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Monoclonal Gammopathy of Undetermined Significance in General Practice

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ABSTRACT

Background: In addition to progression to lymphoproliferative diseases, patients with monoclonal gammopathy of undetermined significance (MGUS) appear to suffer from other types of comorbidities, although the extent to which MGUS contributes to these comorbidities is unclear. The aim of this study is to evaluate the presence of patients with MGUS who attend general practice (GP) in our healthcare area, as well as to describe the comorbidities and abnormal blood test results associated with these patients.

Methods: A retrospective study was carried out whereby demographic data, comorbidities, and the results of certain analytical parameters were collected from 1201 patients, who visited their GP physician: 201 patients with a monoclonal protein and 1000 patients without the presence of monoclonal protein were identified.

Main findings: Of the 6307 proteinograms performed on patients from GP, 201 presented with an M-protein (3.2%). The presence of MGUS increased with age and was significantly higher in men than in women (55.7% vs 44.3%, $p<0.05$). We found that the most frequently associated comorbidities with MGUS were renal and cardiovascular diseases, osteoporosis and bone lesions, anemia, and hyperlipidemia. There was a significant association between MGUS and the following blood parameters: hemoglobin, leukocytes, neutrophils, monocytes, proteins, albumin, globulin, and creatinine, as well as for the indices neutrophil-to-lymphocyte, monocyte-to-lymphocyte and albumin-to-globulin ratio.

Principal conclusions: We conclude that MGUS is a common premalignant plasma cell disorder in GP patients, the prevalence of which increases with age. Likewise, a series of blood parameters and comorbidities associated with MGUS that support the need to implement a program for early detection and monitoring of MGUS was described.

Keywords: MGUS, paraprotein, GP, comorbidities

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INTRODUCTION

Monoclonal gammopathy is defined as a clonal proliferative disorder of B cells or plasma cells, with the capacity to secrete a single type of immunoglobulin, or a constituent part of it, in excessive amounts. MGUS affects 3.2% of ≥50-year-old people and 5.3% of ≥70-year-old people. It is considered a premalignant entity with a low risk of progression to other lymphoproliferative malignancies (1). Although the diagnosis of MGUS is well established by International Myeloma Working Group recommendations (2), the monitoring of these patients is much less defined. Some authors have highlighted the lack of knowledge and awareness in the management of patients with MGUS among GP doctors (2, 3). MGUS screening is not recommended for various reasons: a) the progression risk is too low, b) the monitoring of a large proportion of the study population over a very long period of time would be needed, which would require human/financial resources from the national health system, c) its treatment has not been proven to be effective, d) the negative psychological impact that an MGUS diagnosis has on a patient's quality of life, and e) the risk and drawbacks of the bone marrow test (4). However, although the majority of patients with MGUS remain asymptomatic, a fraction of them develop clinical manifestations (renal, cutaneous, neurological, ocular, cardiovascular disease, infections, etc.), and these have been categorized under the term "Monoclonal Gammopathy of Clinical Significance" (5). Some studies have argued that MGUS patients under monitoring may experience fewer complications and have a longer survival rate than those who do not receive any monitoring treatment; this is because MGUS is known to be associated with a variety of comorbidities, which could be limited when they are identified and treated appropriately, thus improving the patient's health status (6-10).

The aim of this study is to evaluate the number of patients with MGUS, who attend GP in our healthcare area, as well as to describe the comorbidities and abnormal blood test results associated with it.

