PREDICTIVE MODELING AND ANALYSES OF NATIONAL EMERGENCY DEPARTMENT DATA FOR IMPROVING PATIENT OUTCOMES OF NEPHROLITHIASIS

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ABSTRACT

Background: Nephrolithiasis, or kidney stones, impose a significant burden of disease in the United States and come with considerable costs, pain and morbidity. The exact cause of stone formation is undefined, but formation is a process. Risk factors include environmental, diabetes, obesity, metabolic syndromes, low fluid intake, dehydration, diet, inflammatory bowel disorders, irritable bowel syndrome and genetics. Laboratory testing and appropriate diagnostic imaging studies are two key components of assessment and prevention.

Methods: This is a retrospective, quantitative study utilizing the Healthcare Cost and Utilization Project's (HCUP) National Emergency Department Sample (NEDS) existing databases from 2012 to 2014 to classify outcomes for nephrolithiasis patients. ICD-9-CM, billing codes related to nephrolithiasis, relevant medical imaging exams, and procedural and surgical billing codes for interventions and procedures were selected. Descriptive statistical analyses as well as multiple regression models, were used to analyze frequencies and percentages of variables, the relationship of the data, identification of co-linearity amongst variables, and to predict outcomes.

Results: The study sample includes a total of 509,192 emergency department (ED) visits for nephrolithiasis from 2012 to 2014 and reveals that IBS patients are two times more likely to require intervention. Stepwise regression models yield P-values of 0.004 for gender; 0.017 and 0.018 for minor diagnostic procedures; 0.006 and 0.001 for minor therapeutic procedures; 0.000 and 0.001 for major therapeutic procedures when predicting for total cost of care, and have a statistically significant impact on patient outcomes of nephrolithiasis.

Conclusions: This research offers an investigation of the prevalence of nephrolithiasis based on age, gender, and co-morbidity, specifically Irritable Bowel Syndrome, and is the first to report on patient outcomes. This analysis also provides clinicians with recommendations to utilize for a comprehensive assessment of nephrolithiasis patients in the ED.

Keywords: *Nephrolithiasis, Kidney Stones, Medical Imaging, Computed Tomography, Ultrasound, Irritable Bowel Syndrome, Dehydration, Plasma Osmolality*

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DEDICATION

To my husband, for your unyielding love, support and encouragement to follow my dreams and accomplish my life goals.

To my daughters, always remember to follow your hearts and reach for the stars.

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CHAPTER I: INTRODUCTION

1.1 Background of Problem

Nephrolithiasis, or kidney stones, impose a significant burden of disease in the United States and occurrence continues to rise since the early 1980s. The prevalence of nephrolithiasis has grown substantially and comes with considerable healthcare costs, pain and morbidities. Nearly 1 in every 11 patients of the working-age will experience nephrolithiasis and 50% will encounter recurrence.[1] The risk of nephrolithiasis increases with age and stones more commonly affect Caucasians than Hispanics, Asians and African Americans. The rate of emergency department (ED) visits has significantly climbed in correlation with nephrolithiasis occurrence while ED physicians are the first line of care for patients in these acute settings. While most patients are discharged the same day, many will return within 48 hours requiring hospital admission.

The formation of nephrolithiasis is a process, not a single event, in which crystallization and crystal aggregation of minerals from supersaturated urine occurs. Nephrolithiasis can be comprised of calcium oxalate, cystine, uric acid or struvite. The most common type of stone formed is composed of calcium oxalate. Up to 40 percent of patients form these stones due to intestinal hyperabsorption of calcium. Cystine stones are caused by supersaturation of urine with cystine, uric acid stones are caused by excessive acidity of urine and/or excessive excretion of uric acid, and struvite (magnesium ammonium phosphate) stones are caused by ammonium ions from urea, which results in a rise in urine pH. Urine concentration, infection and urinary pH are inherent factors in this crystallization process and nephrolithiasis formation.[2]

Many theories exist regarding the pathogenesis of nephrolithiasis. Normal urine contains calcium oxalate and calcium phosphate crystal-forming inhibitors; in stone formers these inhibitors are often deficient. When deficiency is present, organic material derived of crystal forming compounds is commonly found on the renal pyramids or calyxes. Crystals begin to adhere to the medullary pyramid or minor calyx and will grow in size when urine fails to wash the organic material away. Stones are also often associated with co-morbidities such as inflammatory bowel disorders, diabetes, metabolic disorders and obesity. The strongest theory surrounding the formation of nephrolithiasis is low-fluid intake resulting in low-urine volume. Dietary factors are often considered in stone formation, such as high oxalate, high sodium and high protein diets. Nephrolithiasis are also associated with chronic and recurring urinary tract infections. These variations of pathogenesis make nephrolithiasis one of the leading healthcare burdens for care and cost.

The clinical manifestations of nephrolithiasis can be debilitating as the stone moves from kidney to ureter and to bladder. Patients report flank pain that radiates and often causes pelvic cramping or spasms. In addition to pain, nausea, vomiting, hematuria, and fever are often common symptoms associated with stones. Upon presentation and initial evaluation of the patient, a STONE score is utilized in many hospitals as a clinical prediction tool for uncomplicated stones. The STONE score is rated between 0 and 13 based on five patient factors, sex, timing, origin/race, nausea and erythrocytes. A high STONE score indicates the likelihood of nephrolithiasis.[3] Given a high STONE score, laboratory and medical imaging studies are then utilized to confirm the suspicion of nephrolithiasis.

Laboratory studies and metabolic evaluation are utilized for patients with recurrent nephrolithiasis, however first-time nephrolithiasis occurrence does not always result in metabolic panels due to cost concerns. The National Institute of Health Consensus Development Conference on the Prevention and Treatment of Kidney Stones outlines that all stone formers, whether single stone or recurrent, should experience at minimum a 24-hour urine collection.[3] This 24-hour urine collection allows multiple panels to be evaluated as well as detection of infection or underlying disease. Laboratory evaluation for nephrolithiasis also may include blood urea nitrogen, creatnine, serum electrolytes, calcium, phosphorus and uric acid, in addition to parathyroid hormone levels, vitamin D, serum bicarbonate concentration and urine pH levels, all of which are strong indications for stone risk.

Medical imaging modalities used for diagnosis of nephrolithiasis include intravenous pyelogram (IVP), computed tomography (CT), ultrasound, and magnetic resonance imaging (MRI). IVP was the exam of choice for many decades, however due to contrast media reactions and higher doses of ionizing radiation, IVPs are rarely ordered or performed. The imaging modalities most frequently utilized are ultrasound and CT. Ultrasound is utilized due to availability, cost and is being performed at point-of-care, all without exposing the patient to ionizing radiation. Ultrasound is often times used when there is low suspicion for secondary or alternative diagnoses. General radiography may be used on occasion due to its low costs despite its lack of sensitivity to identify stones smaller than 5mm and therefore, is often used only to follow recurrent stone formers. Computed tomography is considered the gold standard of imaging nephrolithiasis and renal colic due to its sensitivity and specificity. CT can detect the tiniest of stones and provide an exact location in the urinary tract. CT is also more definitive in providing alternative diagnoses when stones are not found to be the cause of symptoms. MRI is a last resort modality for diagnosis and imaging of nephrolithiasis.

Treatment and prognosis of nephrolithiasis varies. Generally, patients with nephrolithiasis can be managed at home with oral medications and are instructed to increase fluids to produce a urine volume greater than 2 liters per day. Dietary modifications are suggested to limit salt and ensure adequate calcium intake. Treatment is specific to stone size, type and location.

Calcium oxalate stones may require dietary oxalate restriction, in addition patients with hypercalciuria may be given a thiazide diuretic, citrate is used to inhibit stone formation where excess urinary citrate is excreted. Patients with excessive protein intake, hypokalemia, metabolic acidosis, hypomagnesemia, infections, androgens, starvation, and acetazolamide commonly present with decreased urinary citrate excretion.[3] Uric acid stones require an increase in urine output and pH, as well as a decrease in excretion of uric acid. Low purine and animal protein diets are recommended, resulting in raising the urinary pH and decreasing uric acid. Struvite stones require medical and surgical management that is often times aggressive. Antibiotics are required to reduce further stone growth and formation. Cystine stones require a decrease of cystine concentration in the urine and increasing urine volume up to 4 liters per day is often necessary.

Patients with stones larger than 5mm or those unable to tolerate oral medications, in addition to those requiring parenteral therapy for pain, are often hospitalized. Patients presenting with obstruction or infection of one or both kidneys require hospital admission for treatment and to closely monitor kidney function with hopes to avoid urosepsis and renal parenchymal damage.[3] Approximately 80 percent of stones will pass without intervention with morbidity occurring more commonly with upper urinary tract infection and urinary tract obstruction. Treatments will vary depending upon stone location (ureteric stones vs. renal stones) and primary methods used include decompression of the collecting system with drainage or stenting and stone treatment with extracorporeal shockwave lithotripsy (SWL) and ureteroscopy or percutaneous nephrolithotomy (PCNL).

1.2 Statement of Problem

Nephrolithiasis present a continual rising concern in healthcare and accurate patient-centered care is imperative for diagnosis, treatment and prognosis. Evidence based clinical guidelines are published for initial assessment, laboratory evaluation, diagnostic imaging selection, pharmacotherapy treatment, surgical treatment and prevention of recurrence for patients presenting with nephrolithiasis. However, it has been found that adherence to these guidelines is minimal. Adherence to diagnostic imaging guidelines is found in approximately 63%, complete guideline based lab testing occurs in only 40% of patient presentations, and pharmacologic therapy to aid in passage of stones is prescribed in only 17% of eligible patients.[1] These numbers are astonishing, as clear guidelines have been established for the most effective diagnosis and treatment of nephrolithiasis and yield such a low percentage of adherence. Current guidelines also suggest that all patients presenting with nephrolithiasis should be assessed for infection, imaged with a non-contrast enhanced computed tomography scan, and consideration of expulsive therapies or surgical interventions dependent of stone size and location may be required. Metabolic disorder evaluation guidelines vary, however increased fluid intake is a common recommendation for all stone formers.

Diagnostic imaging is essential in the clinical decision making process for nephrolithiasis treatment and prevention of recurrence. Computed Tomography is the recommended modality for initial imaging of suspected nephrolithiasis due to its high sensitivity and specificity by the American College of Radiology (ACR), however ultrasound is often times the first modality utilized at point-of-care. Low dose CT scans are recommended for patients with a body mass index (BMI) of 30 kg/m^2 and a full dose scan recommended for those with a greater BMI.[4] Although ultrasound is an acceptable means of imaging nephrolithiasis and a primary means of imaging pediatric and pregnant patients in the first trimester, this modality has its limitations. Often times, ultrasound over or under estimates stone size, presenting physicians with incorrect information and potentially delayed proper treatment of the patient.

There is a large discrepancy of first line imaging clinical decisions upon presentation of symptoms to the emergency department (ED). Although non-contrast CT is the gold standard for flank pain and suspected nephrolithiasis, ultrasound is still being utilized first for patients that would not require alternative imaging (i.e. pediatrics and pregnant patients). Many patients still require CT follow-up imaging after an initial ultrasound is performed to accurately assess stone size and location. Many patients are misdiagnosed altogether and return to the ED hours or days later with more severe symptoms, including a potential for infection and/or obstruction. Although ultrasound may demonstrate kidney stones, stone size may be inaccurate or missed altogether as imaging is operator dependent. Hydronephrosis is accurately depicted with ultrasound, which provides a significant diagnostic benefit. Point-of-care ultrasounds are becoming more common in ED's across the United States with acute care physicians performing these scans. Although these emergency department physicians may have general training in point-of-care scanning, they lack the knowledge that radiologists have in reading and interpreting these imaging exams. This lack of knowledge may result in patients being misdiagnosed or stone size and location incorrectly identified. Patients are then discharged from care under the assumption that stones will spontaneously pass, while many will return to the ED hours or days later. Although ultrasound provides a fast and safe alternative to imaging suspected nephrolithiasis, CT scans are far superior due to their ability to detect even the smallest of nephrolithiasis and determine stone composition, which are keys to management and treatment.

Symptomatic control is provided in the ED with intravenous hydration and anti-emetics, in addition to NSAIDs with narcotics reserved as a secondary therapy to patients who do not respond. For patients with no need for urgent intervention, observation or medical expulsive therapy is recommended. For patients with obstruction, renal impairment, and/or urosepsis urgent interventions are recommended. Patients with increasing symptoms, hydronephrosis and obstruction, in addition to increased stone size or renal function degradation with failure to pass the stone(s) active stone removal is recommended. Surgical treatments are recommended for urgent decompression of the renal collecting system with delay of treatment if infection or sepsis is present.[4]

Although guidelines for evaluation and prevention of recurrence are available, initial evaluation of a newly diagnosed patient does not always include a thorough clinical work-up. Dietary and pharmacological therapies are available and should be closely monitored when employed. Hydration status and co-morbidities such as inflammatory bowel disease, obesity, diabetes and metabolic disorders play an integral role in stone size and upon patient presentation to the ED, these factors alone should direct the physician to more accurately make a clinical decision for proper imaging modality use.

1.3 Hypotheses

Upon presentation to the ED, patients with suspected first-time nephrolithiasis or recurrent stones should be evaluated with a complete laboratory and diagnostic imaging work-up. There is a large area of discrepancy on presentation of flank pain and initial testing that is regularly performed. First, a significant percentage of patients that are initially evaluated with ultrasound, have poorer outcomes and accrue greater healthcare costs due to additional imaging requirements, specifically non-contrast computed tomography for specificity and sensitivity of nephrolithiasis. Second, based on the literature reviewed, the most common and significant recommended treatment and prevention of stones is increased fluid intake and urine output. Therefore, plasma osmolality, copeptin and urine concentration, in addition to any co-morbidity present, should be considered as factors for nephrolithiasis. Chronic dehydration is easily detected with plasma osmolality and copeptin levels, which can easily be determined with laboratory testing. Certain co-morbidities associated with nephrolithiasis produce larger stones, specifically patients with inflammatory bowel disease/disorders (IBD and IBS). IBD and IBS patients have a greater risk of nephrolithiasis due to fluid imbalance and dehydration due to chronic and acute gastrointestinal symptoms (i.e. diarrhea). With evaluation of plasma osmolality, emergency department physicians may be able to more accurately determine assumptions of stone size, therefore allowing a better clinical decision of first line imaging and improved outcomes for the patient. Hydration status and co-morbidities play an integral role in stone size and these factors should be used to guide the physician in better care of the nephrolithiasis patient. Utilization of the HCUP NEDS data sets to classify outcomes for the patient based on these factors will provide insight into improved clinical decision-making and patient-centered care.

1.4 Theoretical and Practical Need for the Study

This study fills the gap between evidence based clinical guidelines and practice in assessing nephrolithiasis with utilization of computed tomography versus ultrasound. Although many studies outline the lack of adherence to guidelines demonstrating that ultrasound is often utilized first despite the ACR's Appropriateness Criteria clearly outlining CT, there are no reports of patient outcomes or hospital admission based on this. Ultrasound often results in inaccurate stone assessment while CT is preferred for its sensitivity and specificity. Plasma osmolality should be considered in assessment of stone formers, whether first time or recurrent, as this may play a significant role in initial estimation of stone size. More specifically, I hope to demonstrate that patients presenting with nephrolithiasis also have a plasma osmolality that indicates dehydration and that those with co-morbidities such as IBD and/or IBS, should only be diagnosed with CT imaging for proper treatment planning. Thus, these methods will improve patient outcomes and decrease overall healthcare costs.

