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Serum Protein Electrophoresis in Healthy Bulgarian Adults

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Abstract

Introduction

Serum protein electrophoresis (SPE) is an informative test primarily used to detect abnormalities in the gamma region, particularly to identify monoclonal immunoglobulins (M- proteins) in multiple myeloma (MM). MM is the second most common hematologic cancer, mainly affecting adults over 65. This study presents SPE results from routine laboratory check- ups in healthy Bulgarian adults.

Methods

A total of 92 clerical and administrative workers (35 males, 57 females; mean age: 53.6 years— (males, 54.9; females, 54.3) were enrolled. Blood samples were collected in the morning after an overnight fast, and serum was prepared following standardized pre-analytical protocols. Lipemic and haemolytic samples were excluded. The MiniCap Flex Piercing Capillary Electrophoresis system (Sebia) was used. Total protein (TP) was measured using the Biuret method (Alinity c, Abbott).

Results

No M-protein was detected in the gamma fraction of the examined group. Of the samples, 71.73% (n = 66) showed no SPE abnormalities. The mean serum total protein (TP) values ± SDs were 75.61 ± 3.16 g/L in males and 75.23 ± 4.25 g/L in females. In 18 participants (19.56%), the beta zone was either increased or decreased. Hypogammaglobulinemia (<8.0 g/L) occurred in 5.43% (n = 5). Three samples (3.26%) showed polyclonal hypergammaglobulinemia (>13.5 g/L), including one with a beta–gamma bridge (protein bands overlapping, indicating chronic inflammation or liver disease). SPE deviations were observed in 28.26% (n = 26)

Conclusions

SPE rarely detects MM in asymptomatic patients. Bulgarian data confirm that fewer than 0.5% of new MM cases are identified by routine screening.

Keywords: serum protein electrophoresis; multiple myeloma; hypergammaglobulinemia; hypogammaglobulinemia; monoclonal gammopathy

Introduction

Serum protein electrophoresis (SPE) is a useful laboratory test that can provide information about various diseases, but its application is limited to the detection of pathology in the gamma zone, and it is primarily intended for detecting serum monoclonal immunoglobulins (M-protein, M-spike, paraprotein) associated with plasma cell dyscrasias and lymphoproliferative disorders. Normal SPE has five fractions: albumin (about two-thirds of serum total protein, TP), alpha-1 (mainly alpha-1-antitrypsin), alpha-2 (alpha-2-macroglobulin and haptoglobin), beta (transferrin and C3), and gamma (immunoglobulins) [1]. Advances in separation techniques have improved the detection of monoclonal proteins, and modern capillary systems for SPE separate the beta zone into two fractions—beta-1 and beta-2 [2]. SPE is mainly interpreted by assessing albumin and gamma-globulins. Albumin produces the largest peak near the positive electrode; gamma-globulins produce a smaller peak near the cathode, with subgroups critical for interpretation [3]. The International Myeloma Working Group recommends SPE and immunofixation (IFE) of serum and urine for screening for suspected multiple myeloma (MM), primary amyloidosis (AL), and related gammopathies [4,5].

The interpretation of SPE mainly includes the following findings: (1) monoclonal gammopathies—mostly seen in the gamma zone and less often in the beta and alpha-2 zones; (2) polyclonal hypergammaglobulinemia, which occurs in infectious diseases, liver diseases, and autoimmune conditions; and (3) hypogammaglobulinemias associated with immune deficiency, AL, or nephrotic syndrome; and, in rare cases, with MM as well [5].

MM is the second most common hematologic malignancy. It mainly affects adults aged 65 and older [6]. According to the global database for assessing cancer morbidity and mortality, GLOBOCAN, for men and women, the data about MM for 2022 are as follows: incidence in men—103.766 new cases; incidence in women—84.007; mortality in men—66.938 of the cases; mortality in women—54.31 of the cases [7]. The incidence of MM in Europe is approximately 3.8–4.6 per 100,000 people per year. The highest rates are reported in Northern and Western Europe, especially Germany, Denmark, and the United Kingdom. The data for Bulgaria indicate an MM incidence of approximately 2.5–3.0 per 100,000 people per year. There has been a trend towards increasing incidence over the past two decades, especially in women over 50 years of age. In Bulgaria, there has been a significant 5.71% [2.15 to 9.39] annual increase in cases ($p = 0.0057$) [8]. Overall, recent reports have presented an increase in incidence, especially in men aged 50 or older. Globally, the increase in incidence is attributed to lifestyle factors, reduced physical activity, obesity, diabetes mellitus, and a higher human development index [8].