MATERIALS AND METHODS

Participants

We conducted a retrospective study of 201 patients recruited from GP between September 2022 and January 2023. Inclusion criteria were patients >18 years old, who underwent serum protein electrophoresis for the first time and had a monoclonal component diagnosed as MGUS. Cases were identified through an electronic health record (EHR); the search algorithm and data were extracted from the EHR. As a control group, a sample of 1000 people aged 18-99 years, seen in GP centers during the same time period, was randomly selected and did not present with monoclonal protein (M-protein) on the serum protein electrophoresis (proteinogram). The diagnostic criteria used for MGUS were based on the following: 1) a monoclonal gammopathy was evident on the proteinogram; 2) the monoclonal protein level was <3.0 g/dL; and 3) there was no evidence of lytic lesions, anemia (hemoglobin >10 g/dL), hypercalcemia (calcium <11 mg/dL) or renal insufficiency (creatinine clearance >40 mL/min or serum creatinine <2.0 mg/dL) related to monoclonal protein. Bone marrow biopsy was not performed to verify that the clonal plasma cell proliferation is indeed less than 10%. This was attributed to the cost and inconvenience to the patient in relation to the procedure. Additionally, the detection of clonal plasma cells greater than 10% in bone marrow is rare when levels of monoclonal proteins are low (<3.0 g/dL) (11). Clinical data were collected including demographic data (sex and age), comorbidities, and routine blood test results (full blood count, calcium, creatinine, uric acid, urea, serum protein electrophoresis, immunoglobulins, and free light chains).

Methods

The proteinogram was performed using Sebia Capillarys 2 System (Lisses, France), and immunofixation electrophoresis was performed on an Interlab G26 using Sebia antisera. Serum free light chains, kappa, and lambda were analyzed on a turbidimeter Optilite® (Binding Site Inc., Birmingham, UK) with the Freelite reagents supplied by Binding Site Ltd (Birmingham, UK). Hematology was performed on an Advia® 2120 Hematology System and testing on creatinine, calcium, uric acid, and urea was performed on an Advia® 2400 Chemistry System (Siemens Healthcare Diagnostic, Germany). The immunoglobulin values were measured with a Dimension Vista 1500 (Siemens Healthcare Diagnostic, Germany) analyzer.

Statistical analysis

Statistical analysis and data processing were performed with the following computer programs: Microsoft® Excel (Microsoft Corporation, USA) and MedCalc® for Windows (MedCalc Software, Belgium). Continuous variables were expressed as mean ± standard deviation (SD) for normal variables or median (interquartile range: IQR) for non-normal variables, and categorical variables were presented as a number and percentage. The Kolmogorov-Smirnov test was applied to check data normality. When parametric conditions were fulfilled, a Student´s t-test was performed, and when non-parametric conditions were fulfilled, a Mann-Whitney U test was performed. A chi-square test was used to compare the proportions of cases (patients of GP with MGUS) with each set of comorbid diagnoses in relation to the proportion of controls (patients of GP without MGUS) with those same diagnoses. The significance criterion was set at $p<0.05$.

RESULTS

Of the 6307 proteinograms performed between September/2022 and January/2023, 201 patients presented with an M-protein (3.2%), with a mean age of 71.7±14.9 years (range: 18-99). MGUS was found in 112 men and 89 women (55.7% vs 44.3%, $p<0.05$). The percentage of patients with MGUS increases with age (Figure 1): 1.5% (≤30-year-old), 1.5% (30-39-year-old), 4.0 (40-49-year-old), 11.9% (50-59-year-old), 21.9% (60-69-year-old), 26.9% (70-79-year-old) and 32.3% (≥80-year-old); the same behavior was observed in both genders.