CHAPTER II: REVIEW OF LITERATURE

2.1 Nephrolithiasis Overview

Nephrolithiasis, or kidney stones, impose a large burden on the healthcare system in the United States as prevalence continues to rise. Stone disease effects a large amount of the working-age population, in fact 1 in every 11 persons is affected.[1] Nephrolithiasis are among the most-costly urologic conditions both in indirect and direct costs. The prevalence of stones coincides with the increase in ED visits due to extreme pain with onset. ED physicians primarily give initial care, with recommendations for follow-up with a urologist. The radiologist is also a significant part of the care of kidney stone formers, as initial diagnosis requires medical imaging.

In their 1980 conference paper, Kleeman et al noted “a progressive increase in the total number of patients with kidney stones during each five-year period” that was studied.[2] This upward trend has continued and demonstrates the need for quality care and further research on prevention in this area. Approximately 50% of patients will experience a recurrence of stones with a lifetime risk greater than that of non-stone formers. A positive family history contributes to the many factors that will be discussed, as kidney stones can be attributed to both genetic and environmental factors.

The formation of nephrolithiasis is not a single event, rather a process in which crystallization and crystal aggregation of minerals from supersaturated urine occurs. The most common type of stone formed is calcium oxalate, in which up to 40 percent of patients form these stones due to intestinal hyperabsorption of calcium. Cystine stones are caused by supersaturation of urine with cystine, uric acid stones are caused by excessive acidity of urine and/or excessive excretion of uric acid, and struvite (magnesium ammonium phosphate) stones are caused by ammonium ions from urea, which results in a rise in urine pH. Urine concentration, infection and urinary pH are inherent factors in this crystallization process and nephrolithiasis formation.[2]

Stones are commonly associated with diabetes, obesity, metabolic syndromes and inflammatory bowel diseases. Additionally, a low fluid intake with low urine output produces highly concentrated urine and increases risk for stone formation. Dietary factors also can contribute to nephrolithiasis with patients following diets high in sodium, oxalate and protein at a higher risk. Inflammatory bowel disorders are commonly associated with calcium oxalate stones and yield a large population of stone formers.

2.2 Pathogenesis

The exact cause of nephrolithiasis remains undefined, however there are many theories that have proven credible. Urine concentration, infection and urinary pH all play a large role in the formation of stones. Studies have “shown that normal urine contains potent inhibitors of calcium oxalate and calcium phosphate crystal growth, one or more of which may be deficient in the urine of persons in whom stones form”.[2] The organic material that comprise stones may be derived from the calyx or renal pyramids as this is the site of crystallization or aggregation. Time is also a factor in stone formation. The kidney requires a regular flow of urine to wash away debris, if low fluid intake is present, low urine output will result, leaving debris behind. The longer organic material sits in the kidney, the greater the opportunity for growth in size, as particles will begin to adhere to each other. Randall developed a concept about the kidney stone process in which there are surface defects in the kidney where patches of plaques are present and act as stone growth centers. These centers were the result of prior infection, or vascular disturbance leading to necrosis and attracting crystallization and stone formation.[2] This process is now known as “Randall’s plaque” and are always composed of calcium phosphate, formed by the interstitium and extruded at the renal papilla. The most prevailing theories of stone formation include supersaturation of urine and that stone formation is initiated by the renal medullary interstitium.

2.3 Types of Stones

There are several types of nephrolithiasis, including calcium oxalate, uric acid stones, struvite stones, and cystine stones. Calcium oxalate is the most common type of stone. Urine from patients with calcium oxalate stones often lacks the saturation-inhibitor and therefore urinary concentrations of calcium and oxalate contribute to stone formation. Calcium oxalate stones are the most likely to cause recurrence. Also, acquired hyperoxaluria occurs most commonly as a consequence of small intestine disease and is associated with extensive absorption of oxalate. Many calcium oxalate stone patients have higher levels of uric acid in plasma and urine.

Uric acid stones are said to be the “oldest renal stone in present-day collections”.[2] The formation of these stones is linked to precipitation of uric acid from oversaturated urine. Most patients with uric acid stones have an inability to increase urinary pH. These stones are commonly found in patients with ulcerative colitis, enteritis and ileostomies. Low urine volume is an important factor in uric acid stone formers because of frequent diarrheal states. Uric acid stone formers require an increase in urine volume and pH and a decrease in excretion of uric acid. Low purine and low animal protein diets are common recommended to raise urinary pH.[3]

Struvite or “staghorn” stones require the most aggressive medical treatments and surgical management due to the sharp edges and large size of stones. These stones are potentiated by bacterial infection and antibiotics are required to reduce further stone formation and growth as bacteria remain in the stone interspaces. Cystine stones require a decrease in urine concentration and increase in urine volume to keep cystine below the limits of solubility.[3]

2.4 Risk Factors

Tan and Lerma provide the most distinct outline of risk factors for nephrolithiasis and stone prevalence including environmental factors, diabetes, obesity and metabolic syndromes. Low-fluid intake is also discussed with a subsequent low-urine volume resulting in high concentrations of stone-forming solutes.[3] In addition to these factors, diet, oxalobacter formigenes and intestinal bacteria as well as chronic or recurrent urinary tract infections (UTIs) are also outlined. Bowel disorders including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS) and gastrointestinal surgery, in addition to medications, also contribute to a greater risk for nephrolithiasis. Genetic factors also may predispose an individual to nephrolithiasis risk formation.

Xu et al discuss future increases in kidney stone prevalence due to “global warming, lifestyle changes, diet and obesity”.[5] With a high rate of occurrence, most patients have risk factors that are easily identified, however the underlying cause of nephrolithiasis requires investigation. A 24-hour urine test is the basis for all stone former evaluations along with dietary modifications and medical oversight to lower urinary supersaturation.

Kidney stone disease is present in the referral of over 30% of patients with nephrocalcinosis and therefore warrants discussion here.[7] Verkoelen discusses nephrolithiasis and nephrocalcinosis referencing the clear, yet misunderstood difference between the two.[6] Nephrolithiasis refers to kidney stones, whereas nephrocalcinosis refers to retention of crystals in the renal tubules. Nephrocalcinosis differs in that epithelial cells that line renal tubules are most likely where crystal attachment occurs leading to abnormal renal tubular cell function, inflammation, and renal damage. This metabolic disease leads to renal tubular cells overgrowing lesions causing diffuse areas of calcification in the renal cortex and medulla. Differentiation of nephrolithiasis and nephrocalcinosis should not be misdiagnosed, as the deposition of calcium salts is common in those 35 years and older.

Randall’s plaque is outlined as plaque on the papilla, which consists of calcium carbonate and phosphate. Stones found attached here are typically calcium oxalate with predominance in those over 50 years of age, however stone formers are usually between 20 and 50 at peak occurrence. Inadequate elimination of crystals with urine accumulates into nephrolithiasis, or nephrocalcinosis in the renal tubules.[6] The literature reviewed does not delineate a clear link between these two as nephrocalcinosis is also found independent of nephrolithiasis.

Nephrocalcinosis is characterized by calcium salt deposits in renal parenchyma and often associated with autoimmune diseases, microcythaemia and electrolyte disturbances. In addition, nephrocalcinosis is identified with acquired diseases involving calcium, phosphate and oxalate metabolism. Increased urinary calcium excretion is discussed in relationship with hyperparathyroidism and sarcoidosis. Distal renal tubular acidosis, medullary sponge kidney and Bartter syndrome are also mentioned as these diseases are all related to nephrocalcinosis and nephrolithiasis.

Several dietary and lifestyle risk factors are correlated with an increased risk of nephrolithiasis. Cohorts studied by Ferraro et al included subjects with a normal BMI that drank adequate amounts of fluids and followed a diet high in vegetables and fruits, in addition to consuming only low fat dairy and sufficient amounts of calcium that demonstrated a "clinically meaningful lower risk of incident kidney stones".[8] Intake of larger volumes of fluid is a repeatable theme throughout the literature with Ferraro et al reporting a reduced risk of stone recurrence of 56% in their randomized controlled trial. Diets high in fruits and vegetables are associated with a reduced risk of stone recurrence of over 45% and adequate amounts of dietary calcium is associated with a 27-44% reduced risk.[8]

Evidence suggests that fatty acid intake is not associated with kidney stone formation or prevention.[9] The intake of EPA and DHA may alter arachidonic acid composition of cell membranes, but does not directly effect urinary excretion of calcium or oxalate. Rather, low fluid intake and resulting low urine volume correlate to an increased risk of nephrolithiasis in CKD patients and should not go without mention. Strippoli et al discuss the importance of fluid consumption and an inverse relationship with CKD.[10] The higher the fluid intake, the lower the risk of renal disease and subsequently high fluid intake has also demonstrated a decidedly lower risk of secondary kidney stone formation in these patients.[10]

Recurrent dehydration and salt loss may yield cause for chronic kidney disease with secondary nephrolithiasis. Experimental studies have indicated that the timing and combination of water and salt intake may influence kidney disease with affects on plasma osmolarity and renal injury. Johnson et al discuss an epidemic of nephrolithiasis among manual workers exposed to higher than normal temperatures in the work environment and hypothesize that changes in osmolarity induced by an imbalance of water and salt intake "drives the development of dehydration-related hypertension and kidney disease".[11] Extremely high temperatures yield dehydration and loss of salt. With persistent exposure and prolonged dehydration, acute kidney injury is likely. Johnson et al also suggest that sufficient hydration is key to prevention of CKD and induction of hyperosmolarity.[11]

Clark et al support this theory of hydration and its effects on CKD, as well as nephrolithiasis. Recurrent dehydration is a substantial cause of concern as increased water intake slows renal cyst growth and suppresses vasopressin, an antidiuretic hormone.[12] Water homeostasis, regulation of body fluid volumes, occurs in the kidney. Vasopressin's effects on kidney function may prove negative in the long term with activation of urinary albumin leakage, glomerular filtration rate (GFR) effects and increases in renal plasma flow. Increasing fluid intake and reducing vasopressin secretion has shown to have a positive effect on renal function in patients with CKD, as renal function is preserved and water intake is a well-documented method for reducing nephrolithiasis risk. Increased levels of copeptin are a surrogate marker of arginine vasopressin and may independently predict decline in eGFR and the greater risks of new-onset CKD.

Hypoparathyroidism is a known risk factor for nephrolithiasis, as the parathyroid hormone (PTH) is the "primary regulator of blood calcium levels and bone metabolism".[13] PTH increases serum calcium by releasing calcium from bone, stimulating renal 1-alpha-hydroxylase increasing active 1,25$(OH)_2$-vitamin D and reabsorbing calcium from the distal renal tubules. Inadequate production of PTH causes low blood calcium levels and elevates serum phosphate levels. Treatments for hypoparathyroidism include oral calcium and active vitamin D and may cause large swings in serum calcium levels resulting in risk of nephrolithiasis, nephrocalcinosis and chronic renal failure.[13]

A study published by O'Connor et al discusses nephrolithiasis and nephrocalcinosis resulting from intestinal resection due to hyperoxaluria.[14] Reduced urine volume is a direct consequence from diarrhea and fluid loss and increased oxalate excretion results from excessive absorption of dietary oxalate in the colon. This study concluded that calcium oxalate stones are common while specifically demonstrating that nephrolithiasis and renal crystallization is produced in rodents that have undergone intestinal resection and where dietary calcium is reduced and oxalate is increased. Hyperoxaluria is associated with inflammatory bowel diseases, ileal resections and certain gastric bypass surgeries and a well-known cause of nephrolithiasis and nephrocalcinosis in addition to contributing to chronic kidney disease.[15] The prevalence of hyperoxaluria in the patient population of gastrointestinal disease with malabsorption has been estimated between 5-24%.[15]

Distal renal tubular acidosis (dRTA) is a risk factor for nephrolithiasis and nephrocalcinosis and should be considered in recurrent stone formers, however diagnosis is often missed. Renal tubular acidosis, cystinuria, and medullary sponge kidney are discussed by Kleeman et al as often associated with nephrolithiasis.[2] Shavit and colleagues discuss distal nephron acidification defects as a common finding in patients with nephrolithiasis and nephrocalcinosis.[16] Both proving the connection between genetic disease and kidney stone risk.

Hereditary diseases must be reviewed as a significant risk factor for nephrolithiasis. Genetic renal tubular disorders have been linked to nephrolithiasis and stone disease, although seemingly rare. Different genetic disorders cause kidney stones, therefore, differential diagnosis and work-up should be considered. More than thirty genes have been identified as cause of nephrolithiasis and nephrocalcinosis with several genes, although not directly involved in kidney function, contributing to stones.[17] Edvardsson and colleagues discuss adenine phosphoribosyltransferase (APRT) deficiency, cystinuria, Dent disease, familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) and primary hyperoxaluria (PH) as causes of nephrolithiasis and stone disease.[18] Although not attributed to a specific gene, familial history of nephrolithiasis also contributes to stone risk. For instance, nephrocalcinosis is commonly found in predominately Caucasian populations of very low birth weight premature infants with significant and independent associations of familial history of stones.[19]

Halbritter et al have determined that fourteen monogenic genes account for 15% of nephrolithiasis with recessive genes causing stones in children and dominant genes causing stones in adults.[20] Dasgupta and colleagues found that mutations in the SLC34A/NPT2c gene are associated with kidney stones and medullary nephrocalcinosis.[21] Lloyd et al have identified mutations of the renal-specific chloride channel gene to be associated with nephrolithiasis in Northern European and Japanese populations, while renal tubular disorders again are identified.[22]

2.5 Laboratory Testing

Onset of nephrolithiasis often sends individuals to the emergency department, with 10% requiring hospital admission.[23] Clinical prediction rules for kidney stones have recently been tested to further direct physicians in the clinical care of patients. The STONE score was utilized as a clinical decision rule to classify patients into scored groups of probability for nephrolithiasis. Although the score does not yield a clear prediction for specific diagnostic testing, it is thought to be superior to physician knowledge and application alone.[23]

Physical examination of patients presenting with kidney stone symptoms include pain, hematuria, nausea, vomiting or urinary tract infection and would include observation of writhing and inability of the patient to find a comfortable position under renal colic, which may induce tachycardia and hypertension. Costovertebral angle percussion tenderness is also common.[24]

Laboratory testing is warranted for all stone formers and metabolic evaluation for recurrence. The National Institute of Health recommends that all patients should undergo at minimum a 24-hour urine collection and this recommendation is supported by the European Association of Urology's guidelines. This evaluation should include "serum electrolytes, blood urea nitrogen, creatnine, calcium, phosphorus, and uric acid. In patients with hypercalcemia, test to investigate the etiology of the metabolic imbalance such as parathyroid hormone level" is said to be appropriate.[3] High urine pH or pyuria requires further investigation with urine cultures and consideration of stone composition.[3] Serum chemistry results are often within normal limits, however elevated creatnine indicate decreased renal function. Elevated creatnine may also occur from dehydration related to nausea and vomiting. Elevated neutrophils and white blood cells are often indicative of urinary tract infection. Microscopic hematuria is common in patients presenting with nephrolithiasis.[24]

2.6 Diagnostic Imaging Studies

Computed tomography (CT) is the gold standard of imaging renal colic and suspected nephrolithiasis. Non-contrast, low dose CT of the abdomen and pelvis is preferred, however low dose can only be utilized for patients with lower BMI. CT has 95% sensitivity and specificity of which is far superior compared to other modalities commonly used to image suspected nephrolithiasis. Calcium stones are always radiopaque, while cystine and struvite stones are often radiopaque but not always, and uric acid stones are never opaque due to the lack of calcium components. Non-calcium stones may be overlooked by general radiography but easily identified with CT. CT also provides a differential diagnosis when nephrolithiasis are not present, but symptoms are indicative of disease.[3] Ultrasound has been identified as an acceptable initial imaging option when there is low suspicion for alternative diagnosis but is secondary to CT. General radiography (x-ray) is limited in diagnosis, despite its low cost, due to its inability to detect stones smaller than 5mm.

