Creatine Kinase, MB Isoenzyme (ng/mL) | 85 (40, 50) | 0.0 (40, 68)                     | 0.03                   | 115 (50, 50)              | 0.32                   |
| Red Cell Distribution Width (RDW) (%) | 149 (13.7, 15.7) | 15.7 (14.2, 16.7)                | < 0.0001               | 145 (13.4, 15.2)          | 0.001                  |
| Total CO2 (mEq/L)              | 240 (22.0, 25.5)  | 24.8 (22.7, 26.9)                 | 0.03                   | 25.9 (24.7, 27.0)         | < 0.0001               |
| Red Blood Cells (cells/mcL)    | 3.7 (3.3, 4.0)    | 3.5 (3.2, 3.8)                    | < 0.0001               | 3.7 (3.3, 4.1)            | < 0.0001               |
| Chloride (mEq/L)               | 1026 (1013, 1037) | 101.9 (1005, 1033)                | 0.001                  | 1019 (1005, 1033)         | < 0.0001               |
| Urea Nitrogen (mg/dL)          | 257 (141, 30.7)   | 34.5 (19.5, 44.4)                 | < 0.0001               | 178 (120, 210)            | < 0.0001               |
| Creatinine (mg/dL)             | 1.4 (0.8, 16)     | 1.9 (1.0, 2.1)                    | 0.03                   | 0.8 (0.7, 1.0)            | < 0.0001               |
| Albumin (g/dL)                 | 3.3 (2.9, 36)     | 3.1 (2.8, 3.5)                    | 0.002                  | 3.5 (3.3, 3.7)            | < 0.0001               |
| Phosphate (mg/dL)              | 3.3 (2.8, 3.7)    | 3.7 (3.1, 4.1)                    | < 0.0001               | 3.3 (3.2, 3.6)            | 0.60                   |
| Oxygen Saturation (mm Hg)      | 90.1 (92.0, 920)  | 90.3 (90.4, 938)                  | 0.78                   | 93.4 (95.3, 95.3)         | < 0.0001               |
| Base Excess (mEq)              | -1.6 (-1.4, 7.3)  | -1.0 (-5.0, -2.5)                 | 0.15                   | 0.1 (0.1, 0.0)            | < 0.0001               |
| pO2 (kPa)                      | 74 (74, 74)       | 7.4 (74, 74)                      | 0.44                   | 7.4 (74, 74)              | < 0.0001               |
| Bicarbonate (mEq/L)            | 48 (46, 49)       | 4.8 (46, 50)                      | 0.79                   | 5.1 (49, 53)              | < 0.0001               |
| Lactate Dehydrogenase (LD) (IU/L) | 291.9 (2373, 2500) | 399.4 (2303, 3200)             | 0.08                   | 2724 (2357, 2357)         | < 0.0001               |

* first 25 lab items or those with a false discovery rate-adjusted p-value < 0.1 are shown
vs. GUD, model (g) achieved AUROC of 88% \((p < 0.0001)\) with sensitivity of 77% and specificity of 87%; for KS vs. OTH, model (g) achieved AUROC of 98% \((p < 0.0001)\), with sensitivity of 88% and specificity of 98%; for KS vs. ALP, model (g) achieved AUROC of 87% \((p < 0.0001)\), with sensitivity of 81% and specificity of 82%. Model (f) had very similar performance (not shown). However, these GUD variables were measured concurrently with KS, so we did not include them in our final prediction model, but it could be used as input if these GUD variables happened in one’s history to improve the predictivity and performance of the models.

When we applied the machine learning techniques, using the same cross-validation settings, for the comparison between KS and GUD or OTH, we did not observe a substantial increase in performance indices with the usage of the LogitBoost selector in alternative to the stepwise, but an increased performance was observed for KS vs. ALP \((p < 0.0001)\). The variables selected by the LogitBoost were concordant with the variables selected from stepwise logistic regression model (g), although the LogitBoost tended to select a few more. The decision tree showed a peculiar behavior as compared to the logistic regression, with increased sensitivity at higher specificity but then lower plateau. The random forest showed higher (almost perfect) AUROC and sensitivity/specificity (significant below the 0.0001 level with respect to the logistic regression and decision tree) and the super learner was comparable to the random forest. In fact, the highest weight of the super learner was that of the random forest, followed by the decision tree, a single rule, and the LogitBoost. The bottom panels of Fig. 3 show the cross-validated ROC curves corresponding to KS vs. GUD, KS vs. OTH, and KS vs. ALP. The decision tree for KS vs. ALP is depicted in Fig. 4. Using the SMOTE, performance results for all models were lower but ranking similar (not shown).