The iStopMM study [9] is the first large-scale, population-based MM screening study, involving 80,759 people aged 40 and over. It showed that SPE detects many MM precursors, but the clinical benefit of mass screening remains unclear, as early detection does not significantly change MM prognosis.

The Fracture Liaison Service program screens patients aged 50 and older and identifies 1 undiagnosed MM case among 195 fragility fractures [10]. MM cases discovered incidentally in high-risk groups (such as those with fractures or over 50) are rare, occurring in fewer than 0.5%. More frequent screening in high-risk groups primarily detects MM precursors [10,11].

Methods that enable detection of M-protein or the pathological free-chain ratio include SPE, serum/urine immunotyping (IT)/immunofixation (IFE), and measurement of serum free light chain (sFLC) levels [12]. These highly specialized tests are rarely performed during routine preventive examinations. Findings of anemia, hypercalcemia, or renal dysfunction may be the first laboratory abnormalities in asymptomatic patients, and they are suggestive of MM diagnosis. In this context, examination of the complete blood count (CBC), serum creatinine, calcium, and β2-microglobulin may be indicative [13]. The erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) levels are not included in the diagnostic panel for MM. Still, high ESR and normal CRP levels strongly correlate with probable MM [14]. Combining the sFLC, β2-microglobulin, and

serum immunoglobulin ratios increases the diagnostic specificity for MM and its precursors. However, establishing such pathological findings requires diagnostic confirmation [12]. According to the College of American Pathologists, the combination of sFLC, SPE, and serum IFE is the standard for the initial laboratory diagnosis of monoclonal gammopathies [12,13].

In some cases of MM, electrophoresis shows a normal pattern, as in free-light-chain myeloma. Performing only SPE may cause a missed diagnosis. According to Marowska et al., approximately 20% of patients with MM and light-chain disease have normal electrophoresis results [14]. Routine screening for MM is not performed [14]. Screening for monoclonal gammopathy of undetermined significance (MGUS) is also not recommended [15]. An appropriate approach to stratifying at-risk patients and screening them is important for diagnosing MM. IFE is a reliable method, but it is not available in routine medical practice.

Knowledge of laboratory constellations and recognition of risk groups are critical for enhancing diagnostic accuracy, initiating early therapy, and improving overall patient outcomes.

In short, SPE is primarily used to detect pathologies in the gamma zone of the serum. Its most important use is detecting M-protein in MM. There are cases with normal SPE appearance but with paraproteins (free light chain disease). Some cases have electrophoresis findings associated with precursor conditions of MM, MGUS, and smoldering multiple myeloma (SMM). The incidental detection of M-protein in MM and its precursors during SPE is low (<0.5%) [10,11]. Thus, the use of SPE for prophylactic purposes outside of at-risk populations is not recommended. In such cases, precursor conditions are more common and require patient management and monitoring. This study aims to present the results of SPE testing from preventive laboratory screening among healthy Bulgarian adults.

Methods

A total of 92 individuals with clerical and administrative roles (n = 92; 35 males, 57 females) were enrolled, with an average age of 53.6 ± 16.4 years (54.9 ± 13.2 for males, 54.35 ± 15.9 for females). All participants received preventive examinations and had no known MM, monoclonal gammopathy of MGUS, or SMM, according to a questionnaire. Each participant provided informed consent to participate in the study. This study was conducted in accordance with the World Medical Association Declaration of Helsinki, revised in 2000 in Edinburgh. It was approved by the Scientific Research Ethics Committee of St. Ivan Rilski University Hospital, Sofia, Medical University of Sofia, under decision number 05/18.03.2026.