Ultrasound is very effective in diagnosis of hydronephrosis, which is often present with obstructing stones. However, stones less than 5mm are difficult to identify and often stone size is overestimated, resulting in unwarranted treatments. Patients presented for ultrasound will often require additional imaging, in which CT imaging is most frequently ordered.[25] However, ultrasound is thought to be most beneficial in caring for recurrent stone formers or solely the presence of hydronephrosis.

Multi-detector CT (MDCT) and dual-energy CT (DECT) are utilized in imaging nephrolithiasis. McCarthy et al discusses the benefits of precise stone localization and comprehensive assessment of associated effects and complications with CT, thus providing more accurate triage of patients.[25] DECT allows for enhanced determination of stone composition with utilization of attenuation of x-ray energies. DECT far exceeds the capabilities of ultrasound and general radiography and can be obtained in under 10 seconds. Radiation doses from DECT are lower than that in older CT scanners and low-dose techniques are readily employed.[26]

In 2015, Villa et al reviewed the essential components of imaging for diagnosis and clinical decision making for nephrolithiasis patients and validated the previous literature reviewed's clear identification of CT being the preferred modality.[27] Zagoria and Dixon identify CT as the only "modality that allows detection of 100% of urinary tract calculi".[28] Metzler and colleagues note the majority of patients with nephrolithiasis undergo CT imaging before surgical interventions and discuss how initial imaging modality affected treatment patterns.[29] This study also identifies that not all ultrasounds are accepted by urologists, as there are too many variations of scanning. Point-of-care ultrasound yielded two times the need for CT follow-up before intervention, as it lacks labeling, measurement capability and detailed anatomical visualization for surgical procedures.[29]

General radiography has a limited yield of clinically useful information in presentation of nephrolithiasis in the ED.[30] Despite lower doses of ionizing radiation in general radiography exams than those of CT, the 2D image is not as valuable in differential diagnosis of suspected nephrolithiasis as CT. Dose reduction techniques can be employed in CT, while radiation exposure factors are manipulated to enhance conventional CT imaging. Detection of millimeter stones is still maintained with lower exposure values while providing a higher quality image than that of general radiography.[31]

Although ultrasound is recommended as the initial imaging modality for pediatric and pregnant patients, Tasian et al conducted a study to review the prevalence of CT utilization as first line imaging of pediatric patients.[32] The study demonstrates a high prevalence of CT imaging in pediatric populations and extensive regional variations across the United States. In some states, nearly 80% of children were imaged with CT first. This study also notes that these practices deviate from the guidelines established by the American College of Radiology substantially.[32]

Neisius and colleagues reviewed digital tomosynthesis in comparison to renal stone protocols of non-contrast CT and radiation doses were compared for these two modalities. Digital tomosynthesis was identified as exposing patients to less radiation with a benefit of lower cost, however, specificity and sensitivity was not identified as being greater than that of CT imaging.[33]

Valencia et al discuss in detail the methodology utilized for the STONE approach and rationale, and confirm CT as the best imaging exam for patients presenting to the ED in comparison to ultrasound.[34] However, Yavuz and colleagues investigate the effectiveness of B-mode and color-Doppler features of ultrasound imaging with focus on a “twinkling-artifact” for detecting nephrolithiasis.[35] Acoustic shadowing is noted as affected by parameters such as stone size, thickness and composition in addition to the nature of the tissue between the transducer and stone. The twinkling-artifact is described as a rapid change between red and blue color patterns and is more resistant to obstacles. When required to image a patient without exposure to ionizing radiation, the use of color Doppler was identified as a preferred method in ultrasound imaging of stones.[35]

In Shafi, Anjum and Shafi’s study of abnormal ultrasound in patients with suspected nephrolithiasis, ultrasound was found to be abnormal in over half of patients, although 97% sensitive in predicting need for surgical intervention.[36] Hsi and Stoller discuss the combination of ultrasound with physical exam and urinalysis as a reasonable method of diagnosis, however, their counterpart Miller disagrees. Miller strongly states that ultrasound is not sufficient, as stones are often missed and further supports the use of CT imaging.[37] Fields et al discuss required admission rates with bedside ultrasound and 30-day outcomes with ureteral jet evaluation in the ED.[38] The study showed that severity of hydronephrosis is clearly identified with ultrasound, and those with moderate hydronephrosis had a higher 30-day admission rate. The use of CT imaging as a preferred method is also discussed by Fields et al.[38]

Smith-Bindman and Bailitz discuss two primary outcomes of high-risk diagnosis with complication and cumulative radiation exposure from imaging. In addition to these primary outcomes, it is noted in this study that “patients assigned to the ultrasonography programs were more likely to undergo additional diagnostic imaging tests” for nephrolithiasis.[39] Sternberg et al evaluated the significant overestimation of stone size with ultrasound and compared low-dose CT in identifying and measuring kidney stones.[40] The results were, again, in favor of the superiority of CT over ultrasound. Smith-Bindman et al concur that CT has a greater sensitivity to identifying kidney stones, although the authors note that ultrasound is associated with lower cumulative radiation exposure.[41] Stoller et al support initial evaluation of nephrolithiasis with ultrasound and echo concerns for higher patient radiation exposure to the studies previously discussed here.[42]

Chen et al reviewed the radiation exposure to patients with nephrolithiasis and discussed the significant risk for increased radiation exposure to recurrent stone formers. Recurrent stone formers are at greater risk of radiation exposure due to diagnostic imaging and interventional procedures which may include fluoroscopy with SWL for treatment of stones.[43] Portis et al discuss postoperative imaging to judge success of interventional procedures with fluoroscopy which again utilizes ionizing radiation, however there is no discussion of radiation exposure concerns.[44] Pan et al review retrograde intra renal surgery (RIRS) versus mini-percutaneous nephrolithotripsy (mPCNL) for management of stones and note that mPCNL is the preferred method.[45] This method utilizes a combination of high-frequency ultrasound waves to “shock” stones into fragments and fluoroscopy, which utilizes ionizing radiation to identify stone location.

Holdgate and Chan reviewed accuracy in interpretation of imaging by ED physicians in 2003, as this is a necessary method for treatment of nephrolithiasis patients in an acute setting.[46] Holdgate and Chan concluded that ED physicians are able to accurately identify nephrocalcinosis but may not be able to identify non-renal abnormalities.[46] This is imperative to note, as discussed earlier, that ED physicians lack the training and knowledge that radiologists bring in interpretation of diagnostic imaging exams.

2.7 ACR Appropriateness Criteria

Imaging modalities such as CT, provide insight into the human anatomy and disease presence. This information is necessary to provide an accurate diagnosis and predict the outcomes of a disease. The American College of Radiology (ACR) established appropriateness criteria to assist physicians in selecting the most useful imaging exam based on clinical indications. The guidelines provide physicians with a rating between 1 and 9, 1 being “least appropriate” and 9 being “most appropriate”.

For over 20 years, CT has been the first line imaging choice for detecting nephrolithiasis with a 95% specificity and sensitivity. Not only does CT identify the location and size of stones, but a clear depiction of composition and any other differential diagnoses. The ACR gives non-contrast CT an appropriateness rating of 8. Abdominal radiography is given a 3, magnetic resonance imaging (MRI) and previously utilized intravenous urography (IVU) a rating of 4.[47]

With investigation into the ACR’s Appropriateness Criteria[48] further, ratings for additional clinical conditions and variants are noted here. For example, a patient presenting with hematuria is listed with several variants given. Variant 1 for hematuria includes patients with vigorous exercise, presence of infection or viral illness, or present or recent menstruation. Variant 2 for hematuria includes patients with disease of renal parenchyma as the cause of hematuria. Variant 3 includes all patients except those that fall into variant 1 or 2. For each variant a rating is given for the most likely considered radiologic procedure. Hematuria, variant 1 provides ratings from 1 to 3, with an x-ray of the abdomen and pelvis (KUB) given a 1 (least appropriate) and ultrasound of the kidneys and bladder a 3 (usually not appropriate). Hematuria, variant 2 provides ratings from 1 to 8, with x-ray of the abdomen and pelvis (KUB) given a 1 (least appropriate) and ultrasound of the kidneys and bladder an 8 (most appropriate). Hematuria, variant 3 provides ratings from 1 to 9, with x-ray of the abdomen and pelvis (KUB) given a 2 (least appropriate) and CT of the abdomen and pelvis without and with IV contrast a 9 (most appropriate).[48]

The ACR’s Appropriateness Criteria[48] for the clinical condition of acute onset of flank pain with suspicion of stone disease provides 3 variants. Variant 1 is suspicion of stone disease, variant 2 is recurrent symptoms of stone disease, and variant 3 is pregnant patient. Variant 1 provides a score of 3 (least appropriate) for KUB, 6 for ultrasound with color Doppler of kidneys and bladder, and an 8 (most appropriate) for CT of the abdomen and pelvis without

IV contrast. Variant 2 provides a score of 2 (least appropriate) for intravenous urography (IVU) and a 7 (usually appropriate) for both ultrasound with color Doppler of kidneys and bladder and CT of the abdomen and pelvis without IV contrast. Variant 3, that of the pregnant patient, provides a score of 1 (least appropriate) for IVU, 2 for CT of the abdomen and pelvis and 8 (most appropriate) for ultrasound with color Doppler of the kidneys and bladder.[48] The ACR's Appropriateness Criteria provides greater insight into the most accurate modality for diagnosis and with use reduces cost for inappropriate and unnecessary imaging exams.

2.8 Prevention

Primary prevention of nephrolithiasis would release a significant healthcare burden on the patient and costs on the national healthcare system. In nephrolithiasis recurrence, prevention should also be considered a treatment option. Lotan et al evaluated the impact of primary prevention of stones with increased fluid intake.[49] "While worldwide economic impacts of nephrolithiasis is unknown, the total annual medical expenditures for nephrolithiasis in the USA were >$2.1 billion in the 2000 alone."[49] Due to the high rate of recurrence impacting 50% of patients, an increased fluid intake is recommended to subjects in Lotan et al's study in an effort to reduce healthcare cost burdens and prevent a common disease.[49] This study found that an increase in fluid intake, water specifically, can provide a significant cost-savings and reduce stone burdens.

Regardless of underlying causes, increasing urine output ensures the mechanical diuresis to prevent stagnation of organic materials and formation of stones in addition to dilution of urine to prevent supersaturation. Prezioso et al discuss dietary treatments of risk factors for stone formers concluding that patients should make necessary dietary changes based on stone composition and regardless of stone composition, all stone formers should increase fluid intake to yield 2 liters of urine daily.[50] A diet balanced in fruit and vegetables is highly recommended and a low-protein, low-salt diet with high hydration is encouraged.

Sakhaee's manuscript provides medical measures for prevention of nephrolithiasis including high oral fluid intake, low animal-protein and salt dietary interventions and high consumption of fruits , vegetables and sugar-free beverages in kidney stone formers.[51] The impact of fluid intake in prevention of nephrolithiasis is described by Lotan et al and their research describes the human body's ability to compensate rapidly for small losses of water through the activation of renal mechanisms to maintain plasma osmolality.[52] This stimulates arginine vasopressin, which promotes water conservation and decreases urine volume. Insufficient hydration and dehydration are causes of adverse effects on the urinary system. Lotan et al support the same dietary interventions as Sakhaee, in that animal protein, dietary sodium and refined sugars should be limited. Additionally, Lotan et al suggest that vitamin C and foods rich in oxalate should be limited. A large daily intake of water is recommended especially for those living in what is referred to as the "stone belt" (southeast United States). The stone belt demonstrates a two-fold prominence of stone risk due to ambient temperatures. CKD is also noted as decreased risk with increased fluid intake in this study and a lower GFR.[52]

Tarplin et al further support an increase in fluid intake for stone formers and note that urologists play an important role in counseling patients for stone prevention.[53] Successful fluid drinkers were less likely to find water preferable and unsuccessful fluid drinkers were less likely to be aware of future stone risks. Another study conducted by Lotan et al investigated the prevalence of stone disease in steel workers.[54] This study was significant in that dehydration was common amongst this workforce due to working conditions. The steel workers were found to have a "high prevalence of abnormal values of other urinary risk factors for stones, including low urine volume, low urine pH and citrate, and high sodium, calcium and oxalate with increased fluid intake recommended.[54]

"Increased water intake over 6 weeks results in an attenuation of circulating copeptin" which may serve as a very simplistic and cost-effective intervention for reducing circulating vasopressin, which conserves water and decreases urine volume.[55] This study demonstrates that plasma copeptin can be modulated by increasing water intake, which is of significant value to this research, as plasma copeptin is associated with kidney disease and may reduce the risk of nephrolithiasis. Tasevska et al found that “increased water intake or pharmacological vasopressin blockade are interesting candidates for preventing the decline of eGFR and development of CKD”.[56] Additionally, Melander’s research on vasopressin demonstrated that high levels of copeptin independently predict kidney disease and water supplementation is under investigation.[57] Vasopressin’s role is outlined further in Garcia-Arroyo and colleagues study in mediation of renal damage induced by fructose.[58] Dehydration is associated with acute kidney injury, as it is a potent stimulus for the release of vasopressin, but is typically reversible. More recently, vasopressin is being investigated not only as a hormone to prevent water loss but also as a mediator of renal injury. This study demonstrates evidence that recurrent dehydration can lead to chronic kidney disease and may result in secondary nephrolithiasis. Water hydration is far more beneficial than that of fructose rehydration due to higher serum vasopressin levels, as fructose “can induce impair renal function and tubular injury”.[58]

Prevention of genetic risk for nephrolithiasis seems daunting given the wide variety of variables. Figueres and colleagues conducted a research study that reviewed the influence of sunlight exposure in patients with idiopathic infantile hypercalcemia and found that long-term kidney disease in affected children and adults may occur with this gene mutation.[59] Although this finding is irrelevant to nephrolithiasis, it is however applicable in further genetic research studies.

Dietary therapy, pharmacological therapy and increased fluid intake have all been found to aide in the prevention of nephrolithiasis recurrence. Fluid intake should be sufficient to achieve urine output of at least 2.5 Liters per day and sodium should be restricted.[4] Cheungpasitporn et al further support the findings of significant risk reduction of nephrolithiasis with high fluid consumption.[60]

Lastly, a study conducted by Blackwell et al reviewed the Healthcare Cost and Utilization Project State Inpatient Database (HCUP SID) from 2007 to 2011 for Florida and California. The study found that delayed intervention for acute stone presentation admissions resulted in increased patient mortality due to the “weekend effect” where race and insurance provider had a significant impact on timing.[61] These studies collectively prove the need for early intervention and prevention of nephrolithiasis in order to improve patient outcomes.

2.9 Summary of Literature Review & Research Aims

The results of this literature review demonstrate that guideline adherence for imaging and laboratory testing of nephrolithiasis is lacking, with increased healthcare costs accruing and recurrence of stones plaguing patients. Current guidelines suggest that all patients presenting with nephrolithiasis should be assessed for infection, imaged with a non-contrast enhanced computed tomography scan, and consideration of expulsive therapies or surgical interventions dependent of stone size and location may be required. Laboratory studies and metabolic evaluation are utilized for patients with recurrent nephrolithiasis, however first-time nephrolithiasis occurrence does not always result in metabolic panels due to cost concerns. Computed tomography is considered the gold standard of imaging nephrolithiasis and renal colic due to its sensitivity and specificity. While ultrasound is recommended as a secondary option when there is low suspicion for secondary or alternative diagnoses.

