

# Utility of Serum and Urine Protein Electrophoresis in Evaluation of Chronic Kidney Disease Patients

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## ABSTRACT

**Background:** Electrophoresis is defined as a method of separating proteins based on their physical properties. The pattern of serum/urine protein electrophoresis (SPEP/UPEP) outcomes depends on the fractions of two significant types of protein: albumin and globulins. This laboratory examination can identify the number of specific proteins present either in the serum or in the urine. Thus, it can help in screening and discovering a specific pathological condition.

Current guidelines for evaluating chronic kidney disease (CKD) do not include routine screening with serum and urine protein electrophoresis (SPEP and UPEP). The converse question of how often the patients presenting to the general kidney clinic as a case of CKD or protein in urine need screening tests to detect M-protein have no clear answer. In addition, the utility of specific tests can have an essential role in forming clinical pathways to evaluate patients with various conditions. Best practices for monoclonal protein testing and screening for paraprotein in patients with CKD are not well established. For this reason, our study aims to examine the use of screening SPEP and UPEP in the evaluation of CKD patients.

**Methodology:** This is a retrospective study (Chart Review) of 149 sequential incident patients referred to a teaching General Nephrology clinic to evaluate CKD between Jan and Nov 2018. The SPEP and UPEP testing frequency and proportion with M-spike were obtained by chart review, along with the routinely performed clinical, blood and urine tests, imaging, and reports of any Hematology consultation, renal and bone marrow biopsies performed.

**Results:** Screening by SPEP/ UPEP test was done in 104 (70 %) patients. M-spike was present in Eleven of them (10.6 %, 96 % CI 5.4 – 18.8 %), 2 IgG- $\kappa$ , 5 IgG- $\lambda$ , 1 IgA- $\lambda$ , 2 LC- $\kappa$ , and 1 LC- $\lambda$ . Eight of the Eleven patients had a Hematology consultation, Six had bone marrow biopsy, and Three had a renal biopsy. Diagnoses were seven have MGUS, Two have myelomas (MM), One has amyloid (AL), and One has MM + AL. On the other hand, of the 45 (30%) patients without SPEP/UPEP, six had a renal biopsy, then One patient was diagnosed with amyloid. Fisher's Exact test has shown no significant association between screening with SPEP/UPEP and hematological conditions.

**Conclusion:** In summary, the prevalence of M-spike in CKD is higher than what has been reported in the literature among the general population. Also, compared to previous studies in CKD, it is considered slightly high. The race of patients, average age, and sample size could affect the results. Until further notice, we suggest screening CKD patients based on clinical presentation. More extensive prospective studies are needed to identify subgroups with a higher likelihood of M-spike to target testing. Also, more work is needed to find if there is an association between the screening and the clinical outcome of the patients. The cost-efficacy is also an area for further studies.

**Keywords:** Electrophoresis, Hematology, Screening, Paraprotein

## INTRODUCTION

Electrophoresis is defined as a method of separating proteins based on their physical properties. The pattern of serum/urine protein electrophoresis (SPEP/UPEP) outcomes depends on the fractions

of two significant types of protein: albumin and globulins. Albumin always lies closest to the positive electrode while the globulin (alpha1, alpha2, beta1, beta2, and gamma) lie toward the negative electrodes. This laboratory examination can identify the number of specific

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proteins present either in the serum or in the urine. Thus, it can help in screening and discovering a specific pathological condition<sup>1</sup>.

Current Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (EMCKD)<sup>2</sup> recommends GFR and albuminuria evaluations at least annually in people with CKD to assess the progression of kidney function. In addition, the guideline recommends identifying, monitoring, and follow-up of factors associated with CKD progression to inform prognosis. Those factors include the GFR and albuminuria category, the degree of albuminuria, ongoing exposure to nephrotoxic agents, blood pressure, hemoglobin level and albumin. Also, the guideline recommends measuring serum levels of calcium, phosphate, Parathyroid hormone, and alkaline phosphatase activity at least once in adult patients to determine baseline values. Accordingly, no guide using SPEP/UPEP among such patients to screening for complications.