Blood was collected in the morning after an overnight fast, and serum was obtained in accordance with pre-analytical standardization requirements. Lipemic and haemolytic samples were excluded. The capillary electrophoresis machine MiniCap (Sebia, France, 91090 Lisses) was used. The separation technique divided 6 separate fractions of serum proteins: albumin, alpha-1, alpha-2, beta-1, beta-2, and gamma. TP was measured by the colorimetric Biuret method on the Alinity c (Abbott). Screening for monoclonal gammopathy was performed on serum specimens from healthy individuals living in Sofia, Bulgaria. All the analyses were performed in the Clinical Laboratory Department of University Hospital St. Ivan Rilski, Sofia, in 2025.

Results

According to the SPE data, no cases of monoclonal gammopathy were found in the examined group. Most patients had serum TP within reference limits, with mean ± SD values of 75.61 ± 3.16 g/L in males and 75.23 ± 4.25 g/L in females. In only one woman (36 years old), the TP result was slightly elevated, at— 84.87 g/L, and polyclonal hypergammaglobulinemia was detected on the proteinogram. Pathological changes in the beta region were detected in 18 participants. Pathological findings in the gamma zone were detected in 8 participants.

The specific findings according to pathology are summarized in (Table 1).

Table 1: Distribution of results based on the presence or absence of pathological findings in the SPE

Sebia CAPILLARIS SPE Results, total n=92		*n*	*%*
Normal SPE (Fig. 2A)		*66*	*71.74*
Monoclonal gammopathy		*0*	*0*
Beta-1 fraction	*increased*	*12*	*13.04*
	decreased	*0*	*0*
Beta-2 fraction	*increased*	*3*	*3.26*
	decreased	*1*	*1.08*
Beta-1 and Beta-2	*both increased*	*2*	*2.17*
	both decreased	*0*	*0*
Gamma region	*hypogammaglobulinemia*	*5*	*5.43*
	policlonal hypegammaglobulinemia (gamma- zone >13.5 g/L), including one SPE result with beta–gamma bridge	*3*	*3.26*

Hypogammaglobulinemia (<8.0 g/L) was observed in 5.43%, (n = 5), and polyclonal hypergammaglobulinemia (>13.5 g/L) in 3.26% (n = 3). In addition to the SPE, the following tests were also performed on all participants: complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT). The results are presented in (Table 2).

Table 2: Demographic and biochemical characteristics of the study population

Lab test	*Reference intervals*	*Male, n=35*	*Female, n=57*
Age, years		*54.9±13.2*	*54.35±15.9*
Hgb, g/L	*M (130 – 166); F (115 – 150)*	*154.2±9.6*	*134.58±7.85*
RBC x 10^12/L	*M (3.90 – 5.47); F (3.76 – 5.34)*	*5.05±0.33*	*4.59±0.27*
WBC x 10^9/L	*3.50 – 10.80*	*7.28±1.65*	*6.50±2.08*
Plt x 10^9/L	*M (320 – 370); F (112 – 330)*	*263.2±66.84*	*292.74±74.01*
TP, g/L	*64.00 – 83.00*	*75.61±3.16*	*75.23±4.25*
AST IU	*M < 40.00; F < 32.00*	*22.47±6.05*	*21.83±8.51*
ALT IU	*M < 41.00; F < 33.00*	*24.73±16.29*	*16.80±8.28*
GGT IU	*M < 60.00; F < 40.00*	*38.74±35.02*	*30.23±17.35*
Glucose mmol/L	*3.5 – 6.1*	*5.89±0.69*	*5.87±0.94*

None of the patients included in the study exhibited anemic syndrome. Elevated gamma- glutamyl transferase (GGT) levels were identified in 11 women and 3 men. In one case, a male patient presented with a GGT level of 208 UI/L and SPE findings indicating polyclonal hypergammaglobulinemia, distortion, and an increased beta-2 fraction, interpreted as evidence of a beta-gamma bridge. Impaired fasting blood glucose was identified in three patients, defined as a value greater than 7.00 mmol/L according to the American Diabetes Association criteria for the diagnosis of diabetes in nonpregnant individuals [16]. The quantitative results from SPE in all the participants are presented in (Table 3).

Table 3: Results of protein fractions in SPE; mean ± SDs g/L.