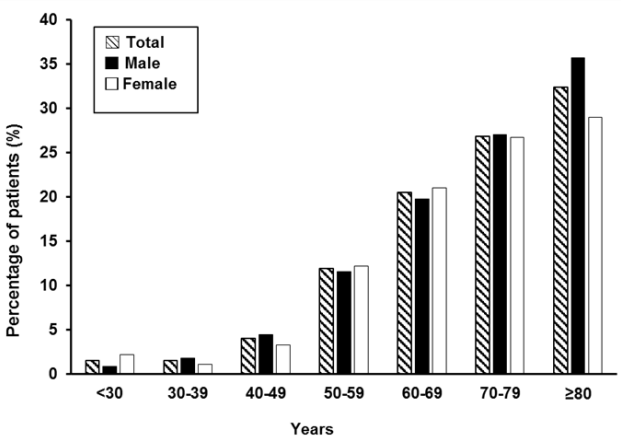

Figure 1. Percentage of MGUS with different ages and gender

Initial M-protein serum values ranged from unquantifiable (small band on electrophoresis: <0.5 g/dL) to 1.51 g/dL, with 85.1% of patients (171 out of 201 patients) presenting a low concentration (<0.5 g/dL). The most frequent monoclonal immunoglobulin isotype was IgG (136 patients, 67.7%), followed by IgM (36 patients, 17.1%) and IgA (18 patients, 9.0%). Moreover, there was one patient with light chains (0.5%) and 10 patients with biclonal behavior (5.0%). The kappa light chain was present in 122 patients (60.7%) and the lambda light chain in 71 patients (35.3%); eight patients (4.0%) had biclonal MC with both types of light chain. In relation to the free light chains (FLC), 146 patients (72.6%) had a normal FLC-ratio (kappa/lambda ratio: 0.26-1.65) and 55 patients (27.4%) had an abnormal FLC-ratio (kappa/lambda ratio: <0.26 or >1.65), of which 10 patients (18.2%) had a FLC-ratio <0.26 and 45 patients (81.8%) had a FLC-ratio >1.65.

According to the model for MGUS risk progression into malignant lymphoproliferative processes, proposed by

the Mayo Clinic (12), 99 out of 201 patients (49.2%) presented with a low risk of progression (M protein level <1.5 g/dL, IgG type, and normal FLC ratio), 82 out of 201 (40.8%) had an intermediate-low risk of progression (one of these three factors was abnormal), 19 out of 201 (9.5%) had an intermediate-high risk (two of these three factors were abnormal), and only one patient (0.5%) presented with a high risk of progression (in this case, all three factors were abnormal).

With regard to assessing the association of MGUS with different blood parameters for all patients (Table I), significant differences between both groups were found in the case of nine parameters: hemoglobin, leukocytes, neutrophils, monocytes, proteins, albumin, globulin, creatinine, and urea, and for the indices: neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and albumin-to-globulin ratio (AGR).

Table 1. Demographic data and laboratory features of the total number of patients.

	Patients of GP with MGUS (n=201) Mean (SD) or Median (IQR)	**Patients of GP without MGUS (n=1000) Median (IQR)**	**Significance p Value**
Age (years)	71.7±14.9 (range: 18.0-99.0)	62.0 (48-74) (range: 18.0-99.0)	**<0.001**
Gender (♂/♀)	112/89	405/595	-----
Hemoglobin (g/dL)	13.8±1.70 (range: 10.2-18.0)	14.1 (13.2-15.1) (range: 10.9-18.4)	**0.009**
Leukocytes (10^3/uL)	6.73 (5.47-8.22) (range: 3.06-22.36)	6.33 (5.15-7.60) (range: 2.07-19.82)	**0.003**
Platelets (10^3/uL)	248±78 (range: 83-562)	236 (200-273) (range: 240-603)	0.438
Neutrophils (10^3/uL)	3.66 (2.67-4.79) (range: 0.99-13.29)	3.33 (2.57-4.17) (range: 0.78-10.18)	**0.003**
Lymphocytes (10^3/uL)	2.09 (1.64-2.68) (range: 0.70-14.64)	2.13 (1.71-26.3) (range: 0.37-9.24)	0.561
Monocytes (10^3/uL)	0.44 (0.35-0.55) (range: 0.20-1.35)	0.39 (0.31-0.49) (range: 0.13-1.70)	**<0.001**
Protein (g/dL)	6.9±0.54 (range: 4.9-9.0)	6.8 (6.6-7.1) (range: 4.4-8.3)	**0.01**
Albumin (g/dL)	4.3 (4.0-4.5) (range: 2.7-5.0)	4.4 (4.2-4.6) (range: 2.50-5.2)	**<0.001**
Globulin (g/dL)	2.6 (2.3-2.9) (range: 1.6-5.2)	2.4 (2.2-2.6) (range: 0.6-4.0)	**<0.001**
Creatinine (g/dL)	0.83 (0.7-1.0) (range: 0.2-1.7)	0.77 (0.67-0.92) (range: 0.36-2.40)	**<0.001**
Uric acid (g/dL)	5.71±1.83 (range: 2.6-12.4)	5.3 (4.3-6.5) (range: 2.2-13.6)	0.143
Urea (g/dL)	44.0 (36.0-56.0) (range: 12.0-162)	40.0 (32.0-49.0) (range: 4.0-143)	**<0.001**
Calcium (g/dL)	9.5 (9.2-9.7) (range: 7.5-10.5)	9.5 (9.3-9.8) (range: 8.2-11.9)	0.279
PLR	111.7 (86.6-147.1) (range: 18.0-423.3)	109.6 (86.2-136.2) (range: 13.3-502.4)	0.323
NLR	1.72 (1.2-2.4) (range: 0.18-9.96)	1.51 (1.17-2.02) (range:0.34-13.40)	**0.01**
MLR	0.21 (0.15-0.28) (range: 0.06-0.88)	0.18 (0.14-0.23) (range: 0.07-0.76)	**<0.001**
AGR	1.64±0.32 (range: 0.73-2.50)	1.85 (1.67-2.04) (range: 0.69-750)	**<0.001**