Monoclonal gammopathy occurs due to the clonal proliferation of cells of B-cell lineage, particularly plasma cells. The large majority of individuals with monoclonal gammopathy have Monoclonal Gammopathy of Undetermined Significance (MGUS). It is one of the most common premalignant disorders in Western countries. It is an asymptomatic condition characterized by the presence of a monoclonal immunoglobulin (M-protein) in the absence of any clinical signs or symptoms of lymphoproliferative malignancies<sup>2</sup>. MGUS occurs in 3.2 percent of the general population over 50 years and in 5.3 percent of age 70 years or older<sup>3</sup>. In addition, MGUS is typically detected as an incidental finding when patients undergo a serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) as part of an evaluation for a wide variety of clinical symptoms and disorders.

MGUS incidence and prevalence rise with patient age; it is higher in men than women and is two- to threefold higher in Africans and African Americans than Caucasians<sup>4,5</sup>. As we all know, there are multiple diseases associated with paraprotein-related kidney disease like multiple myeloma, smoldering multiple myeloma, monoclonal gammopathy of renal significance (MGRS), and Lymphoproliferative diseases. Because of the wide range of biology and disease presentations, the identification of the monoclonal immunoglobulin may often be the first clue to the diagnosis. Undoubtedly, 60% to 80% of multiple myeloma patients will have a kidney involvement during their disease course. In addition to 20% of these patients may have Bence-Jones proteinuria as initial renal involvement<sup>6</sup>.

Renal diseases of paraprotein have a variety of histopathological characteristics and clinical presentations. These histopathological features can consequently arise from tissue injury due to precipitation or deposition of clonal immunoglobulin<sup>7</sup>. Also, some clinical manifestations include acute kidney injury or chronic renal impairment with proteinuria. Par paraprotein's renal diseases can be any of the following diseases; For example, cast nephropathy (most common) causes tubular injury and intratubular cast obstruction<sup>8</sup>. Hypercalcemia can cause renal impairment by renal vasoconstriction, intratubular calcium deposit, pre-renal AKI form polyuria and volume depletion, interstitial nephritis, kidney injury from nephrotoxic medication used in the treatment of MM, hyperviscosity syndrome, thrombotic microangiopathic anemia TMA, amyloidosis, immunotactoid disease, fibrillary disease, monoclonal cryoglobulinemia, monoclonal immunoglobulin deposition disease (LCDD and HCDD) and C3 Glomerulopathy<sup>8,9</sup>.

Poor prognosis has historically been linked with monoclonal gammopathy of renal significant patients. Equally important, treatment

of the underlying clone will improve kidney outcomes, as suggested by recent studies<sup>10</sup>. Over and above, growing recognition of paraprotein-associated kidney disease is important, but up to now unresolved issue regarding screening of monoclonal gammopathy in patients with CKD, and when present, determining whether the monoclonal Ig is causing kidney damage or is of undetermined significance (MGUS).

Current guidelines for evaluating chronic kidney disease (CKD) do not include routine screening with serum and urine protein electrophoresis (SPEP and UPEP). The converse question of how often the patients presenting to the general kidney clinic as a case of CKD or protein in urine need screening tests to detect M-protein have no clear answer. In addition, the utility of specific tests can have an essential role in forming clinical pathways to evaluate patients with various conditions. Best practices for monoclonal protein testing and screening for paraprotein in patients with CKD are not well established. For this reason, our study aims to examine the use of screening SPEP and UPEP in the evaluation of CKD patients. And, the objectives of the present study are: 1-Assess the frequency of screening with SPEP and/ UPEP in the initial assessment of patients referred to Nephrology for evaluation of proteinuria or CKD to screening for a hidden Monoclonal gammopathy. 2- Determine the screened proportion of patients that have a monoclonal protein and the clinical outcomes. 3- Determine the patients' proportion of monoclonal protein with multiple myeloma, MGRS, and MGUS.