SPE fractions	*Albumin*	*Alpha-1*	*Alpha-2*	*Beta-1*	*Beta-2*	*Gamma*
Reference values for serum protein fractions used in the laboratory						
g/L	*40.2 – 47.6*	*2.1 – 3.5*	*5.1 – 8.5*	*3.4 – 5.2*	*2.3 – 4.7*	*8.0 – 13.5*
Patients results						
Male, n=35						
g/L	*45.12±2.85*	*3.18±0.45*	*7.88±1.19*	*5.06±0.75*	*3.75±0.91*	*10.52±2.22*
Female, n=57						
g/L	*44.82±3.17*	*3.13±0.37*	*7.65±1.13*	*4.98±0.61*	*3.68±1.07*	*11.02±2.21*
Total, n=92						
g/L	*44.97±3.06*	*3.15±0.40*	*7.74±1.15*	*5.01±0.67*	*3.70±1.01*	*10.83±2.23*

An abnormal serum SPE was defined by the presence of a hypergammaglobulinemia of more than 13.5 g/L, and a hypogammaglobulinemia of less than 8.0 g/L, according to accepted consensus reference values for SPE in the Clinical Laboratory Department.

In 28.26% (n = 26) of the study participants, deviations in the SPE were observed (Table 1).

The findings from capillary electrophoresis, categorized by pathology type, are shown in Tables 1 and 4, and in Figures 1 and 2.

Table 4: Hypogammaglobulinemia was established in 5.43% of the participants

Sample number	*Age, gender*	*Gammaglobulines g/L*
Sample 1	*53, M*	*6.8*
Sample 2	*45, M*	*7.3*
Sample 3	*64, M*	*7.5*
Sample 4	*75, W*	*7.4*
Sample 5	*67, W*	*6.2*

Discussion

In the present study, the incidence of dysproteinemia was 28.26% (26 patients), without cases of M-protein in the gamma zone. Clinical interest is usually focused on the gamma zone of the SPE, where immunoglobulins migrate. The detection of hypergammaglobulinemia or an M- protein is the most common change in the electrophoretic profile of serum proteins in dysproteinemias [17]. Most often, paraprotein is detected in the gamma zone of the serum, although in cases of monoclonal IgA, it may migrate to the beta zone of the electrophoretic profile [1,16].

Beta-Fraction Abnormalities

In 19.56% (n = 18) of the patients in the present study, pathological findings were identified in the beta zone of the proteinogram. In capillary electrophoresis, the beta fraction is divided into beta-1 and beta-2 fractions. When the beta-2 fraction exceeds the beta-1 fraction, as seen in 1.08% (n = 1) of cases in this study (Figure 1B), it is interpreted as a potential indicator of a monoclonal immunoglobulin, most often IgA, which migrates in the beta region of the proteinogram [1,2]. According to Chan

PC et al., dividing the beta zone into two fractions, beta- 1 and beta-2, enhances the likelihood of detecting a monoclonal protein [2]. An increase in beta fractions may be associated with monoclonal gammopathies or polyclonal increases due to inflammatory, autoimmune, or liver diseases. Detecting a monoclonal protein in the alpha-2, beta-1, or beta-2 fraction is challenging because its electrophoretic mobility closely matches that of proteins normally present in this region, making the monoclonal component difficult to detect [18,19].

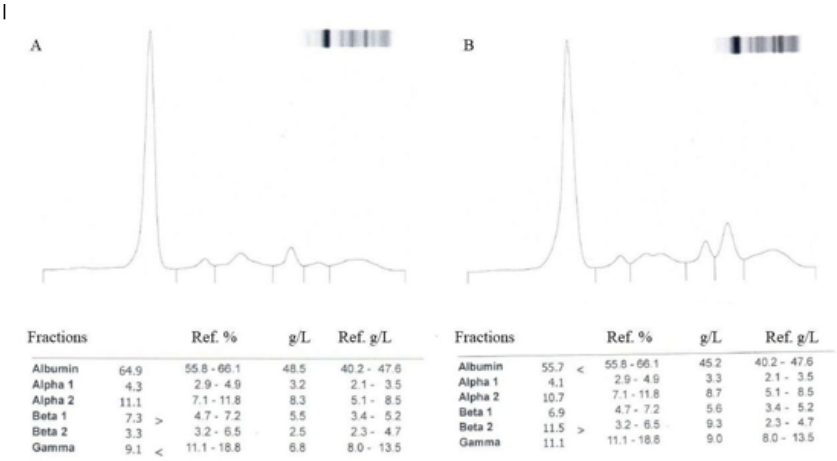

Figure 1: Serum protein electrophoresis: A – Hypogammaglobulinemia; B - beta-2 fraction exceeds the beta-1 fraction

Beta––gamma bridges are not linked to beta-migrating monoclonal immunoglobulins [2]. The beta––gamma bridge indicates liver disease and appears on electrophoretic images as a broad increase in the beta region with distortion of the electrophoretic profile (Figure 2B).