| Model/Outcome | Model/Outcome | AUC | Sensitivity | Specificity | J  |
|---------------|---------------|-----|-------------|-------------|----|
| Kidney stones (KS) vs. Other Genitourinary Diseases (GUD) | Demographic | 0.63 (0.02) | 0.69 | 0.51 | 0.20 |
|               | Charlson’s comorbidity index | 0.69 (0.02) | 0.69 | 0.62 | 0.31 |
|               | eGFR | 0.62 (0.02) | 0.65 | 0.56 | 0.21 |
|               | ICD | 0.74 (0.02) | 0.75 | 0.63 | 0.38 |
|               | Labs | 0.76 (0.02) | 0.67 | 0.74 | 0.41 |
|               | All | 0.81 (0.02) | 0.75 | 0.76 | 0.51 |
|               | All (Stepwise) | 0.80 (0.02) | 0.76 | 0.71 | 0.47 |
|               | STONE | 0.62 (0.02) | 0.55 | 0.64 | 0.19 |
| Kidney stones (KS) vs. Other Conditions (OTH) | Demographic | 0.65 (0.02) | 0.64 | 0.62 | 0.27 |
|               | CCI | 0.65 (0.02) | 0.68 | 0.57 | 0.25 |
|               | eGFR | 0.71 (0.02) | 0.59 | 0.75 | 0.35 |
|               | ICD | 0.82 (0.02) | 0.68 | 0.87 | 0.55 |
|               | Labs | 0.90 (0.01) | 0.81 | 0.87 | 0.68 |
|               | All | 0.92 (0.01) | 0.90 | 0.80 | 0.70 |
|               | All (Stepwise) | 0.92 (0.01) | 0.90 | 0.81 | 0.71 |
|               | STONE | 0.64 (0.02) | 0.62 | 0.65 | 0.27 |
| Kidney stones (KS) vs. AcuteLocalized Pain (ALP) | Demographic | 0.60 (0.02) | 0.71 | 0.47 | 0.18 |
|               | Charlson’s comorbidity index | 0.62 (0.02) | 0.60 | 0.61 | 0.21 |
|               | eGFR | 0.57 (0.02) | 0.59 | 0.44 | 0.15 |
|               | ICD | 0.77 (0.02) | 0.74 | 0.69 | 0.43 |
|               | Labs | 0.85 (0.02) | 0.66 | 0.90 | 0.56 |
|               | All | 0.88 (0.01) | 0.78 | 0.85 | 0.63 |
|               | All (Stepwise) | 0.86 (0.01) | 0.81 | 0.82 | 0.63 |
|               | STONE | 0.61 (0.02) | 0.58 | 0.60 | 0.18 |
The final model of choice was the stepwise-selected model (g), because in conjunction with optimal performance, it included fewer variables than model (f) (15 variables for each comparison vs. 50 variables in model (f)). Table 5 displays the final model (with odds ratios and confidence intervals) which we name as the Diagnostic Acute Care Algorithm for Kidney Stones (DACA-KS). The stepwise regression for KS vs. GUD yielded a few nonspecific predictors (e.g. nonspecific findings on examination of blood (ICD-9: 790), Other complications of procedures (ICD-9: 998)) which were removed without loss in performance. In addition, although random forest and super learner showed better performance, given the high class imbalance we have in the sample population, we cannot sure about the generalizability of these models in different dataset, so we focused more on interpretability especially when the logistic regression model had good performance as well. In fact, the SMOTE performance estimates of the super learner as well as of the random forest are lower.