## METHODOLOGY

**Study Design and Setting:** This is a retrospective, case control study (Chart Review) of 149 sequential incident patients referred to a teaching General Nephrology clinic to evaluate CKD between January and November 2018 at Kingston General hospital, Kingston, Ontario, Canada. The SPEP and UPEP testing frequency and proportion with M-spike were obtained by chart review, along with the routinely performed clinical, blood and urine tests, imaging, and reports of any Hematology consultation, renal and bone marrow biopsies performed.

**Data Collection Instruments:** The data was collected and documented via Microsoft Excel Sheets version 2016 at Nephrology clinic, Kingston General hospital, Kingston, Ontario. The Excel sheet involved 57 columns that display the clinical and investigative informations for each patient's name located in row. The following variables were considered:

Age, Sex, Race, Weight, Cause of referral to General Nephrology clinic, diabetes, Hypertension, patient on ACE-I, ARB, SGLT-2i and Metformin, urine analysis (WBC, RBC, and protein), ACR (albumin-creatinine ration), Urine Creatinine, 24 hours urine for protein, Serum protein, Serum Urea, Serum Sodium, Serum chloride, Serum potassium, Serum bicarb, Serum, Glucose, Serum Calcium, Serum Phosphate, Serum Albumin, Serum Troponin, WBC, Hemoglobin, Platelet count, size of both Kidney on Ultrasound, immune globulin levels (IgA, IgG, IgM, IgD), Serum Free light chain and protein electrophoresis (Kappa and Lambda), Urine protein electrophoresis, Bone Marrow biopsy, Percent % of Plasma cell on Bone Marrow biopsy, number of patients diagnosed with Multiple Myeloma or amyloidosis, Renal biopsy, diagnosis and type of paraprotein related kidney disease, Follow up Serum Creatinine, patient develop ESRD and Death.

**Analysis:** Regarding data analysis, the data were coded, checked and entered into statistical software ( IBM® SPSS®) version 26.

**RESULTS**

The Sample size was 149 with a mean age of 70 years. Eighty-four patients were female (56.4%), and 69 (46.3%) patients had diabetes, 9 (7.7%) patients had proteinuria >3g/dl, all patients had a normal range total serum protein, and the majority of patients were Caucasian. More than 80% of the patients were referred to nephrology clinic for screening of myeloma, approximately 7.4% because of amyloid, and less than 3% referred to the clinic because of DM, HTN, and Glomerulonephritis (Figure 2). The average duration between the date of referral and date of follow up was 5 to 6 months with 20 months maximum and 1-month minimum (Figure 1).

Screening by SPEP/ UPEP tests was done in 104 (70 %) patients. M-spike was present in Eleven of them (10.6 %, 96 % CI 5.4 – 18.8 %), 2 IgG-κ, 5 IgG-λ, 1 IgA-λ, 2 LC-κ, and 1 LC-λ. Eight of the Eleven patients had a Hematology consultation, Six had bone marrow biopsy,

and Three had a renal biopsy. Diagnoses were Seven have MGUS, Two have myelomas (MM), One has amyloid (AL), and One has MM + AL. On the other hand, of the 45 (30%) patients without SPEP/ UPEP, six had a renal biopsy, then One patient was diagnosed with amyloid. Fisher's Exact test has shown no significant association between screening with SPEP/UPEP and hematological conditions (Figure 3).

The following results determined that four patients from 149 had developed ESRD; three underwent screening by SPEP/UPEP. No Death case was recorded. Also, most patients had comorbid conditions; DM and HTN were the leading causes of CKD in most of the cases (24.8% DM and 24.2% HTN). Other conditions like Cardiorenal syndrome, renovascular diseases, Amyloid and Ischemicnephropathy were leading causes. There was no precise data about the treatment and outcome of all patients (Figure 4).