**U-test was used*, SD: standard deviation; IQR: interquartile range; PLR: platelet/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; AGR: albumin/globulin ratio.

Table 2**.** Demographic data and laboratory features in patients ≥60 years.

	Patients with MGUS ≥60 years (n=160) Mean±SD or Median (IQR)	**Patients without MGUS ≥60 years (n=550) Mean±SD or Median (IQR)**	**Significance p Value**
Age (years)	77.0±9.59 (range: 60-99)	73.5 (66-80) (range: 60-99)	**<0.001**
Gender (♂/♀)	82/78	215/335	**-----**
Hemoglobin (g/dL)	13.7±1.69 (range: 10.3-18.0)	14.1 ± 1.41 (range: 10.9-18.4)	**0.010**
Leukocytes (10^3/uL)	7.0±2.21 (range: 3.1-16.2)	6.4 (5.2-7.6) (range: 3.1-14.0)	**0.033**
Platelets (10^3/uL)	242±81.5 (range: 83-562)	229 (195-269) (range: 72-531)	0.706
Neutrophils (10^3/uL)	4.03±1.92 (range: 0.99-13.29)	3.31 (2.58-4.27) (range: 0.78-10.18)	**0.016**
Lymphocytes (10^3/uL)	1.98 (1.58-2.66) (range: 0.70-6.56)	2.13 (1.71-26.3) (range: 0.40-7.50)	0.509
Monocytes (10^3/uL)	0.44 (0.35-0.56) (range: 0.20-1.08)	0.40 (0.33-0.50) (range: 0.13-1.70)	**0.007**
Protein (g/dL)	6.8±0.57 (range: 4.9-9.0)	6.7 (6.5-7.0) (range: 4.4-8.3)	**0.010**
Albumin (g/dL)	4.3 (4.0-4.5) (range: 2.7-4.9)	4.4 (4.2-4.5) (range: 2.5-5.0)	**<0.001**
Globulin (g/dL)	2.6 (2.3-2.9) (range: 1.6-5.2)	2.4 (2.2-2.6) (range: 1.2-4.0)	**<0.001**
Creatinine (g/dL)	0.85 (0.72-1.04) (range: 0.20-1.90)	0.80 (0.70-0.97) (range: 0.36-2.44)	**0.010**
Uric acid (g/dL)	5.82±1.89 (range: 2.6-12.4)	5.76±1.63 (range: 2.3-13.6)	0.681
Urea (g/dL)	45 (37-59) (range: 12.0-162)	44 (36-56) (range: 4.0-143)	0.086
Calcium (g/dL)	9.5±0.40 (range: 7.5-10.5)	9.5 (9.3-9.7) (range: 8.2-11.9)	0.276
PLR	110.3 (85.8-148.2) (range: 29.4-423.3)	109.3 (87.1-134.8) (range: 35.4-502.4)	0.390
NLR	1.78 (1.21-2.52) (range: 0.41-9.96)	1.56 (1.19-2.11) (range:0.34-13.40)	**0.043**
MLR	0.21 (0.16-0.28) (range: 0.07-0.63)	0.19 (0.15-0.25) (range: 0.07-0.76)	**0.006**
AGR	1.62±0.32 (range: 0.73-2.50)	1.84±0.29 (range: 0.69-3.07)	**<0.001**

SD: standard deviation; IQR: interquartile range; PLR: platelet/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; AGR: albumin/globulin ratio.