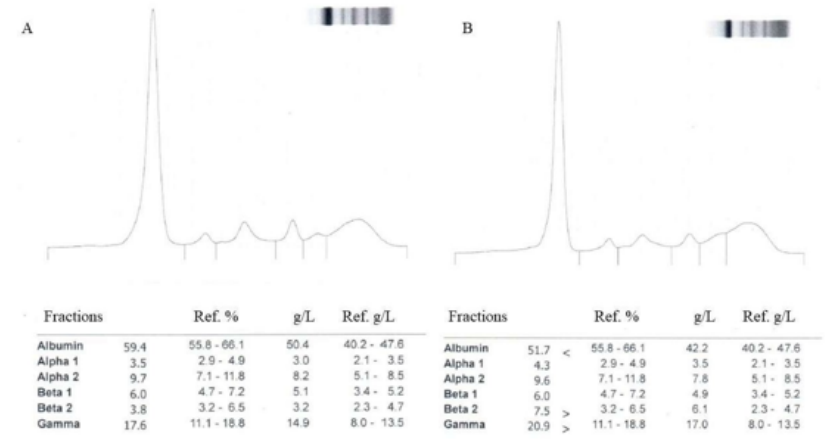

Figure 2: SerumproteinElectrophoresis: A–normal appearance; B Hypergammaglobulinemia

In cases where a pathological finding is present in the beta zones of the SPE, such as elevated beta-1 and/or beta-2 or qualitative features like distortion and peaks, further studies are necessary to search for monoclonal protein-IFE [19,20]. There is uncertainty about whether IFE should be performed after every SPE or only under specific circumstances, as it helps identify and increase the detection of peaks that may have questionable clinical significance and may be transient phenomena related to inflammation and autoimmune diseases [18]. CRP is an acute-phase protein with electrophoretic mobility matching the serum's beta-globulin fraction. During acute inflammation, it may appear as a separate component in the beta-2 fraction [21].

In patients with elevated beta fractions but no visible monoclonal peak, IEF is recommended. Additional analyses after SPE in cases of beta-zone abnormalities can be guided by the following criteria: suspicion of a beta -region spike, a beta-1-beta-2 bridge, or an unexplained increase in the beta region [22]. Kitson et al. reported that, among 1841 participants, 56 beta- migrating M-proteins with qualitative features progressed to MM [22]. Typically, transferrin is mainly found in the beta-1 zone, and the C3 fraction of complement is found in the beta-2 zone [1,22].

Hypogammaglobulinemia

Hypogammaglobulinemia itself is a laboratory definition and does not necessarily indicate a clinically significant disease. It means that the serum levels of gammaglobulins, mainly immunoglobulins IgG, IgA, and IgM. Moderate hypogammaglobulinemia was observed in 5.42% (n = 5) of the participants in the study group (Table 4, Figure 1A). This could be interpreted as a reduced immune function because of primary immunodeficiency or secondary causes such as medication effects, protein loss (nephrotic syndrome, enteropathies), and haematological or neurological diseases [23]. In some cases of severe hypohammaglobulinemia, MM should also be considered. In 1–2% of all MM cases, there is no M-protein , and these cases are called non-secretory multiple myeloma [13]. In these patients, serum and urine electrophoresis did not show a monoclonal protein. The participants in the present study did not have severe hypogammaglobulinemia, the values were between 6.0 and 8.0 g/L, nevertheless, in such cases, it is recommended to perform additional tests such as the IEF testing of both serum and urine samples, the quantitative assessment of immunoglobulin's and sFLC, a bone marrow biopsy, and imaging studies (such as computer tomography and magnetic resonance imaging) [24,25].