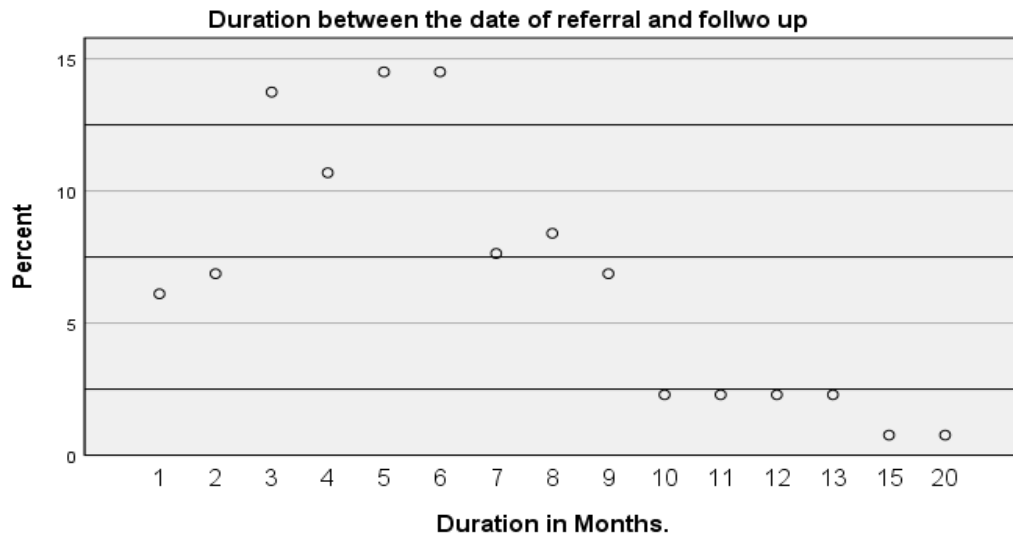


Figure 1: Duration between the date of referral and follow-up

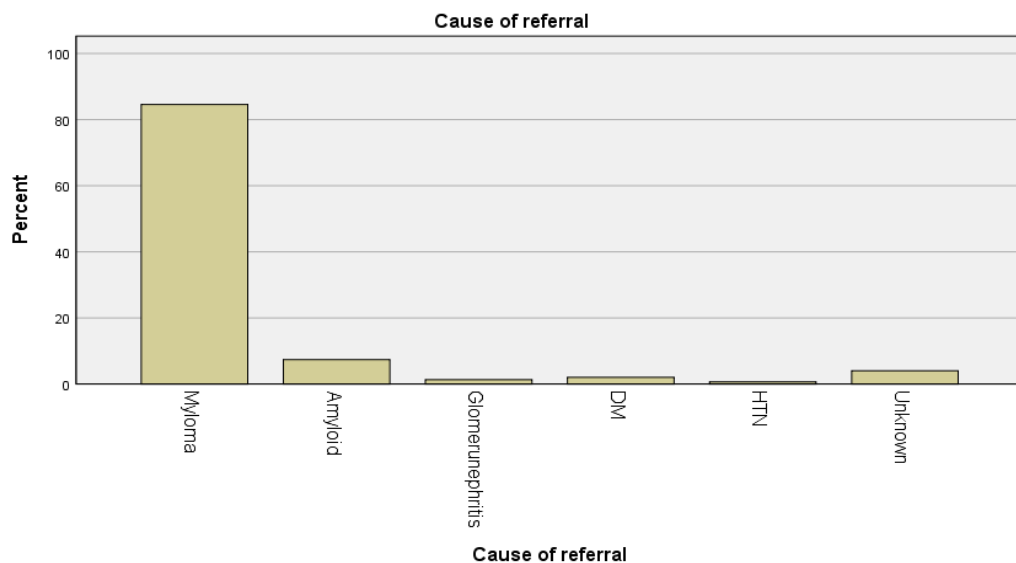


Figure 2: Cause of referral

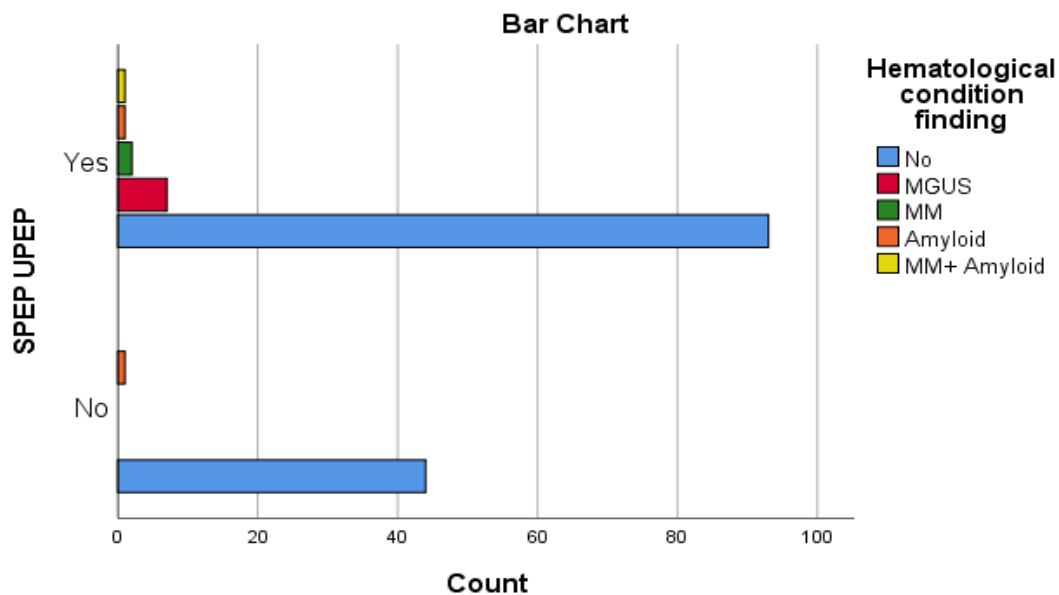


Figure 3: Bar chart

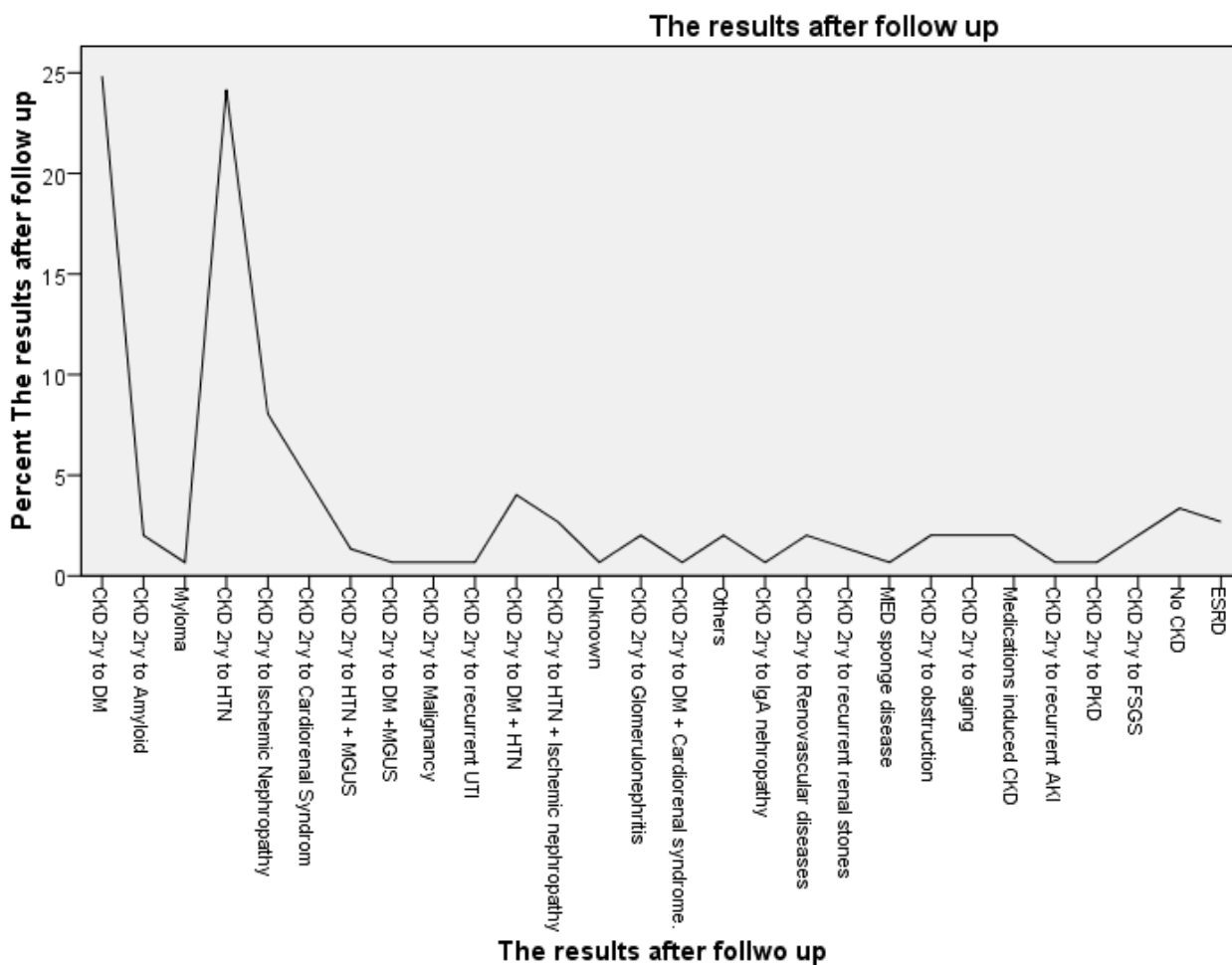


Figure 4: Results after follow-up

## DISCUSSION

The World Health Organization (WHO) estimates approximately 58 million deaths worldwide in 2005, with 35 million attributed to chronic disease<sup>11</sup>. Chronic kidney disease (CKD) is increasingly recognized as a global public health problem. Now, there is convincing evidence that treatment and screening can prevent or delay complications of decreased kidney function, slow the progression of kidney disease, and reduce the risk of cardiovascular disease (CVD)<sup>12</sup>.

Recognize underlying diseases early (in our study Diabetes and HTN were the majority in most patients 24.8% DM and 24.2% HTN) will improve kidney outcomes with treatment and decrease complications. In contrast, the latter case showed that patients diagnosed with MGRS