Discussion

In this large sample of individuals admitted to acute care between 2000 and 2012, we aimed to infer a multi-domain, personalized, diagnostic algorithm risk assessment for KS disease. With a robust model collection and selection framework, under cross-validation settings, we demonstrated that the integrated model improves both specificity and sensitivity as compared to a single domain model. Also, it includes more extensive parameters compared to the STONE score. The STONE score utilizes presentations of KS-related symptoms (pain, hematuria, nausea/vomiting) and two demographic predictors (gender and race). In our sample population, only a small proportion of (KS) patients had hematuria and nausea/vomiting present or recorded. Our study evaluated thousands of potential predictors among the different domains, comparing relative proportions and shifts in distributions between KS formers and the GUD, OTH and ALP groups, our model can make personalized prediction for each individual based on his/her parameters from different domains. The features used in our final models are usually routinely tested in critical care.
unit, or tested at admission, therefore, all information to implement our model should be available in an ICU setting, and can be easily adapted to different clinical settings by adding or removing features. We report a series of novel findings in KS that are significantly different than GUD, OTH and ALP populations and which could aid in the triage of patients when they present to the ED or are admitted/transferred into critical care. A number of these variables are worth of discussion in detail.

In our study cohort, we found that KS peaked at the 7th decade of age; with variation of prevalence at different age groups between both genders, overall, we found a higher prevalence of females in this cohort. KS prevalence was the highest in non-Hispanic whites, similarly to other studies [1]. Lower rates of private insurance coverage were found in KS (comparing with OTH), which suggests that socio-economic status may contribute to risk factors associated with KS. Previous studies showed that lower income [1] and lower coverage of private insurance [24] are associated with higher risk of KS [25].

In our population, KS formers had the highest prevalence of obesity when compared to the GUD/OTH/ALP groups, and our final multivariate model suggested that patients with obesity are two times more likely to be diagnosed with KS comparing with GUD or ALP patients.

We found that KS, OTH and ALP were a healthier cohort with lower CCI and higher eGFR when compared to the GUD. Previous studies have demonstrated that KS formers have higher risk of developing chronic kidney diseases [4, 26]; in fact, in our study we found a tendency to a decreased eGFR in KS with respect to OTH/ALP groups, and this points to the necessity of monitoring and management of KS to prevent progression into chronic kidney disease.

The most common diagnosis associated with ED visits was hypertension, and its prevalence was higher in patients with KS comparing to GUD and ALP. Disorders of fluids, electrolytes, and acid-base balance was also frequently found in KS and GUD, but not in the diagnosis in the OTH/ALP group. A meta-analysis found that
increasing water intake was associated with significantly reduced risk of kidney stones and it was dose dependent for each increase of 500 ml of water [27]. For KS formers, the single most significant preventive measure is increasing fluid intake. In the GUD population, disorders of fluids and electrolytes are a well-known entity. In addition, diseases of acid base and electrolytes such as renal tubular acidosis (RTA) and partial RTA, which may present with hyperchloremic acidosis, hypokalemia, and normal or minimally reduced GFR [28], also have a higher prevalence of KS [29]. Interestingly, in our KS cohort we found higher levels of serum chloride and lower levels of serum bicarbonate, lower serum potassium levels, and elevated urine protein comparing to the GUD/OTH/ALP groups. Additional research efforts may be able to fully elucidate the significance of these findings.

We found that purpura and other hemorrhagic conditions were higher in the KS population when compared to the OTH/ALP population but there was no significant difference when compared to the GUD group. The distribution of serum lipase and creatinine kinase MB isoenzyme were significantly lower in KS as compared to the GUD and OTH/ALP groups. Renal handling of lipase involves removal of lipase from serum by glomerular filtration of lipase with nearly complete absorption of free oxalate in the bowel lumen [30]. Disorders of lipid metabolism have been associated with the metabolic syndrome and obesity [31]. Lower levels of lipase in the KS group needs to be further elucidated as there have not been previous reports of this finding. Creatinine kinase MB (CK-MB) is an enzyme that is elevated in renal disease and it may be elevated even in the absence of myocardial injury; however, the significance of its elevation is