Throughout the literature reviewed here the aims of this research continue to focus on the discrepancies of initial testing (laboratory and diagnostic imaging) for presentation of nephrolithiasis. First line imaging clinical decisions lack adherence to the ACR’s well established guidelines and many patients are misdiagnosed or return to the ED with more severe symptoms and higher mortality rates. Initial laboratory testing is lacking despite low cost and potential to improve patient outcomes. Co-morbidities should be considered and chronic dehydration should be assessed as an indication of stone disease and utilized for clinical decision-making.

CHAPTER III: METHODS

3.1 Study Design and Data Source

Occurrence of nephrolithiasis in the United States amongst the adult population continues to grow, as does the burden of healthcare costs and recurrence of stones for many patients. The discrepancies of initial medical imaging performed versus that recommended by the ACR are abundant despite the clear recommendations of appropriateness criteria for first line imaging of suspected nephrolithiasis. Additionally, laboratory and metabolic testing as well as close evaluation and consideration of co-morbidities, such as inflammatory bowel disease, irritable bowel syndrome and chronic dehydration linked to nephrolithiasis, must be investigated.

This is a retrospective, quantitative study utilizing the Healthcare Cost and Utilization Project's (HCUP) National Emergency Department Sample (NEDS) existing databases from 2012 to 2014 to classify outcomes for nephrolithiasis patients. This study will analyze frequencies and percentages of variables, as well as relationship of data selected with multiple regression models and identification of co-linearity amongst the variables using IBM SPSS Statistics. The key objective is to be able to analyze and produce a predictive model for improving patient outcomes of nephrolithiasis.

The HCUP NEDS is "a unique and powerful database that yields national estimates of emergency department visits" which was "created to enable analyses of ED utilization patterns and support public health professionals, administrators, policymakers, and clinicians in their decision-making".[62] The NEDS is the largest dataset of hospital care and is drawn from states that provide ED data from visits that result in both hospital discharges and admissions and includes diagnosis codes, procedure codes, discharge information, de-identifiable patient demographics and total hospital charges including those for inpatient admissions. The NEDS database has been selected for this study as it shows much promise in maximizing internal and external validity of the formulated hypotheses presented.

While the HCUP NEDS is a valuable research tool, there are limitations of the databases. The NEDS databases are missing information about ED charges for a variety of weighted percentages, 15% for 2012 and 2013, and 16% for 2014.[62,63,64] The NEDS focus on entry-level versus patient-level records and therefore patients that may revisit the ED multiple times in a given year may be present as separate patient entries, this is due to de-identification requirements. The NEDS are also limited by direct admission from the ED to the hospital, as only one discharge record is included. This makes differentiation of procedures performed in the ED versus part of the inpatient stay unattainable. Also important to note, the NEDS target is community, non-rehabilitation hospital based EDs in the United States.[63] The number of states included in the 2012, 2013 and 2014 databases utilized is not largely varied as the number of hospital-owned ED numbers are very consistent ranging from 950 in 2012, 947 in 2013 and 945 in 2014.[64] The number of un-weighted ED visits are also quite comparable ranging from 31,091,029 in 2012, 29,581,718 in 2013 and 31,026,417 in 2014 and therefore will not be considered to have an impact on this study.

3.2 Selection of Participants

Identification of ED visits in patients 18 years of age and older that have International Classification of Diseases, Ninth Revision, ICD-9-CM, billing codes related to nephrolithiasis; calculus of kidney (592.0), calculus of ureter (592.1), calculus unspecified (592.9), calculus in diverticulum of bladder (594.0), other calculus in bladder (594.1) calculus in urethra (594.2), other lower urinary tract calculus (594.8), calculus of lower urinary tract unspecified (594.9), uric acid nephrolithiasis (274.11), as well as hematuria (599.71), hydronephrosis (591.0), renal colic (788.0), dehydration (276.51) and inflammatory bowel disorders (564.1 Irritable Bowel Syndrome, 555 Enteritis, and 556 Ulcerative Colitis) will be identified.

Relevant medical imaging exams billed including Computed Axial Tomography (CT) exams of the abdomen (88.01, 88.02) and kidney (87.71), general radiography of the abdomen (88.19), abnormal findings on radiography exam (793), Intravenous Pyelogram (IVP) (87.73), as well as ultrasound of the abdomen (88.76) and ultrasound of the urinary system (88.75) will also be utilized in this study.

Finally, procedural and surgical billing codes for ureteroscopy (56.31), cystoscopy (57.32), ultrasonic fragmentation of urinary stones (59.95), retrograde pyelogram (87.74), percutaneous pyelogram (87.75), extracorporeal shockwave lithotripsy (ESWL) (98.5) and extracorporeal shockwave lithotripsy (ESWL) of kidney, ureter and/or bladder (98.51) will be utilized.

3.3 Variables Examined

Multiple patient level variables from the HCUP core datasets including age, gender and co-morbidities of obesity, diabetes, IBS, dehydration and hyperosmolality, as well as relevant medical imaging exams and procedures in addition to total charges and discharge versus admission, will be extracted. Statistical analysis will be performed utilizing IBM SPSS Statistics version 26 on an OS X Yosemite operating system. The core file, hospital weights and supplemental files will be extracted and "Key" files merged for analysis. HCUP NEDS data elements utilized in this study are outlined below.

Data Element	**Descriptive Title & File Location**
AGE	Age in years at admission (Core)
DXn	ICD-9-CM Diagnosis (Core)
FEMALE	Indicator of sex (Core)
KEY_ED	HCUP NEDS record identifier (Core, Supplemental ED & Supplemental Inpatient)
PCLASS_EDn	Procedure class (Supplemental ED)
PCLASS_IPn	Procedure class (Supplemental Inpatient)
PR_EDn	ICD-9-CM Procedure Code (Supplemental ED)
PR_IPn	ICD-9-CM Procedure Code (Supplemental Inpatient)
TOTCH_ED	Total charge for ED services (Core)
TOTCH_IP	Total charge for ED and inpatient services (Supplemental Inpatient)

3.4 Outcome Measures

The primary outcome to be measured in this study is the medical imaging exam performed during an ED visit. Additionally, where ultrasound and CT imaging are both utilized it will be reasonably assumed that the ultrasound is performed first for chronological reference. Patients will be separated into two groups, those that have CT imaging first and those that have an ultrasound performed first.

Secondary outcomes measured will include patient co-morbidities and dehydration which are hypothesized to have a profound impact on stone size, location and need for procedural and surgical interventions, as well as total charges for ED services and total charges for ED and Inpatient services.

3.5 Predictive Modeling & Statistical Analysis Methods

A statistical analysis of the NEDS core data sets from 2012 to 2014 will be examined using descriptive analytics of frequencies and percentages which provides a detailed summary of the data sets. Regression analyses will also be performed in SPSS to determine the variables for use and to ensure the model fits the data.

A linear, or standard, regression method will be utilized, as well as stepwise and hierarchical multiple regression models explored. Multiple regression models are flexible, as well as powerful. The standard multiple regression method allows for simultaneous input of variables and evaluation of each independent variable for its predictive power. The stepwise regression method allows for ease of analyzing large numbers of independent variables allowing the program to select which variables are entered and in what order, and is frequently utilized in machine learning. Whereas, hierarchical multiple regression, also known as sequential regression, will allow for independent variables to be entered into the model in a specified sequence based on hypothetical theory. This approach will allow for sets of variables, for example CT and/or ultrasound exams would be entered in block 1, followed by co-morbidities being entered in block 2, to be entered in steps. This allows each independent variable to be assessed in terms of what it adds to the prediction of the dependent variables, once previous variables are controlled for. These statistical methods will allow for identification of unique variances and relative contributions of block variables to be assessed.

CHAPTER IV: RESULTS

4.1 Summary of Results

HCUP NEDS datasets for 2012, 2013 and 2014 were analyzed for patients with a primary, secondary, tertiary or quaternary diagnosis of nephrolithiasis. The results measure frequencies and percentages of variables with descriptive statistical analysis which provide insight whether there are statistically significant numerical observations within the datasets. Total number of nephrolithiasis ED visits investigated in this study is 509,192.

4.2 Descriptive Statistical Analysis

Analyses of the HCUP NEDS databases has identified 164,410 emergency department (ED) visits for nephrolithiasis in 2012, 163,254 in 2013 and 181,528 in 2014 (see Table 1).

Table 1. Primary diagnoses in nephrolithiasis cases

2012

Statistics

		Diagnosis 1	Diagnosis 2	Diagnosis 3	Diagnosis 4
N	Valid	164410	164410	164410	164410
	Missing	0	0	0	0

Diagnosis 1

	Frequency	Percent	Valid Percent	Cumulative Percent
5641	38	.0	.0	4.8
591	447	.3	.3	8.1
5920	103037	62.7	62.7	70.7
5921	12894	7.8	7.8	78.6
7880	3139	1.9	1.9	89.6
V1301	3	.0	.0	99.9

2013

Statistics

		Diagnosis 1	Diagnosis 2	Diagnosis 3	Diagnosis 4
N	Valid	163254	163254	163254	163254
	Missing	0	0	0	0

Diagnosis 1

	Frequency	Percent	Valid Percent	Cumulative Percent
5641	30	.0	.0	5.0
591	548	.3	.3	8.2
5920	103612	63.5	63.5	71.6
5921	12832	7.9	7.9	79.5
7880	2903	1.8	1.8	90.3
V1301	8	.0	.0	99.9

2014

Statistics

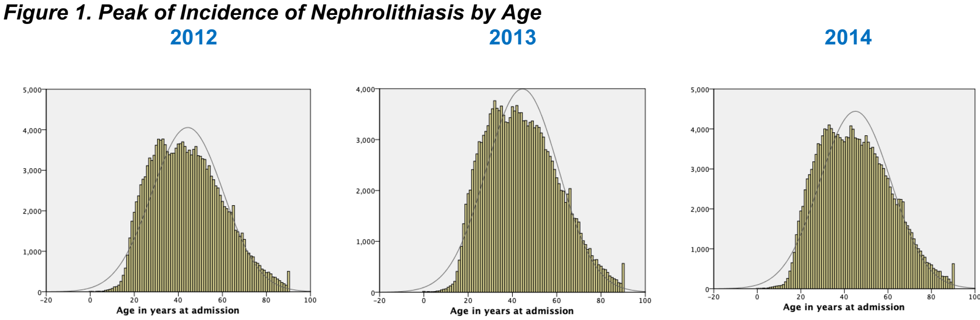
		Diagnosis 1	Diagnosis 2	Diagnosis 3	Diagnosis 4
N	Valid	181528	181528	181528	181528
	Missing	0	0	0	0

Diagnosis 1

	Frequency	Percent	Valid Percent	Cumulative Percent
5641	37	.0	.0	5.5
591	748	.4	.4	8.9
5920	115624	63.7	63.7	72.6
5921	13472	7.4	7.4	80.0
7880	2946	1.6	1.6	90.8
V1301	7	.0	.0	99.9

Nephrolithiasis is identified as the principle diagnosis, or chief responsible condition for hospital care, in approximately 71% of these visits across 2012, 2013 and 2014. The characteristics of nephrolithiasis patients identified exhibits an average age for peak of incidence between 30 to 42 years of age over the 3-year period with slightly greater frequency among males (53.8% in 2012; 53.6% in 2013; 53.1% in 2014) than females (46.2% in 2012; 46.4% in 2013; 46.9% in 2014) (see Figure 1). Secondary diagnoses of interest aside from nephrolithiasis in this population include hydronephrosis, Irritable Bowel Syndrome (IBS) and personal history of renal calculi. Results from descriptive analyses used in this study provide additional insight into the HCUP NEDS database. Initial cases selected were filtered for Inflammatory Bowel Disorders (IBD) and Irritable Bowel Syndrome (IBS). Interestingly, there were minimal cases of nephrolithiasis patients returned with IBD (ulcerative colitis, enteritis) as compared to IBS and therefore the principal focus of this research will be on IBS patients.

Figure 1. Peak of Incidence of Nephrolithiasis by Age



While the focus of this study is the link between IBS and nephrolithiasis, the prevalence of obesity and diabetes in patients with nephrolithiasis was briefly analyzed as each of these two co-morbidities were highlighted in the review of literature as a probable contributing factor. Diabetic patients make up 4.8% of this population and had a larger yield of nephrolithiasis, with an average of 32% secondary diagnosis (7914 patients in 2012; 7499 in 2013; 8971 in 2014) than that of obese patients consisting of 0.57% of this population, which was rather low yielding an average of 23% (1013 patients in 2012; 902 in 2013; 986 in 2014).

The prevalence of nephrolithiasis in patients with IBS across the 3 years analyzed presented 359 patients in 2012, 272 in 2013 and 327 patients in 2014 for a total of 958 patients. Patients with a documented co-morbidity make up 0.19% of this nephrolithiasis population, with a lower incidence observed in males (28.1% in 2012; 32% in 2013; 32.7% in 2014) than that of females (71.9% in 2012; 68% in 2013; 67.3% in 2014) (see Table 2). Therefore, gender in IBS patients should be considered as a key component of nephrolithiasis. Further evaluation of IBS patients is examined once all preliminary descriptive statistical analyses are presented. This approach allows for a baseline to be established for factors contributing to nephrolithiasis, as well as validation of the literature reviewed.

Table 2. Prevalence of IBS in Males vs. Females

2012

Indicator of sex

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	101	28.1	28.1	28.1
	1	258	71.9	71.9	100.0
	Total	359	100.0	100.0	

2013

Indicator of sex

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	87	32.0	32.0	32.0
	1	185	68.0	68.0	100.0
	Total	272	100.0	100.0	

2014

Indicator of sex

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	107	32.7	32.7	32.7
	1	220	67.3	67.3	100.0
	Total	327	100.0	100.0	

The prevalence of dehydration as a primary diagnosis and/or secondary diagnosis (see Table 3) was investigated as well as hyperosmolality (see Table 4). As the primary recommendation for prevention of nephrolithiasis is increased fluid intake and based on the process of stone formation, dehydration would likely be present in these patients. Hyperosmolality in patients with nephrolithiasis is worth noting in this study as this is an indicator of dehydration and an alternative method of assessment as plasma osmolality is not identified in ICD-9 coding. As plasma osmolality is a key indicator of chronic dehydration, hyperosmolality is also a key indicator of dehydration. The total number of patients from 2012 to 2014 with a diagnosis of dehydration in this study is 4605 (0.9%). The total number of patients with a diagnosis of hyperosmolality in this study is 204 (0.04%). This low yield results in question of whether data collection or assessment of hydration status is lacking.