had been associated with poor prognoses. Also, recent studies suggest improved kidney outcomes with the treatment of the underlying clone (1). For that reason, screening to increase recognition of paraprotein-associated kidney disease has led to the critical observation that the measure of CKD prevalence among hematologic malignancies is unknown<sup>12</sup>.

SPEP has a high sensitivity rate and relatively low cost with ease of use. It is the most commonly used test for the detection of M proteins globally<sup>13</sup>. Conjointly, UPEP can distinguish between underlying histopathological causes in patients with M protein<sup>13</sup>. However, a recent study suggested the utility of serum-free light chain (FLC) assay as a first-line test in screening pathways for a light chain clone in patients with kidney disease. Furthermore, this has contributed to significant improvements in care for patients with monoclonal gammopathy<sup>7</sup>. While another study suggested that serum IFE, SPEP, and FLC combined with urine IFE and UPEP is the most comprehensive and inclusive panel to screen for monoclonal gammopathy<sup>14</sup>.

Our present study showed that 7.4 % of n=149 had M-spike protein (10.5% of the 70% of patients with SPEP/UPEP with One patient out of 30% in those who did not undergo SPEP/UPEP). On the contrary, a sample size of 2,156,317 patients in a retrospective cohort study conducted by Burwick et al. demonstrated that 2% (4593 patients) were classified as having monoclonal gammopathy out of 21,898 patients who had undergone testing by either SPEP or UPEP<sup>15</sup>. In like manner, a previous study was conducted in a single center by Mendu, Mallika L<sup>16</sup>; the study retrospectively reviewed the laboratory tests used in the initial evaluation among CKD patients presenting to nephrology clinics. 68% of patients were tested with SPEP and 35% with UPEP (n=1538 tests) 7% of serum or urine paraprotein tests were positive for monoclonal protein. Anyhow, none of which compared the rate of hematologic findings in the subgroup among CKD patients, the population who had a screening, and the other population who had not.