Hypergammaglobulinemia

The interpretation of SPE results is linked to a variety of clinical conditions, with different diseases showing characteristic electrophoretic patterns—such as inflammation, malignancy, liver disease, trauma, and necrosis [3]. It is also very important to distinguish polyclonal from monoclonal increases in protein levels. In this study, cases with hypergammaglobulinemia were polyclonal. The causes of polyclonal hypergammaglobulinemia can include infection and inflammation, connective tissue diseases, liver conditions, vasculitis, malignancies, hematologic and lymph proliferative disorders, IgG4-related disease, and inflammatory conditions like ulcerative colitis and Crohn's disease, as well as pulmonary and endocrine diseases (Graves' disease and Hashimoto's thyroiditis) [1,3,26]. In this study, three patients exhibited polyclonal hypergammaglobulinemia (Figure 1A,B). Inflammation with persistent CRP values ≥30 mg/L is a cause of polyclonal hypergammaglobulinemia. Measuring CRP and serum IgG levels can aid in diagnosing these cases [26].

The incidental recognition of MM in asymptomatic patients by SPE is rare. Data on the Bulgarian population are consistent with the literature, which reports fewer than 0,5% of newly diagnosed MM cases among adults over 40 during routine check-ups. MGUS and SMM are more often detected, representing early stages of the disease, but are also rare [11,27]. Common conditions suggestive of MM include the presence of symptoms or evidence of anemia, renal failure, hypercalcemia, or bone pain [28].

The conditions that are considered precursors to MM development are MGUS and SMM. They are characterized by the presence of an M-protein characterizes them, but there is no evidence of organ damage or symptoms in patients. In people over 65 years of age, MGUS occurs at a frequency of 3–5%, and SMM has a lower frequency but a higher risk of progression to MM [13]. The risk of progression to MM in MGUS is about 1% per year, whereas in SMM, it is 10% per year in the first 5 years [13,28]. The monitoring of MGUC and SMM is based on risk stratification, regular laboratory tests, and imaging. This includes testing for CBC, creatinine, calcium, SPE (M-protein), sFLC, and urinary Bence-Jones protein, as well as imaging [13,28,29].

A cautious approach is necessary in cancer screening, as the benefit-risk balance may be uncertain. Key risks include over diagnosis, unnecessary follow-up, invasive procedures such as bone marrow biopsy, and psychological distress for patients [9,30]. Current medical literature does not recommend SPE as a screening test for MM in the general population. This is due to insufficient evidence of clinical benefit, the lack of a defined target population, and the risks of over diagnosis and unnecessary follow-up [15]. The International Myeloma Workshop and College of American Pathologists recommend SPE only in patients with suspected MM or monoclonal gammopathy [12,20].

Conclusions

The present study reports the results of SPE conducted on participants from the Bulgarian population as part of preventive investigations. The frequency of incidentally detected MM was low, with no cases identified among the 92 patients examined. This finding aligns with existing literature reporting rates below 0.5%. In this cohort, other alterations in the electrophoretic profile were observed in 28.26% of cases, most frequently in the beta zone, potentially indicating inflammation, renal failure, or liver disease. The use of SPE as a screening tool for MM is not generally recommended or justified. However, SPE remains a highly informative technique for identifying other pathologies and should be employed when clinically indicated. For MM screening, more sensitive and specific methods, such as the serum free light chain assay and IFE, are recommended, as these tests facilitate earlier and more accurate detection. These diagnostic methods should be available in primary care settings to expedite diagnosis and the initiation of treatment. Recommendations include managing MM risk in at-risk populations and monitoring for MM precursors. Studying the population incidence of the disease provides a good basis for proper health policies.

Abreviations

AL – primary amyloidosis

ALT - alanine aminotransferase

AST - aspartate aminotransferase

C3 – compliment component 3

CBC – complete blood count

CRP – C-reactive protein

ESR – erythrocyte sedimentation rate

F – Female

GGT - gamma-glutamyl transferase

Hgb – haemoglobin

IEF – immunofixation electrophoresis

IgA – immunoglobulins A

IgG – immunoglobulins G

IgM – immunoglobulins M

M – Male

MGUS - monoclonal gammopathy of undetermined significance

MM – multiple myeloma

Plt – platelets

RBC – red blood cells

SFLC – serum free light chain

SMM – smoldering multiple myeloma

SPE – serum protein electrophoresis

TP – total protein

Acknowledgment

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Conflict of Interest

The authors declare no conflicts of interest.

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