Table 3. Prevalence of Dehydration in Nephrolithiasis

2012

Statistics

		Diagnosis 1	Diagnosis 2	Diagnosis 3	Diagnosis 4
N	Valid	1624	1624	1624	1624
	Missing	0	0	0	0

Diagnosis 1

	Frequency	Percent	Valid Percent	Cumulative Percent
27651	160	9.9	9.9	12.4
5920	756	46.6	46.6	75.1
5921	104	6.4	6.4	81.5

Diagnosis 2

	Frequency	Percent	Valid Percent	Cumulative Percent
27651	570	35.1	35.1	39.0
5920	320	19.7	19.7	79.2
5921	35	2.2	2.2	81.3

2013

Statistics

		Diagnosis 1	Diagnosis 2	Diagnosis 3	Diagnosis 4
N	Valid	1402	1402	1402	1402
	Missing	0	0	0	0

Diagnosis 1

	Frequency	Percent	Valid Percent	Cumulative Percent
27651	145	10.3	10.3	13.0
5920	633	45.1	45.1	76.5
5921	69	4.9	4.9	81.5

Diagnosis 2

	Frequency	Percent	Valid Percent	Cumulative Percent
27651	515	36.7	36.7	41.9
5920	280	20.0	20.0	81.2
5921	27	1.9	1.9	83.1

2014

Statistics

		Diagnosis 1	Diagnosis 2	Diagnosis 3	Diagnosis 4
N	Valid	1579	1579	1579	1579
	Missing	0	0	0	0

Diagnosis 1

	Frequency	Percent	Valid Percent	Cumulative Percent
27651	178	11.3	11.3	14.6
5920	717	45.4	45.4	77.1
5921	98	6.2	6.2	83.3

Diagnosis 2

	Frequency	Percent	Valid Percent	Cumulative Percent
27651	563	35.7	35.7	38.6
5920	327	20.7	20.7	79.4
5921	34	2.2	2.2	81.6

Table 4. Prevalence of Hyperosmolality in Nephrolithiasis

2012

Statistics

		Diagnosis 1	Diagnosis 2	Diagnosis 3	Diagnosis 4
N	Valid	52	52	52	52
	Missing	0	0	0	0

Diagnosis 1

	Frequency	Percent	Valid Percent	Cumulative Percent
5920	20	38.5	38.5	88.5
5921	1	1.9	1.9	90.4

Diagnosis 2

	Frequency	Percent	Valid Percent	Cumulative Percent
2760	28	53.8	53.8	57.7
5920	1	1.9	1.9	88.5
5990	4	7.7	7.7	96.2

2013

Statistics

		Diagnosis 1	Diagnosis 2	Diagnosis 3	Diagnosis 4
N	Valid	70	70	70	70
	Missing	0	0	0	0

Diagnosis 1

	Frequency	Percent	Valid Percent	Cumulative Percent
5920	28	40.0	40.0	77.1
5921	4	5.7	5.7	82.9

Diagnosis 2

	Frequency	Percent	Valid Percent	Cumulative Percent
2760	40	57.1	57.1	62.9

2014

Statistics

		Diagnosis 1	Diagnosis 2	Diagnosis 3	Diagnosis 4
N	Valid	82	82	82	82
	Missing	0	0	0	0

Diagnosis 1

	Frequency	Percent	Valid Percent	Cumulative Percent
5920	33	40.2	40.2	84.1
5921	2	2.4	2.4	86.6

Diagnosis 2

	Frequency	Percent	Valid Percent	Cumulative Percent
2760	48	58.5	58.5	59.8
5920	3	3.7	3.7	90.2
5921	1	1.2	1.2	91.5

Medical imaging is a key component of nephrolithiasis assessment and care. Patients included in the HCUP NEDS 2012, 2013 and 2014 Supplemental Emergency Department Files, which provide "information on procedures that were performed in the ED for treat and release",[62] had ultrasound imaging of the urinary system performed as the principal procedure (see Figure 2), more often than Computed Tomography (CT) imaging (see Figure 3) which the ACR's evidence based clinical guidelines recommend for initial imaging of suspected nephrolithiasis. These percentages are based on the total number of imaging exams per modality.

Figure 2. Ultrasound as Principal Procedure in ED with Nephrolithiasis

2012 **2013** **2014**

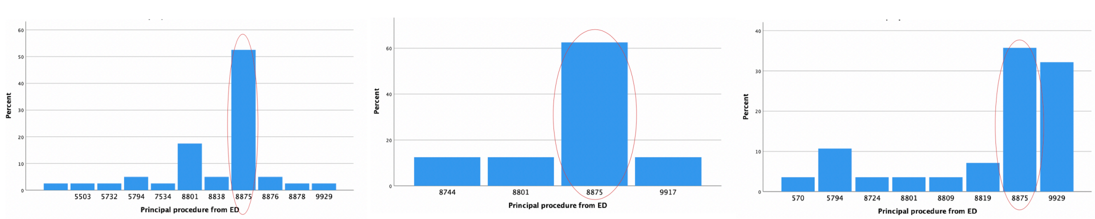
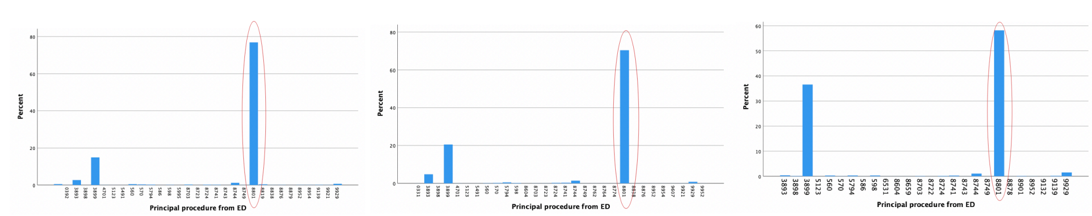


Figure 3. CT as Principal Procedure in ED with Nephrolithiasis

2012 **2013** **2014**



Patients included in the HCUP NEDS Supplemental Inpatient Files, which provide "information on inpatient admissions after ED visits",[62] demonstrate a higher incidence of CT imaging (See Figure 4) than that of ultrasound (see Figure 5) demonstrating the need to analyze this data to further support or negate the hypothesis that patients imaged with ultrasound before CT have poorer outcomes and greater overall hospital charges for combined ED and inpatient services.

Figure 4. CT as Principal Procedure for Inpatients with Nephrolithiasis

2012 **2013** **2014**

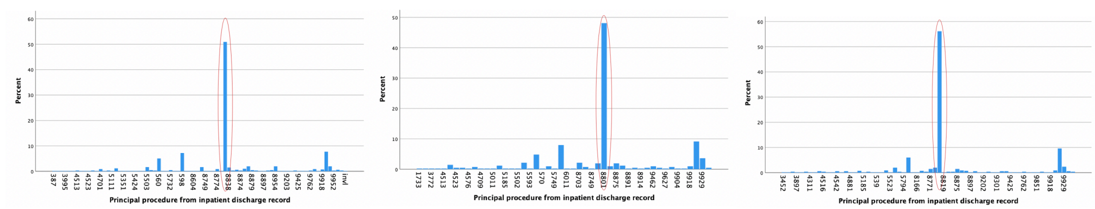
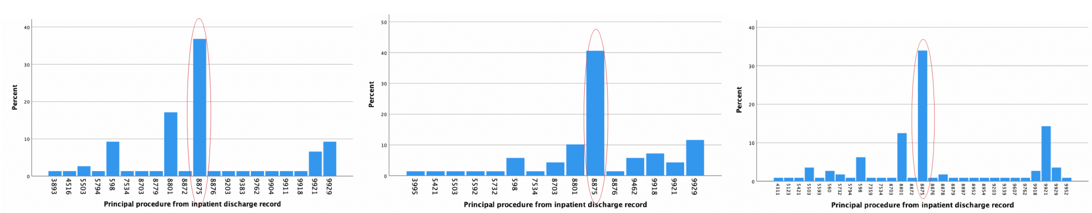


Figure 5. Ultrasound as Principal Procedure for Inpatients with Nephrolithiasis

2012 **2013** **2014**



Intervention of nephrolithiasis is a strong indicator of stone size, as the ability of a smaller stone to pass is far more likely than that of a larger stone. Generally, stones that are too large to pass on their own or that result in bleeding or infection require intervention. The HCUP NEDS datasets include a procedure class data element that "categorizes ICD-9 procedure codes into one of four broad categories".[64] These categories include minor diagnostic, minor therapeutic, major diagnostic and major therapeutic. Minor categories represent non-operating room procedures and therapies, whereas major categories represent valid operating room procedures and therapies. Of the nephrolithiasis cases found in the datasets, interventions were performed in 9158 (5.6% of this population) inpatients in 2012, 8542 (5.2% of this population) inpatients in 2013 and 9628 (5.3% of this population) inpatients in 2014 (see Table 5) for a total of 27,328 (5.4% of this overall population) interventions. The 2012 interventions include 2038 minor diagnostic procedures, 3978 minor therapeutic procedures, 58 major diagnostic and 3048 major therapeutic for those admitted to the hospital with nephrolithiasis. The types of interventions related to nephrolithiasis identified in this study include percutaneous nephrostomy without fragmentation, percutaneous nephrostomy with fragmentation, ureteroscopy, cystoscopy, ultrasonic fragmentation of urinary stones, retrograde pyelogram, percutaneous pyelogram, extracorporeal shockwave lithotripsy (ESWL) and ESWL of the kidney, ureter or bladder.

Table 5. Principal Procedure Class for Inpatients with Nephrolithiasis

2012

Principal procedure class for inpatient procedure

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2038	1.2	22.3	22.3
	2	3978	2.4	43.4	65.7
	3	58	.0	.6	66.3
	4	3084	1.9	33.7	100.0
	Total	9158	5.6	100.0	
Missing	System	155252	94.4		
Total		164410	100.0		

2013

Principal procedure class for inpatient procedure

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1806	1.1	21.1	21.1
	2	3849	2.4	45.1	66.2
	3	43	.0	.5	66.7
	4	2844	1.7	33.3	100.0
	Total	8542	5.2	100.0	
Missing	System	154712	94.8		
Total		163254	100.0		

2014

Principal procedure class for inpatient procedure

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	2024	1.1	21.0	21.0
	2	4391	2.4	45.6	66.6
	3	48	.0	.5	67.1
	4	3165	1.7	32.9	100.0
	Total	9628	5.3	100.0	
Missing	System	171900	94.7		
Total		181528	100.0		

Table 6. Principal Interventions and Procedures for Inpatients with Nephrolithiasis

2012

Principal procedure from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
5503	7	1.1	1.1	1.7
5504	4	.6	.6	2.3
5631	53	8.0	8.0	80.8
5732	10	1.5	1.5	82.9
5995	5	.8	.8	95.3
8774	13	2.0	2.0	97.6
9851	9	1.4	1.4	99.7

2013

Principal procedure from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
5503	238	.1	.1	95.9
5504	62	.0	.0	96.0
5631	65	.0	.0	97.2
5732	171	.1	.1	97.3
5995	27	.0	.0	98.6
8774	399	.2	.2	99.0
8775	21	.0	.0	99.0
9851	363	.2	.2	99.7

2014

Principal procedure from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
5503	352	.2	.2	96.0
5504	92	.1	.1	96.0
5631	63	.0	.0	97.1
5732	175	.1	.1	97.2
5995	51	.0	.0	98.5
8774	360	.2	.2	98.9
8775	19	.0	.0	98.9
9851	373	.2	.2	99.6

Total charges for ED services of nephrolithiasis patients versus total charges for inpatients was assessed. The mean for ED services is $5639 in 2012, $5946 in 2013 and $6426 in 2014 (see Figure 6). The mean for inpatient services is $27,165 in 2012, $29503 in 2013 and $32801 (see Figure 7). The significance of cost for patients admitted to the hospital for nephrolithiasis represent additional care, as well as diagnostic and therapeutic procedures.

Figure 6. Total Charges for ED Services

2012 **2013** **2014**

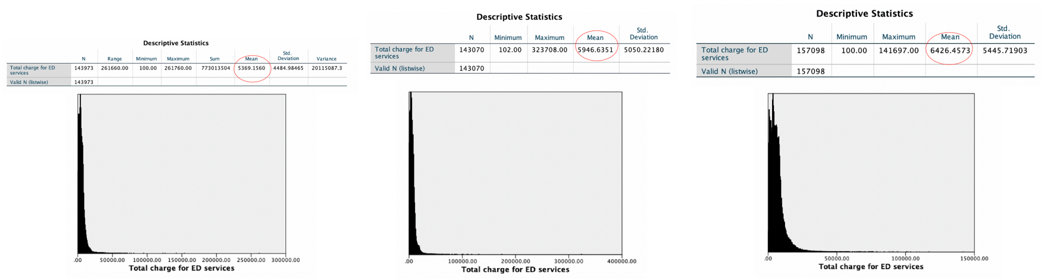
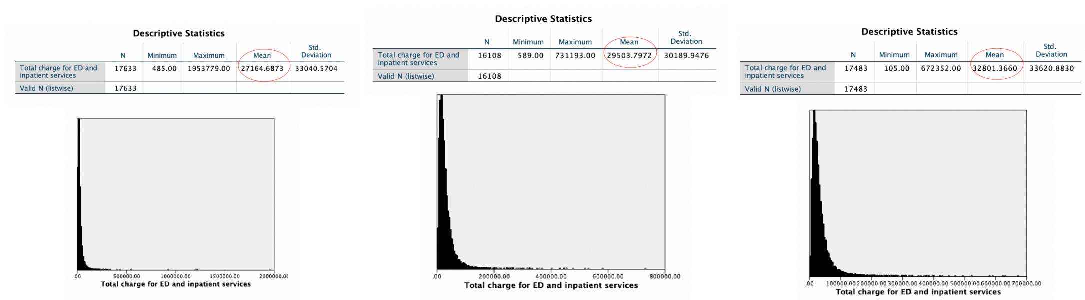


Figure 7. Total Charges for ED & Inpatient Services

2012 ***2013*** ***2014***



These preliminary results of nephrolithiasis demonstrate the significance of this study in its aim of filling the gap between evidence based clinical guidelines and practice in assessing nephrolithiasis with CT versus ultrasound, assessment of patient outcomes and hospital admission. Further investigation into the link between nephrolithiasis and irritable bowel syndrome as a co-morbidity and key indicator of stone occurrence and size, with need for intervention is reviewed. IBS patients commonly present with dehydration, a common risk factor in nephrolithiasis. This particular patient population is at a greater risk of chronic dehydration due to frequent bouts of diarrhea.

4.3 Descriptive Statistical Analysis of IBS

Analyses of the 2012, 2013 and 2014 HCUP NEDS databases have identified a total of 958 ED visits for nephrolithiasis in patients with Irritable Bowel Syndrome. Although the prevalence of nephrolithiasis was found to be more common in males than females in the initial analyses, the prevalence is far greater in females (67%) with IBS. Of these patients identified, only 22 patients across the 3 years analyzed were assessed or diagnosed with computed tomography (CT) and none were assessed with ultrasound. 104 of these 958 IBS patients (10.9% of this population) underwent diagnostic or therapeutic procedures (see Table 7). This number represents a total of 81 minor diagnostic or therapeutic procedures and 27 major diagnostic or therapeutic procedures. Principal interventions and procedures directly related to nephrolithiasis in patients with IBS include a total of 17 in 2012, 16 in 2013 and 11 in 2014 (see Table 8).