Indeed, the ethnicity, average age (70 years), presence of proteinuria, and a number of the sample size could explain why our result showed a percent that was slightly higher than the previous ones in the literature. As most patients are Caucasian, this also explains the presence of (IgG) isotype in Seven out of Eleven hematologic findings among the screened patients. Moreover, this is consistent with Landgren, O.'s study<sup>4</sup>, who demonstrated that the prevalence of monoclonal gammopathy rises consistently with advancing age in the Caucasian population. It peaked in those older than 80 years old (6-8.3 %) with (IgG) more other isotypes, whereas the age distribution of the prevalence of MGUS differs among the other races such as African Americans.

Furthermore, our results have shown that 22.2% (2 of 9) patients had M-spike with proteinuria. This result is consistent with the results from

a recent study was done by Stephen T. H.<sup>6</sup> It showed the presence of M-spike in 11.5% (19 of 165) of patients presenting to nephrology clinic with nephrotic range proteinuria, 1.8% of patients have newly diagnosed with MM or systemic Amyloidosis. However, As we aim to evaluate the utility of using SPEP/UPEP among the CKD, we agree with another study suggesting targeting the whole population of CKD instead of high-risk subgroup (like patients with proteinuria, anemia, and hypercalcemia)<sup>17</sup>.

The screening results provide better detection of the suspected cases, but there are limited data about the follow-up duration with no given data about the effectiveness of screening results on treatment and outcome. As reported by Mendu, Mallika L's study<sup>16</sup>, in most cases of 7% with monoclonal protein, positive test results did not affect diagnosis or management. At this point, we agree with Wang, Christina Hao's study as no sufficient studies cover this area and found an association between the screening, presence of monoclonal gammopathy, and kidney outcome.

The analysis has shown the average duration of following up 5-6 months, and this period is not sufficient to measure the benefit of screening and the progression of kidney functions. Also, the data lack the estimated glomerular filtration rate (eGFR). Conversely, Burwick et al. study<sup>15</sup> calculated ESKD risk up until Ten years, with an average follow-up time of 123.5 months (interquartile range 77.5-128.5 months). The authors concluded that the presence of a positive test for monoclonal protein does not provide meaningful information on the risk of ESKD except for those with the lowest levels of eGFR. Also, only a tiny percentage of cases of ESKD was attributed to a monoclonal process, with the vast majority of cases attributed to diabetes and hypertension. This is similar to our analyzed results which showed diabetes and HTN play a significant role in the progression of kidney functions in most cases. According to this conclusion of Burwick's study and the result of Mendu, Mallika L's study<sup>16</sup>, a prospective study with large sample size is needed to compare between the screened vs. not screened groups and interpretations of the results with clinical outcome. Also, the cost-effectiveness of tests is an important area to highlight.

In this study, the cost for testing and interpretation fees for SPEP and UPEP was CDN \$ 25.53 and \$ 32.99, respectively which is cost-effective. Also, \$ 553.28 of detection costs per M-spike and \$ 1,521.25 per myeloma or amyloid. These costs are consistent with a previous study was done in North Carolina, And considering the benefits of SPEP and UPEP, the author suggested using both of these laboratory tests as part of the routine evaluation of nephrotic range proteinuria.

## CONCLUSION

**In summary, the prevalence of M-spike in CKD is higher than what has been reported in the literature among the general population. Also, compared to previous studies in CKD, it is considered slightly high. The race of patients, average age, and sample size could affect the results. Until further notice, we suggest screening CKD patients based on clinical presentation. More extensive prospective studies are needed to identify subgroups with a higher likelihood of M-spike to target testing. Also, more work is needed to find if there is an association between the screening and the clinical outcome of the patients. The cost-efficacy is also an area for recommendation for further study.**

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and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

**Potential Conflict of Interest:** None

**Competing Interest:** None

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