### Table 5 The Diagnostic Acute Care Algorithm - Kidney Stones (DACA-KS)

| Items                                                      | Kidney Stones vs. Other Genitourinary Diseases | Kidney Stones vs. Other Conditions | Kidney Stones vs. Acute Localized Pain |
|------------------------------------------------------------|-----------------------------------------------|----------------------------------|----------------------------------------|
|                                                           | OR (95% CI)                                   | p-value                          | OR (95% CI)                            | p-value                          | OR (95% CI)                            | p-value                          |
| Insurance                                                 | 1.70 (1.25, 2.32)                             | 0.001                            | 0.91 (0.84, 0.97)                      | 0.01                            | 0.88 (0.82, 0.94)                      | 0.001                            |
| Charlson Comorbidity Index                                | 0.81 (0.75, 0.88)                             | < 0.0001                         | 0.63 (0.44, 0.96)                      | < 0.0001                        | 0.83 (0.79, 0.87)                      | < 0.0001                         |
| Certain adverse effects (ICD-9: 995)                      | 2.93 (2.14, 4.00)                             | < 0.0001                         | 6.33 (4.47, 8.96)                      | < 0.0001                        | 6.33 (4.47, 8.96)                      | < 0.0001                         |
| Hypertensive renal disease (ICD-9: 403)                   | 0.55 (0.34, 0.89)                             | 0.01                             | 5.37 (2.96, 9.77)                      | < 0.0001                        | 5.37 (2.96, 9.77)                      | < 0.0001                         |
| Obesity and other hyperalimentation (ICD-9: 278)          | 2.06 (1.28, 3.32)                             | 0.003                            | 2.18 (1.25, 3.82)                      | 0.04                            | 2.18 (1.25, 3.82)                      | 0.04                            |
| Candidiasis (ICD-9: 112)                                  | 2.37 (1.39, 4.06)                             | 0.002                            |                                       |                                 | 3.04 (1.85, 5.03)                      | 0.001                            |
| Decreased libido and other ill-defined conditions (ICD-9: | 2.30 (1.35, 3.93)                             | 0.002                            | 1.98 (1.08, 3.64)                      | 0.03                            | 3.40 (1.85, 6.27)                      | 0.001                            |
| 799)                                                      |                                               |                                  |                                       |                                 | 3.40 (1.85, 6.27)                      | 0.001                            |
| urine white blood cells (WBC)                             | 1.13 (1.10, 1.16)                             | < 0.0001                         | 1.26 (1.22, 1.30)                      | < 0.0001                        | 1.15 (1.11, 1.19)                      | < 0.0001                        |
| urine pH                                                   | 1.45 (1.20, 1.74)                             | < 0.0001                         |                                       |                                 | 1.99 (1.61, 2.45)                      | < 0.0001                         |
| urine protein                                             | 1.26 (1.01, 1.57)                             | 0.04                             | 2.19 (1.78, 2.69)                      | < 0.0001                        | 1.99 (1.61, 2.45)                      | < 0.0001                         |
| blood Magnesium                                           | 0.17 (0.08, 0.35)                             | < 0.0001                         |                                       |                                 | 3.01 (1.80, 6.02)                      | 0.001                            |
| blood Chloride                                            | 3.97 (2.06, 7.65)                             | < 0.0001                         | 5.05 (2.02, 12.59)                     | 0.001                           | 2.67 (1.01, 7.03)                      | 0.05                            |
| blood Albumin                                             | 1.78 (1.37, 2.32)                             | < 0.0001                         |                                       |                                 | 1.77 (1.24, 2.52)                      | 0.002                            |
| blood red blood cells (RBC)                               | 1.60 (1.22, 2.10)                             | 0.001                            | 1.49 (1.11, 1.99)                      | 0.01                            | 1.77 (1.24, 2.52)                      | 0.002                            |
| Disorders of fluid, electrolyte, and acid-base balance    | 1.70 (1.23, 2.37)                             | 0.002                            | 1.70 (1.23, 2.37)                      | 0.002                           | 1.70 (1.23, 2.37)                      | 0.002                            |
| (ICD-9: 276)                                               |                                               |                                  |                                       |                                 | 5.47 (3.60, 8.31)                      | < 0.0001                         |
| Other bacteria infections (ICD-9: 041)                    | 3.06 (1.76, 5.31)                             | < 0.0001                         | 2.07 (1.13, 3.79)                      | 0.02                            | 2.07 (1.13, 3.79)                      | 0.02                            |
| Sleep disorders (ICD-9: 327)                              | 3.14 (1.38, 7.14)                             | 0.01                             | 3.14 (1.38, 7.14)                      | 0.01                            | 3.14 (1.38, 7.14)                      | 0.01                            |
| Chronic pulmonary heart disease (ICD-9: 416)              |                                               |                                  |                                       |                                 | 0.52 (0.36, 0.76)                      | 0.001                            |
| Acute and subacute necrosis of liver (ICD-9: 570)         |                                               |                                  |                                       |                                 | 2.28 (1.34, 3.88)                      | 0.03                            |
| blood pO2                                                 |                                               |                                  |                                       |                                 | 2.88 (1.48, 5.60)                      | 0.02                            |
| Neurotic disorders (ICD-9: 300)                            |                                               |                                  |                                       |                                 | 0.70 (0.61, 0.80)                      | < 0.0001                         |
| Hyperplasia of prostate (ICD-9: 600)                      |                                               |                                  |                                       |                                 | 0.60 (0.47, 0.76)                      | < 0.0001                         |
| blood CO2                                                 |                                               |                                  |                                       |                                 | 1.15 (1.07, 1.24)                      | 0.002                            |
| blood phosphate                                           |                                               |                                  |                                       |                                 | 0.79 (0.71, 0.88)                      | < 0.0001                         |
| urine bands                                               |                                               |                                  |                                       |                                 | 0.79 (0.71, 0.88)                      | < 0.0001                         |
| urine RDW                                                 |                                               |                                  |                                       |                                 | 0.79 (0.71, 0.88)                      | < 0.0001                         |
A set of neurologic findings in our study demonstrated that migraine headaches were higher in KS and OTH compared to GUD/ALP. Sleep disorder, neurotic disorder, and depression disorder were also higher in KS patients. Migraine headache medications such as Topamax promote an (RTA)-like phenomenon. Sleep disorders and fatigue have been associated with migraine headaches. In our analysis, sleep disturbances and low libido were correlated with the diagnosis of KS when compared to GUD, OTH and ALP. Low libido due to low testosterone could be correlated with poor sleep quality, since a normal circadian rhythm/cycle is necessary for central effects on normal testosterone production.