Table 7. Principal Procedure Class for IBS Patients

2012

Principal procedure class for inpatient procedure

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	25	7.0	62.5	62.5
	2	10	2.8	25.0	87.5
	4	5	1.4	12.5	100.0
	Total	40	11.1	100.0	
Missing	System	319	88.9		
Total		359	100.0		

2013

Principal procedure class for inpatient procedure

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	11	4.0	35.5	35.5
	2	10	3.7	32.3	67.7
	4	10	3.7	32.3	100.0
	Total	31	11.4	100.0	
Missing	System	241	88.6		
Total		272	100.0		

2014

Principal procedure class for inpatient procedure

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	15	4.6	45.5	45.5
	2	10	3.1	30.3	75.8
	4	8	2.4	24.2	100.0
	Total	33	10.1	100.0	
Missing	System	294	89.9		
Total		327	100.0		

Table 8. Principal Interventions & Procedure Total for IBS

2012

Principal procedure from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
5631	1	.3	.3	95.3
5732	1	.3	.3	95.5

Procedure 2 from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
5631	1	.3	.3	96.1
5732	1	.3	.3	96.4
598	4	1.1	1.1	97.5
5995	1	.3	.3	97.8
8774	1	.3	.3	98.6

Procedure 3 from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
8774	4	1.1	1.1	99.4

Procedure 4 from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
5631	1	.3	.3	99.2
8774	2	.6	.6	99.7

2013

Principal procedure from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
5503	1	.4	.4	93.8
9851	1	.4	.4	99.3

Procedure 2 from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
5503	1	.4	.4	94.5
8774	2	.7	.7	99.3

Procedure 3 from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
5631	1	.4	.4	97.1
8774	5	1.8	1.8	98.9
8775	1	.4	.4	99.3
9851	1	.4	.4	100.0

Procedure 4 from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
5732	1	.4	.4	99.3
8774	2	.7	.7	100.0

2014

Principal procedure from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
5504	1	.3	.3	94.8
8774	1	.3	.3	96.9
9851	1	.3	.3	99.1

Procedure 2 from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
5503	1	.3	.3	95.1
5631	3	.9	.9	96.0
8774	2	.6	.6	98.5

Procedure 3 from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
5732	1	.3	.3	97.6

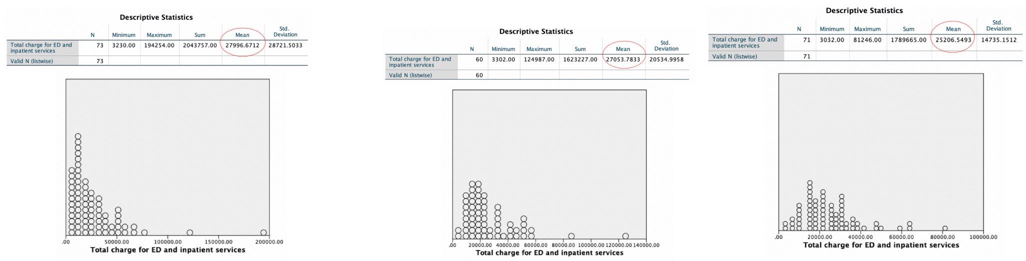
Procedure 4 from inpatient discharge record

	Frequency	Percent	Valid Percent	Cumulative Percent
8774	1	.3	.3	99.7

Total charges for ED and inpatient services of nephrolithiasis patients with IBS were assessed. The mean for total charges is $27,997 in 2012, $25,207 in 2013 and $27,054 in 2014 (see Figure 8). The significance of cost for IBS patients admitted to the hospital for nephrolithiasis represent additional care as well as diagnostic and therapeutic procedures.

Figure 8. Total Charges for ED & Inpatient Services in IBS

2012 2013 2014



4.4 Multiple Regression Analysis

A standard multiple regression was performed on the HCUP NEDS 2012, 2013 and 2014 datasets for nephrolithiasis patients with IBS. This method allows for all independent, or predictor, variables to be simultaneously entered into the model. Independent variables are each evaluated in terms of their predictive power in comparison to that of the other independent variables. Insight is provided where each of the independent variables may explain unique variances in a dependent variable.

In the 2012 HCUP NEDS dataset linear regression model tested, the primary diagnosis of nephrolithiasis was utilized as the dependent variable, while age, gender, comorbidities, principal and secondary procedures from the ED, as well as principal and secondary procedures from the inpatient discharge record were utilized as independent variables. The P value for principal procedure from the inpatient discharge record rejects the null hypothesis that these procedures happen by chance, with a return of 0.001 (see Table 9). This information demonstrates that the principal procedure from the inpatient discharge record represents a statistically significant contribution. Principal procedures include medical imaging modalities such as ultrasound and CT as well as minor and or major procedures and interventions. Based on the information provided in the descriptive statistical analysis of IBS patients in 2012, ureteroscopy and cystoscopy were the only principal procedures returned related to nephrolithiasis demonstrating the significance of these procedures to nephrolithiasis in IBS patients. While the 2013 dataset does not provide the same results, the 2014 dataset rejects the null hypothesis with a P value of 0.024 for principal procedure from the ED (see Table 10). The information provided in the descriptive statistical analysis of IBS patients in 2014 returned CT of the abdomen as the most common procedure in the ED. These results from the linear regression models in 2012 and 2014 require additional regression models of analysis to better understand the data and determine which variables may have higher predictability.

Table 9. Linear Regression of IBS for 2012

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	32.604	3.006		10.846	.000	26.692	38.517
	Age in years at admission	-.009	.040	-.012	-.222	.825	-.086	.069
	Indicator of sex	1.381	1.298	.056	1.063	.288	-1.173	3.934
	Principal procedure from ED	.522	.368	.091	1.421	.156	-.201	1.246
	Procedure 2 from ED	-.961	.809	-.076	-1.189	.235	-2.551	.629
	Principal procedure from inpatient discharge record	-.902	.278	-.241	-3.241	.001	-1.450	-.355
	Procedure 2 from inpatient discharge record	.349	.298	.087	1.173	.242	-.236	.935
	Diagnosis 2	.026	.038	.037	.685	.494	-.048	.100
	Diagnosis 3	.003	.031	.005	.084	.933	-.058	.063
	Diagnosis 4	-1.819E-5	.030	.000	-.001	1.000	-.058	.058

a. Dependent Variable: Diagnosis 1

Table 10. Linear Regression of IBS for 2014

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	19.247	2.130		9.037	.000	15.057	23.437
	Age in years at admission	.026	.029	.051	.912	.363	-.030	.083
	Indicator of sex	1.578	.873	.101	1.808	.072	-.140	3.295
	Diagnosis 2	.048	.031	.087	1.567	.118	-.012	.109
	Diagnosis 3	.025	.018	.077	1.356	.176	-.011	.061
	Diagnosis 4	-.011	.019	-.034	-.596	.551	-.049	.026
	Principal procedure from ED	-1.326	.584	-.170	-2.270	.024	-2.474	-.177
	Procedure 2 from ED	.611	.606	.075	1.008	.314	-.581	1.803
	Principal procedure from inpatient discharge record	-.091	.175	-.041	-.520	.603	-.435	.253
	Procedure 2 from inpatient discharge record	-.248	.277	-.070	-.897	.371	-.794	.297

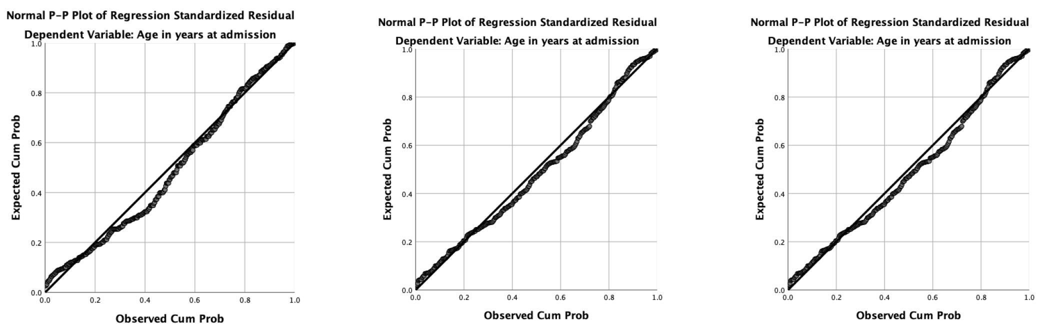
a. Dependent Variable: Diagnosis 1

A stepwise regression model was then tested with age as the dependent variable as it has been determined to be a contributing factor of nephrolithiasis and gender, diagnoses, principal procedures from the ED, principal procedures from the inpatient discharge record as independent variables. This stepwise regression allows SPSS to automatically select variables based on statistical criteria and enter it in order of the equation. Although this method can be controversial for its false positive errors, in machine learning stepwise procedures have been utilized with remarkable success. Because this study is exploratory, this method has also been tested.

The 2012 HCUP NEDS dataset yields an adjusted R square of 0.011, demonstrating 1% of variance of age (dependent variable) is explained by independent variables. These results determine that age does not influence the principal procedures performed, including ultrasound vs. CT, however does not indicate that age does not contribute to nephrolithiasis. The Normal Probability Plot (P-P) for age does not suggest any major deviations from normality demonstrating age as a standardized result. The 2013 and 2014 HCUP NEDS datasets, age is normalized against the 2012 dataset results with R square (0.061 or 6% in 2013 and 0.026 or 2% in 2014) and P-Plots showing very similar results (see Figure 9).

Figure 9. P-Plot of Age in IBS

2012 **2013** **2014**



Principal procedure class was then assessed using the stepwise model of regression. This method allowed for assessment of independent variables such as primary diagnosis and co-morbidity to predict outcomes. In the 2012 analysis, procedures play a role in predictability which is seen in values of 0.002 and 0.035 (see Table 10) and in 2013 although not statistically significant, the P value for the principal procedure from the inpatient discharge record returned .054 (see Table 10). In 2014, co-morbidity played a role in predictability which can be seen in the P value as 0.025 (see Table 10). While there is variability in these stepwise regression models, the data provided gives insight into the diagnostic and therapeutic procedures for IBS patients, a key component of this study.

Table 11. Stepwise Regression of Principal Procedure Class for Inpatients with IBS

2012

Coefficients[a]

Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	t	Sig.	95.0% Confidence Interval for B Lower Bound	95.0% Confidence Interval for B Upper Bound
1	(Constant)	.703	.763		.921	.364	-.853	2.259
	Diagnosis 1	.024	.015	.212	1.629	.113	-.006	.054
	Diagnosis 2	.001	.009	.009	.080	.937	-.017	.019
	Diagnosis 3	-.004	.007	-.065	-.544	.590	-.019	.011
	Diagnosis 4	-.007	.007	-.122	-1.022	.315	-.020	.007
	Principal procedure from inpatient discharge record	-.020	.028	-.093	-.719	.478	-.077	.037
	Procedure 2 from inpatient discharge record	-.023	.028	-.137	-.792	.434	-.081	.036
	Procedure 3 from inpatient discharge record	.225	.064	.576	3.481	.002	.093	.356
	Procedure 4 from inpatient discharge record	.266	.121	.334	2.205	.035	.020	.513

a. Dependent Variable: Principal procedure class for inpatient procedure

2013

Coefficients[a]

Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	t	Sig.	95.0% Confidence Interval for B Lower Bound	95.0% Confidence Interval for B Upper Bound
1	(Constant)	.911	1.305		.698	.492	-1.796	3.618
	Diagnosis 1	.013	.024	.085	.532	.600	-.037	.062
	Diagnosis 2	-.008	.012	-.108	-.667	.512	-.034	.017
	Diagnosis 3	.009	.019	.084	.466	.646	-.031	.049
	Diagnosis 4	.005	.018	.047	.255	.801	-.033	.042
	Principal procedure from inpatient discharge record	.143	.070	.388	2.037	.054	-.003	.289
	Procedure 2 from inpatient discharge record	.084	.084	.192	.995	.330	-.091	.258
	Procedure 3 from inpatient discharge record	.210	.139	.290	1.515	.144	-.078	.498
	Procedure 4 from inpatient discharge record	-.659	.453	-.271	-1.456	.160	-1.597	.280

a. Dependent Variable: Principal procedure class for inpatient procedure

2014

Coefficients[a]

Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	t	Sig.	95.0% Confidence Interval for B Lower Bound	95.0% Confidence Interval for B Upper Bound
1	(Constant)	1.872	1.222		1.532	.139	-.650	4.394
	Diagnosis 1	-.005	.028	-.034	-.195	.847	-.063	.052
	Diagnosis 2	-.021	.019	-.185	-1.070	.295	-.060	.019
	Diagnosis 3	.028	.012	.412	2.392	.025	.004	.052
	Diagnosis 4	-.012	.010	-.204	-1.188	.246	-.033	.009
	Principal procedure from inpatient discharge record	.053	.045	.241	1.186	.247	-.040	.146
	Procedure 2 from inpatient discharge record	.028	.049	.113	.566	.577	-.074	.130
	Procedure 3 from inpatient discharge record	.383	.207	.415	1.855	.076	-.043	.810
	Procedure 4 from inpatient discharge record	-1.253	.635	-.398	-1.973	.060	-2.563	.057

a. Dependent Variable: Principal procedure class for inpatient procedure

Additional stepwise regression models were analyzed with total charges as the dependent variable, while age, gender and procedure class were independent variables. Total charges for ED services as the outcome variable were analyzed first for the 2012, 2013 and 2014 datasets and then total charges for ED and Inpatient services for each dataset were analyzed.

The 2012 stepwise regression model for total charges for ED services yields a P-value of 0.000 for principal procedure class for major therapeutic procedures which include interventions requiring the use of the operating room (OR), and a P-value of 0.017 for minor diagnostic procedures which include ultrasound and CT imaging (see Table 12). These P-values reject the null hypothesis that major therapeutic and minor diagnostic procedures and interventions happen by chance, and represent statistically significant contributions to total charges for ED visits. The adjusted R-square goes up slightly with the addition of minor diagnostic procedures by 0.092.

Table 12. Stepwise Regression of Total Charges for ED Services 2012

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	5208.518	268.249		19.417	.000	4680.630	5736.405
	PCLASS_MAJORTX_ED	22980.482	4661.665	.274	4.930	.000	13806.779	32154.186
2	(Constant)	5078.792	271.632		18.697	.000	4544.239	5613.345
	PCLASS_MAJORTX_ED	23110.208	4625.730	.275	4.996	.000	14007.097	32213.320
	PCLASS_MinorDX_ED	3253.958	1360.423	.132	2.392	.017	576.742	5931.175

a. Dependent Variable: Total charge for ED services

The 2012 stepwise model with total charges for ED and Inpatient services as the dependent variable yields P-values of 0.006 and 0.001 for minor therapeutic non-OR procedures, as well as a P-value of 0.018 for minor diagnostic procedures which, again include ultrasound and CT imaging (see Table 13). These P-values reject the null hypothesis that these minor therapeutic and minor diagnostic procedures happen by chance, and represent statistically significant contributions to total charges for ED and Inpatient services. The adjusted R-square goes up slightly with the addition of minor diagnostic procedures by 0.147.

Table 13. Stepwise Regression of Total Charges for ED and Inpatient Services 2012

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	24591.547	3427.299		7.175	.000	17757.706	31425.388
	PCLASS_MinorTX_IP	27619.342	9760.953	.318	2.830	.006	8156.555	47082.129
2	(Constant)	18176.359	4248.106		4.279	.000	9703.779	26648.939
	PCLASS_MinorTX_IP	34034.530	9810.580	.392	3.469	.001	14467.946	53601.114
	PCLASS_MinorDX_IP	16422.881	6796.969	.273	2.416	.018	2866.754	29979.008

a. Dependent Variable: Total charge for ED and inpatient services

The 2013 stepwise regression model for total charges for ED services yields a P-value of 0.000 for principal procedure class for major therapeutic procedures which include interventions requiring the use of the operating room (OR), and a P-value of 0.006 for minor therapeutic, or non-OR, procedures (see Table 14). These P-values reject the null hypothesis that major therapeutic and minor therapeutic procedures and interventions happen by chance, and represent statistically significant contributions to total charges for ED visits. The adjusted R-square goes up slightly with the addition of minor therapeutic procedures by 0.156.

Table 14. Stepwise Regression of Total Charges for ED Services 2013

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	4995.332	281.106		17.770	.000	4441.341	5549.323
	PCLASS_MAJORTX_ED	24577.668	4197.804	.366	5.855	.000	16304.820	32850.516
2	(Constant)	4857.417	281.464		17.258	.000	4302.706	5412.129
	PCLASS_MAJORTX_ED	24715.583	4136.664	.369	5.975	.000	16563.023	32868.143
	PCLASS_MinorTX_ED	4373.869	1585.079	.170	2.759	.006	1249.987	7497.750

a. Dependent Variable: Total charge for ED services

The 2013 stepwise model with total charges for ED and Inpatient services as the dependent variable yields P-values of 0.004 for gender as an independent variable and reject the null hypothesis and represents a statistically significant contribution to total charges for ED and Inpatient services (see Table 15).

Table 15. Stepwise Regression of Total Charges for ED and Inpatient Services 2013

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	34462.750	3487.699		9.881	.000	27504.981	41420.519
	Indicator of sex	-11948.914	3962.660	-.341	-3.015	.004	-19854.204	-4043.624

a. Dependent Variable: Total charge for ED and inpatient services

The 2014 stepwise regression model for total charges for ED services yields a P-value of 0.000 for principal procedure class for major therapeutic procedures which include interventions requiring the use of the OR (see Table 16). This P-values rejects the null hypothesis and represents a statistically significant contribution to total charges for ED visits.

Table 16. Stepwise Regression of Total Charges for ED Services 2014

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	6371.311	329.259		19.350	.000	5723.154	7019.468
	PCLASS_MAJORTX_ED	23037.689	5509.553	.243	4.181	.000	12191.948	33883.431

a. Dependent Variable: Total charge for ED services

The 2014 stepwise model with total charges for ED and Inpatient services as the dependent variable yields P-values of 0.001 for major therapeutic, OR procedures (see Table 17). This P-values rejects the null hypothesis and represents a statistically significant contribution to total charges for ED and Inpatient services.

Table 17. Stepwise Regression of Total Charges for ED and Inpatient Services 2014

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	23668.058	2601.319		9.098	.000	18460.952	28875.164
	PCLASS_MAJORTX_IP	25392.942	7124.006	.424	3.564	.001	11132.695	39653.189

a. Dependent Variable: Total charge for ED and inpatient services

The 2012, 2013 and 2014 stepwise regression analyses with total charges as the dependent variable and gender and procedure class as independent variables contributing to the model confirm the hypothesis that patients with a co-morbidity of IBS that are assessed with ultrasound before CT have poorer outcomes and accrue greater healthcare costs, due to additional imaging and the need for intervention.

4.5 Hierarchical Regression Analysis

Further analyses of the HCUP NEDS 2012, 2013 and 2014 datasets were then performed using hierarchical multiple regression, or sequential regression. This method allows for variables to be manually entered in predetermined blocks, or steps. The dependent variable is a primary diagnosis of nephrolithiasis with the first block entered into the analysis for co-morbidities. The second block in this analysis is for principal procedures in the ED, and the third block is for principal procedures for inpatients.

In the 2012 hierarchical regression analysis, the R Square values are reviewed and the overall model yields 0.3% of the variance, with block 2 variables included in the model there is 0.9% variance and with block 3 variables included in the model there is 4.7% variance. When R Square changed is reviewed for overall variance explained by variables of interest, the inpatient principal procedures add an additional 3.8% of the variance in nephrolithiasis patients with IBS (see Table 18). There is only one variable, principal procedure from inpatient discharge record, that provides a statistically significant contribution to the model (P value of 0.001 or 0.1%) with evaluation of each independent variable. Although not considered a unique contribution, the principal procedure from the ED yields a P value of 0.142 or 14% and is the next closest result.

Table 18. Hierarchical Regression Analysis 2012

Model Summary[d]

					Change Statistics				
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	R Square Change	F Change	df1	df2	Sig. F Change
1	.055[a]	.003	-.005	11.053	.003	.358	3	355	.784
2	.097[b]	.009	-.008	11.065	.006	.750	3	352	.523
3	.217[c]	.047	.020	10.915	.038	3.437	4	348	.009

a. Predictors: (Constant), Diagnosis 4, Diagnosis 2, Diagnosis 3

b. Predictors: (Constant), Diagnosis 4, Diagnosis 2, Diagnosis 3, Principal procedure from ED, Procedure 4 from ED, Procedure 2 from ED

c. Predictors: (Constant), Diagnosis 4, Diagnosis 2, Diagnosis 3, Principal procedure from ED, Procedure 4 from ED, Procedure 2 from ED, Procedure 4 from inpatient discharge record, Principal procedure from inpatient discharge record, Procedure 3 from inpatient discharge record, Procedure 2 from inpatient discharge record

d. Dependent Variable: Diagnosis 1

Coefficients[a]

		Unstandardized Coefficients		Standardized Coefficients			Correlations			Collinearity Statistics	
Model		B	Std. Error	Beta	t	Sig.	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	31.139	2.080		14.971	.000					
	Diagnosis 2	.038	.038	.053	1.003	.317	.054	.053	.053	.991	1.010
	Diagnosis 3	.004	.031	.007	.119	.905	.013	.006	.006	.938	1.067
	Diagnosis 4	.004	.030	.007	.120	.905	.008	.006	.006	.946	1.058
2	(Constant)	31.577	3.552		8.889	.000					
	Diagnosis 2	.037	.038	.052	.968	.334	.054	.052	.051	.988	1.012
	Diagnosis 3	.005	.031	.009	.170	.865	.013	.009	.009	.932	1.073
	Diagnosis 4	.002	.030	.004	.073	.941	.008	.004	.004	.942	1.062
	Principal procedure from ED	.547	.372	.095	1.471	.142	.060	.078	.078	.677	1.478
	Procedure 2 from ED	-.760	1.134	-.060	-.670	.503	-.010	-.036	-.036	.351	2.852
	Procedure 4 from ED	-.342	3.603	-.008	-.095	.924	-.014	-.005	-.005	.437	2.290
3	(Constant)	34.232	3.851		8.890	.000					
	Diagnosis 2	.029	.037	.041	.775	.439	.054	.042	.041	.984	1.016
	Diagnosis 3	.005	.031	.009	.168	.867	.013	.009	.009	.928	1.077
	Diagnosis 4	.001	.030	.002	.028	.978	.008	.002	.001	.941	1.062
	Principal procedure from ED	.482	.368	.083	1.311	.191	.060	.070	.069	.675	1.482
	Procedure 2 from ED	-.757	1.118	-.060	-.677	.499	-.010	-.036	-.035	.351	2.852
	Procedure 4 from ED	-.453	3.554	-.010	-.128	.899	-.014	-.007	-.007	.437	2.291
	Principal procedure from inpatient discharge record	-.919	.284	-.246	-3.241	.001	-.185	-.171	-.170	.477	2.096
	Procedure 2 from inpatient discharge record	.530	.376	.132	1.410	.159	-.084	.075	.074	.313	3.190
	Procedure 3 from inpatient discharge record	-.281	.958	-.025	-.293	.770	-.097	-.016	-.015	.371	2.699
	Procedure 4 from inpatient discharge record	-.858	1.795	-.034	-.478	.633	-.065	-.026	-.025	.528	1.893

a. Dependent Variable: Diagnosis 1

In the 2013 hierarchical regression analysis, the R Square values are reviewed and the overall model yields 0.7% of the variance, with block 2 variables included in the model there is 1.1% variance and with block 3 variables included in the model there is 2.9% variance. When R Square changed is reviewed for overall variance explained by variables of interest, the inpatient principal procedures add an additional 1.8% of the variance in nephrolithiasis patients with IBS (see Table 19).

Table 19. Hierarchical Regression Analysis 2013

Model Summary[d]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics: R Square Change	F Change	df1	df2	Sig. F Change
1	.081[a]	.007	-.005	9.321	.007	.585	3	268	.625
2	.104[b]	.011	-.015	9.371	.004	.286	4	264	.887
3	.169[c]	.029	-.012	9.357	.018	1.200	4	260	.311

a. Predictors: (Constant), Diagnosis 4, Diagnosis 2, Diagnosis 3

b. Predictors: (Constant), Diagnosis 4, Diagnosis 2, Diagnosis 3, Principal procedure from ED, Procedure 4 from ED, Procedure 3 from ED, Procedure 2 from ED

c. Predictors: (Constant), Diagnosis 4, Diagnosis 2, Diagnosis 3, Principal procedure from ED, Procedure 4 from ED, Procedure 3 from ED, Procedure 2 from ED, Principal procedure from inpatient discharge record, Procedure 4 from inpatient discharge record, Procedure 3 from inpatient discharge record, Procedure 2 from inpatient discharge record

d. Dependent Variable: Diagnosis 1

Coefficients[a]

Model		Unstandardized Coefficients B	Std. Error	Standardized Coefficients Beta	t	Sig.	95.0% Confidence Interval for B Lower Bound	Upper Bound	Correlations Zero-order	Partial	Part	Collinearity Statistics Tolerance	VIF
1	(Constant)	24.715	2.136		11.573	.000	20.511	28.920					
	Diagnosis 2	.010	.033	.019	.304	.762	-.055	.075	.020	.019	.018	.984	1.016
	Diagnosis 3	.028	.044	.038	.619	.537	-.060	.115	.050	.038	.038	.961	1.041
	Diagnosis 4	.032	.031	.062	1.006	.315	-.030	.093	.068	.061	.061	.970	1.031
2	(Constant)	23.978	3.171		7.562	.000	17.735	30.222					
	Diagnosis 2	.009	.033	.016	.261	.794	-.057	.075	.020	.016	.016	.975	1.026
	Diagnosis 3	.030	.045	.043	.675	.500	-.058	.119	.050	.042	.041	.944	1.059
	Diagnosis 4	.033	.032	.065	1.048	.296	-.029	.096	.068	.064	.064	.961	1.041
	Principal procedure from ED	.287	.607	.035	.472	.637	-.909	1.483	.033	.029	.029	.689	1.452
	Procedure 2 from ED	3.052	4.919	.145	.620	.536	-6.635	12.738	-.005	.038	.038	.069	14.552
	Procedure 3 from ED	-3.184	3.953	-.184	-.805	.421	-10.967	4.600	-.019	-.050	-.049	.072	13.974
	Procedure 4 from ED	.455	2.471	.014	.184	.854	-4.409	5.320	-.008	.011	.011	.634	1.578
3	(Constant)	22.319	4.624		4.826	.000	13.213	31.425					
	Diagnosis 2	.008	.033	.016	.253	.801	-.057	.074	.020	.016	.015	.974	1.026
	Diagnosis 3	.038	.046	.053	.835	.404	-.052	.128	.050	.052	.051	.918	1.089
	Diagnosis 4	.039	.032	.076	1.206	.229	-.024	.101	.068	.075	.074	.944	1.059
	Principal procedure from ED	.237	.607	.029	.391	.696	-.958	1.433	.033	.024	.024	.688	1.454
	Procedure 2 from ED	3.094	4.912	.147	.630	.529	-6.578	12.767	-.005	.039	.039	.069	14.554
	Procedure 3 from ED	-3.265	3.947	-.189	-.827	.409	-11.038	4.508	-.019	-.051	-.051	.072	13.976
	Procedure 4 from ED	.393	2.467	.012	.159	.874	-4.465	5.251	-.008	.010	.010	.634	1.578
	Principal procedure from inpatient discharge record	-.346	.406	-.084	-.853	.395	-1.145	.453	-.109	-.053	-.052	.389	2.570
	Procedure 2 from inpatient discharge record	-.590	.706	-.085	-.836	.404	-1.979	.800	-.107	-.052	-.051	.362	2.766
	Procedure 3 from inpatient discharge record	.262	1.199	.019	.218	.827	-2.100	2.623	-.055	.014	.013	.495	2.021
	Procedure 4 from inpatient discharge record	2.470	3.666	.048	.674	.501	-4.749	9.689	-.008	.042	.041	.731	1.367

In the 2014 hierarchical regression analysis, the R Square values are reviewed and the overall model yields 0.1% of the variance, with block 2 variables included in the model there is 2.9% variance and with block 3 variables included in the model there is 3.9% variance. When R Square changed is reviewed for overall variance explained by variables of interest, the inpatient principal procedures add an additional 1.1% of the variance in nephrolithiasis patients with IBS (see Table 20). Although not considered a unique contribution, the principal procedure from the ED yields a P value of 0.063.

Table 20. Hierarchical Regression Analysis 2014

Model Summary[d]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics: R Square Change	F Change	df1	df2	Sig. F Change
1	.107[a]	.011	.002	7.342	.011	1.248	3	323	.292
2	.169[b]	.029	.007	7.323	.017	1.416	4	319	.228
3	.198[c]	.039	.006	7.329	.011	.861	4	315	.488

a. Predictors: (Constant), Diagnosis 4, Diagnosis 2, Diagnosis 3

b. Predictors: (Constant), Diagnosis 4, Diagnosis 2, Diagnosis 3, Procedure 2 from ED, Principal procedure from ED, Procedure 3 from ED, Procedure 4 from ED

c. Predictors: (Constant), Diagnosis 4, Diagnosis 2, Diagnosis 3, Procedure 2 from ED, Principal procedure from ED, Procedure 3 from ED, Procedure 4 from ED, Procedure 4 from inpatient discharge record, Procedure 2 from inpatient discharge record, Procedure 3 from inpatient discharge record, Principal procedure from inpatient discharge record

d. Dependent Variable: Diagnosis 1

Coefficients[a]

Model		Unstandardized Coefficients B	Std. Error	Standardized Coefficients Beta	t	Sig.	95.0% Confidence Interval for B Lower Bound	Upper Bound	Correlations Zero-order	Partial	Part	Collinearity Statistics Tolerance	VIF
1	(Constant)	20.496	1.511		13.566	.000	17.524	23.469					
	Diagnosis 2	.038	.031	.068	1.230	.220	-.023	.098	.076	.068	.068	.989	1.011
	Diagnosis 3	.024	.019	.075	1.316	.189	-.012	.061	.071	.073	.073	.937	1.067
	Diagnosis 4	-.012	.019	-.037	-.653	.514	-.050	.025	-.024	-.036	-.036	.939	1.065
2	(Constant)	19.312	2.258		8.554	.000	14.870	23.754					
	Diagnosis 2	.050	.031	.091	1.603	.110	-.011	.112	.076	.089	.088	.954	1.048
	Diagnosis 3	.024	.019	.073	1.273	.204	-.013	.060	.071	.071	.070	.930	1.075
	Diagnosis 4	-.014	.019	-.041	-.711	.477	-.051	.024	-.024	-.040	-.039	.929	1.076
	Principal procedure from ED	-1.087	.599	-.140	-1.814	.071	-2.266	.092	-.099	-.101	-.100	.514	1.947
	Procedure 2 from ED	-.334	1.445	-.041	-.231	.817	-3.178	2.509	-.032	-.013	-.013	.096	10.453
	Procedure 3 from ED	-1.047	1.416	-.142	-.739	.460	-3.832	1.739	-.036	-.041	-.041	.083	12.100
	Procedure 4 from ED	3.409	3.175	.247	1.074	.284	-2.838	9.657	-.019	.060	.059	.058	17.309
3	(Constant)	19.676	4.158		4.732	.000	11.495	27.857					
	Diagnosis 2	.050	.031	.090	1.580	.115	-.012	.111	.076	.089	.087	.950	1.053
	Diagnosis 3	.024	.019	.074	1.285	.200	-.013	.061	.071	.072	.071	.925	1.081
	Diagnosis 4	-.013	.019	-.038	-.656	.512	-.050	.025	-.024	-.037	-.036	.924	1.082
	Principal procedure from ED	-1.120	.600	-.144	-1.866	.063	-2.300	.061	-.099	-.105	-.103	.513	1.949
	Procedure 2 from ED	-.369	1.447	-.046	-.255	.799	-3.216	2.477	-.032	-.014	-.014	.096	10.456
	Procedure 3 from ED	-1.030	1.417	-.140	-.727	.468	-3.818	1.758	-.036	-.041	-.040	.083	12.101
	Procedure 4 from ED	3.402	3.178	.246	1.071	.285	-2.851	9.656	-.019	.060	.059	.058	17.312
	Principal procedure from inpatient discharge record	-.128	.179	-.057	-.713	.476	-.480	.225	-.087	-.040	-.039	.471	2.125
	Procedure 2 from inpatient discharge record	-.132	.321	-.037	-.411	.681	-.763	.499	-.086	-.023	-.023	.369	2.709
	Procedure 3 from inpatient discharge record	-.485	1.245	-.030	-.390	.697	-2.935	1.964	-.074	-.022	-.022	.500	2.002
	Procedure 4 from inpatient discharge record	.636	3.970	.011	.160	.873	-7.175	8.447	-.038	.009	.009	.685	1.459

CHAPTER V: DISCUSSION

5.1 Discussion

Nephrolithiasis impose a significant burden of disease in the United States and comes with considerable costs, pain and morbidity. The rates of ED visits have increased since the 1980s in correlation with kidney stones and most are discharged, only for many to return within 48 hours. Recurrence of nephrolithiasis is seen in 50% of stone formers. The objective of this study is to fill the gap between evidence based clinical guidelines and practice in assessing nephrolithiasis with CT versus ultrasound and to assess patient outcomes and hospital admission. Additionally, this study sought to assess the impact of inflammatory bowel disorders and irritable bowel syndrome as a co-morbidity of nephrolithiasis, as well as dehydration as a link to stone size to improve patient outcomes and decrease overall healthcare costs.