Perhaps the most important finding and among high morbidity and mortality conditions, septicemia and candidiasis were found to be a high correlation with KS formers. Reyner et al. reported that of patients with didiasis were found to have a high correlation with KS morbidity and mortality conditions, septicemia and can save both the role of low lipase and CK-MB isoenzyme in KS formers.

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Abbreviations
ALP: Acute localized pain; AUROC: Area under the receiver operating characteristics; BMI: Body mass index; CCI: Charlson Comorbidity Index; DACA: Diagnostic acute care algorithm; ED: Emergency department; eGFR: Estimated glomerular filtration rate; GUD: Genitourinary diseases; KS: Kidney stones; OTH: Other conditions; SMOTE: Synthetic Minority Over-sampling Technique.

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Availability of data and materials
The datasets generated and analysed during the current study are available in the MIMIC-III databases, https://mimic.physionet.org/ [10].

Authors’ contributions
ZC designed the study, carried out the analysis, revised the results, drafted and revised the manuscript. MP designed the study, carried out the analysis, revised the results, drafted and revised the manuscript and gave final approval for submission. VVB, MR, MJS, JB, SRK and MCE revised the manuscript and gave relevant intellectual contribution. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The use of MIMIC-III database was approved by the data provider (Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology) after completion of required Collaborative Institutional Training Initiative (CITI) training, and a Data Use Agreement was signed. The requirement for individual patient consent was waived because the study did not impact clinical care and all protected health information was deidentified. De-identification was performed in compliance with Health Insurance Portability and Accountability Act (HIPAA) standards in order to facilitate public access to MIMIC-III, and protected health information (PHI) were removed. The study protocol of this specific analysis was approved by the University of Florida Institutional Review Board.

Consent to publication
Not applicable.

Competing interests
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