This research was conducted utilizing the Healthcare Cost Utilization Project (HCUP) National Emergency Department Sample (NEDS) existing databases from 2012, 2013 and 2014 with a focus on patients with nephrolithiasis. The study analyzed variables including age, gender and co-morbidities of obesity, diabetes, IBS, as well as dehydration and hyperosmolality, relevant medical imaging exams, interventions and procedures, total charges and discharge versus admission. The study sample included 164,410 emergency department (ED) visits for nephrolithiasis in 2012, 163,254 in 2013 and 181,528 in 2014 for a total of 509,192 visits.

The prevalence of nephrolithiasis is highest among adults between the ages of 30 to 42 and was found to be more common in males than females. While there is a slight prevalence of nephrolithiasis in patients with a co-morbidity of obesity (0.57%), there is a higher rate in those with diabetes (4.78%). However, the focus of this study is on patients with IBS, as this population is at greater risk of dehydration due to regular bouts of diarrhea.

The link between nephrolithiasis and dehydration has been clearly outlined in the literature reviewed. While this link seems to be well known there is a lack of study on laboratory values for dehydration such as plasma osmolality, which is a strong indicator of chronic dehydration.

While dehydration is found in patients across the databases utilized in this study, there is a lack of confidence that this is consistently assessed, if at all, upon presentation to the ED and therefore most likely does not accurately represent the prevalence in the IBS population studied, and more importantly stone formers as a whole. While hyperosmolality can also be an indicator of dehydration, this variable was also found to have a very low yield of assessment.

Overall data represents ED visits for nephrolithiasis between 2012-2014 which often includes medical imaging for assessment and diagnosis. Prevalence of ultrasound and computed tomography (CT) exams was reviewed for both ED cases and those that were admitted to the hospital. Where ultrasound and CT are seen in the same visit, it can be assumed that ultrasound was performed first as this method of assessing patients is more frequently utilized despite the American College of Radiology's (ACR) Appropriateness Criteria guidelines. Non-contrast CT has been the first line imaging choice for detecting nephrolithiasis with a 95% sensitivity and specificity. CT is considered the gold standard for its ability to identify the location and size of stones, as well as the composition and ability to provide differential diagnoses.

Ultrasound of the urinary system was more commonly utilized in the ED than CT, however it was found that CT was commonly utilized for patients admitted to the hospital with nephrolithiasis. This is interesting as those that are admitted to the hospital due to nephrolithiasis are due to larger stone size, requiring intervention, blood or infection.

Analysis of procedure class for inpatient procedures yielded 9158 minor and major diagnostic and therapeutic procedures in 2012, 8542 in 2013 and 9628 in 2014. Total charges for patients with nephrolithiasis presenting to the ED and then admitted to the hospital were found to be significantly higher than that of patients discharged from the ED. In 2012 the mean total charges for ED services were $21,796 less than the combined ED and Inpatient charges; in 2013 the mean total charges for ED services were $23,557 less than the combined ED and Inpatient charges; and in 2014 the mean total charges for ED services were $26,555 less than the combined ED and Inpatient charges. This is a significant burden of cost to patients and healthcare systems.

Irritable Bowel Syndrome (IBS) was assessed as a co-morbidity of nephrolithiasis in this study as dehydration is very common in patients with recurrent bouts of diarrhea. In the HUCP NEDS databases, 359 patients were identified in 2012 with nephrolithiasis and IBS, 272 patients in 2013, and 327 patients in 2014. There is a predominance of females (70% female versus 30% male) within this population. Somewhat shocking to this study was that within this patient population from 2012-2014, zero patients had ultrasound imaging and only 22 patients had a CT. While medical imaging is low in this group, 104 (10.9%) required an intervention and/or procedure and of the 104, 44 interventions (42%) were directly related to stone removal. The mean total charge for nephrolithiasis patients with IBS admitted to the hospital from the ED is $26,753, which is similar to that of the non-IBS nephrolithiasis population.

Clinical decision making is an integral part of patient outcomes and its accuracy is a necessary entity in today's healthcare environment. Several variables in this study were compared to better understand the prevalence of nephrolithiasis and to analyze and investigate a predictive model for improving patient outcomes of nephrolithiasis. Statistical analysis of the HCUP NEDS 2012, 2013 and 2014 datasets were examined using descriptive statistics for frequencies and percentages as well as multiple regression analysis including linear, stepwise, and hierarchical regression models. Multiple regression models are known for their ability to allow the researcher to simultaneously input variables and evaluate each independent variable for its predictive power, allow for independent variables to be entered into the model in a specified sequence, or blocks, based on hypothetical theory.

While descriptive statistics of this study align with the literature review of medical imaging in nephrolithiasis patients, in that ultrasound is utilized more frequently than CT upon presentation to ED, and confirming the lack of adherence to the ACR's guidelines, the lack of laboratory testing and/or results available in the dataset proves difficult to validate adherence to recommended laboratory studies and metabolic evaluations. Multiple regression models demonstrate that principal procedures, which include medical imaging modalities such as ultrasound and CT, as well as minor and or major procedures and interventions, from the inpatient discharge record represents a statistically significant contribution to nephrolithiasis. Based on the information provided in the descriptive statistical analysis of IBS, a variety of principal procedures returned were related to nephrolithiasis demonstrating the significance of these to nephrolithiasis in IBS patients.

Although a hierarchical regression model was presented in this study there is no major significance found in this analysis aside from the inpatient principal procedure as an influential factor of nephrolithiasis. This hierarchical model worked from diagnosis to outcome vs outcomes back to diagnosis due to the data available in the HCUP NEDS.

While this study confirms the continued lack of adherence to medical imaging guidelines for first line imaging of CT in nephrolithiasis patients, it also brings forth the lack of adherence to complete laboratory testing. This study shows that although many patients are discharged directly from the ED, there is a significant number of patients admitted to the hospital for nephrolithiasis many of which were assessed with ultrasound first. This confirms the hypothesis that patients assessed with ultrasound before CT have poorer outcomes and accrue greater healthcare costs.

Certain co-morbidities associated with nephrolithiasis may produce larger stones due to chronic dehydration, however due to the lack of available data within the HCUP NEDS datasets on plasma osmolality this theory is difficult to confirm. We can see that obesity, diabetes and Irritable Bowel Syndrome (IBS) are all contributing factors to nephrolithiasis risk and proves the hypothesis that certain co-morbidities are most closely linked to nephrolithiasis. IBS patients are at greater risk due to frequent bouts of diarrhea which results in fluid imbalance and dehydration. Interventions in IBS patients are often more invasive and fall into the minor diagnostic and therapeutic procedure class categories as well as large number in the major therapeutic category. Patients with IBS have a two-fold likelihood of requiring an intervention than that of the general nephrolithiasis population, again poorer outcomes and accrual of greater healthcare costs.

Hydration is a significant factor for kidney stone formers, and the literature highlights the need for increased fluids in prevention. However, there is little information available in the HCUP NEDS datasets for dehydration assessment upon presentation to the ED, which should be considered given the link between fluid intake and stone formation. Prevention of nephrolithiasis would release a significant healthcare burden on the patient and the national healthcare system. Increased fluid intake should increase urine output and ensure mechanical diuresis to prevent stagnation of organic materials and formation of stones. Increased water intake has resulted in attenuation of circulating copeptin, serving as a simple and cost-effective intervention to reduce circulating vasopressin, which conserves water and decreases urine volume.[55] Chronic dehydration can be assessed with plasma osmolality and copeptin levels and should be considered as part of the initial assessment upon presentation to the ED with suspected nephrolithiasis.

5.2 Limitations of Study

The HCUP NEDS database has provided insight and results in this study of nephrolithiasis, however it is limited due to its retrospective nature. The NEDS databases are missing information about ED charges for a variety of weighted percentages, 15% for 2012 and 2013, and 16% for 2014[62,63,64] and focuses on entry-level versus patient-level records. Therefore, patients that may revisit the ED multiple times in a given year may be present as separate patient entries. The NEDS are also limited by direct admission from the ED to the hospital, as only one discharge record is included. This makes differentiation of procedures performed in the ED versus part of the inpatient stay unattainable. There is inability of the researcher to control for considerations such as condition severity or imaging strategy as the diagnostic and procedural coding is utilized. It should also be noted that the HCUP NEDS acquires its database information from community, non-rehabilitation hospitals.

There is potential misclassification of variables inherent to administrative data which relies heavily on diagnosis codes entered by individual hospital personnel. Because IBS is not always reported, or diagnosed, the overall data may be incomplete or exposed to bias.

Therefore, this exploratory study and analysis may be skewed. Additionally, as previously discussed the lack of ICD-9 coding for plasma osmolality, and perhaps the sheer lack of testing, prevents this study from confirming the hypothesis of plasma osmolality and copeptin levels as a link to nephrolithiasis risk and stone formation.

Despite these limitations, the HCUP NEDS datasets allow for a national perspective of trending in nephrolithiasis patient populations and has provided a great deal of insight.

CHAPTER VI: SUMMARY AND CONCLUSIONS

6.1 Summary and Conclusions

The HCUP NEDS datasets for 2012, 2013 and 2014 have provided insight into the prevalence of nephrolithiasis based on age, gender, co-morbidity, diagnostic assessment, and procedures or interventions required in the course of ED and hospital care. The highest rate of nephrolithiasis occurrence is between 30 and 42 years of age and is more common in the general population of males. Female patients amongst this same age group with Irritable Bowel Syndrome (IBS) have a higher prevalence of nephrolithiasis than males, however. Adherence to medical imaging guidelines and laboratory testing for nephrolithiasis is lacking. This study demonstrates that patients assessed with ultrasound first versus are more likely to be admitted to the hospital than those assessed following the ACR's recommended low-dose CT imaging, and accrue greater healthcare costs overall. Although many studies outline this lack of adherence to the ACR's Appropriateness Criteria, there are no available reports on patient outcomes or hospital admissions. This study is the first to report on patient outcomes, specifically IBS as a co-morbidity, as well as the prevalence of procedures and interventions in nephrolithiasis, and total charges for ED versus inpatient hospital care.

6.2 Recommendations

This analysis provides clinicians with recommendations to utilize for a comprehensive assessment of nephrolithiasis patients upon presentation to the ED. First, the clinician should begin with a physical exam. A STONE score should then be utilized to determine the likelihood of stones, keeping in mind that the higher the score the more likely the patient is to have nephrolithiasis.

Once a high STONE score is established, laboratory testing should be ordered and include plasma osmolality for assessment of hydration status and chronic dehydration, serum electrolytes, BUN, creatinine, calcium, phosphorus, uric acid, parathyroid hormone (PTH) levels, urine cultures, 24-hour urine and stone composition. Medical imaging orders should strictly adhere to the ACR's Appropriateness Criteria, which guides the clinician in selecting the most useful imaging exam based on clinical indications and ratings between 1 (least appropriate) to 9 (most appropriate). The ACR outlines an Appropriateness Score of 8 for a non-contrast CT, which provides 95% sensitivity and specificity in detection of nephrolithiasis. CT imaging is considered the gold-standard for detection of stones, accurate assessment of size and location, and provides valuable information about the composition of the stone. Although ultrasound is effective in detecting hydronephrosis, it should be reserved for pregnant or pediatric patient assessment only.

Co-morbidities, such as Irritable Bowel Syndrome (IBS), diabetes and obesity, play a role in nephrolithiasis formation and should not be overlooked when taking the patient history and performing a physical examination. IBS patients are two times more likely to require an intervention for nephrolithiasis than a non-IBS nephrolithiasis patient.

Currently, there is only 63% adherence to recommended guidelines for medical imaging and a 40% adherence for laboratory testing. The ED clinician plays an integral role in nephrolithiasis patient care and improved outcomes. Following the recommendations presented in this study ensures best practices in the initial assessment and treatment of nephrolithiasis patients.

6.3 Future Directions

Linear models for classification are the simplest method and have been widely used in computer-aided classification.[65] Parloff discusses breakthroughs in healthcare attributing all to advances in artificial intelligence and machine learning.[66] Parloff notes that "as long as you have data to train the software the possibilities are endless".[66] This statement is true and applicable to classification. Massat reviews the Radiological Society of North America's 2016 technology trends in machine learning and the main focus is in clinical decision support.[67]

Support Vector Machines are a means of providing decision support through classification of data and predicting outcomes. The ACR's 2016 Intersociety Summer Conference reviewed applications of machine learning to image analysis and the enormous opportunities for radiologists to augment the quality of patient-centered care.[68] The conference reviewed the future of data-driven advancements in radiology and the new paradigm shift to machine learning, deep learning and artificial neural networks.

Although the use of SVMs has not been included in this study, the scope of this research is to improve patient outcomes of nephrolithiasis. The use of support vector machines for further classification of co-morbidities may be warranted in future studies to train and further classify while differentiating between CT and ultrasound groups of nephrolithiasis patients. Despite robust literary searches there are a very limited number of studies done in this area. Scales et al briefly discuss the need for sensitivity analyses regarding clinical decision support, as the study showed no benefit in increasing guideline adherence.[1] This study had several limitations and reports classification bias in utilization of previously validated algorithms to identify patients, diagnostic codes that only identified those with confirmed stones rather than differential diagnoses of nephrolithiasis, and lack of laboratory testing examined which the authors believe may be associated with an increased risk of ED revisit.

Finally, the literature reviewed outlines that plasma osmolality is easily assessed with laboratory testing and is a detector of chronic dehydration. This simple test to detect chronic dehydration in IBS patients may also play a key role in predicting stone size and the need for interventions. Further evaluation and analysis should be considered and would be best suited for a clinical setting rather than a retrospective study. The initial assessment of nephrolithiasis patients is key to improving outcomes, decreasing overall healthcare costs and preventing reoccurrence.

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