In relation to the association of MGUS with other comorbidities (Table III), a significantly higher presence of MGUS was found in cases with cardiovascular disease (9.5% vs 4.9%, p<0.05), hyperlipidemia (7.0% vs 3.8%, <0.05), renal disease (6.0% vs 1.5%, p<0.05), anemia (5.0% vs 2.2%, p<0.05) and osteoporosis and bone lesions (4.0% vs 1.5%, p<0.05). When considering only ≥60-year-old patients (Table IV), the same results were found.

When considering only ≥60-year-old patients (Table II), the same results were found except for urea, where no significant differences were observed.

DISCUSSION

The occurrence of MGUS among patients who attend GP (3.2%) was higher than that indicated by other authors such as Han et al. (MGUS in 843 of the 154597 participants: 0.54%) (13) or Iwanaga et al. (MGUS in 1088 of the 52781 study participants: 2.1%) (14), although the studies carried out by these authors refer to the general population. The higher rate of MGUS observed in this study may be due, at least in part, to two causes: on the one hand, GP patients have a higher average age compared to the general population and it is already known that there is an age-MGUS causal relationship (1,13-15).

On the other hand, MGUS is more likely to be detected as part of a medical study for another disease (6).

Table 3**.** Comorbidities of the total number of patients (NA: not applicable)

Diagnoses	Total patients with MGUS (n=201)	Total patients without MGUS (n=1000)	*p* Value
Cardiovascular disease	19 (9.5%)	49 (4.9%)	**0.016**
Diabetes mellitus	19 (9.5%)	58 (5.8%)	0.070
Hypertension	17 (8.5%)	50 (5.0%)	0.070
Hyperlipidemia	16 (8.0%)	38 (3.8%)	**0.015**
Renal diseases	12 (6.0%)	15 (1.5%)	**<0.001**
Anemia	10 (5.0%)	22 (2.2%)	**0.044**
Osteoporosis and bone lesions	8 (4.0%)	15 (1.5%)	**0.037**
Two or more of the above diagnoses	11 (5.5%)	79 (7.9%)	0.302
Hematological diseases	8 (4.0%)	24 (2.4%)	0.296
Inflammatory rheumatic diseases	14 (7.0%)	67 (6.7%)	0.998
Disorders of thyroid	7 (3.5%)	70 (7.0%)	0.07
Malignancy	6 (3.0%)	38 (3.8%)	0.730
Diseases of the skin	6 (3.0%)	20 (2.0%)	0.533
General and non-specific problems	19 (9.5%)	140 (14.0%)	0.109
Other diagnoses*	29 (14.4%)	315 (31.5%)	NA

*Other diagnoses occurring in less than ≤2.5%: infections, asthenia and weakness, asthma, shortness of breath, fatigue, headache, diarrhea, vomiting, adenopathy, abnormal liver function test, syncope, abdominal pain, overweight, benign prostate hyperplasia, hair loss, weight loss, allergies, losing appetite, etc.

Table 4. Comorbidities in patients ≥ 60 years (NA: not applicable)

Diagnoses	Patients with MGUS ≥60 years (n=160)	Patients without MGUS ≥60 years (n=550)	*p* Value
Cardiovascular disease	18 (11.3%)	34 (6.2%)	**0.041**
Diabetes mellitus	18 (11.3%)	47 (8.5%)	0.354
Hypertension	16 (10.0%)	38 (6.9%)	0.257
Hyperlipidemia	12 (7.51%)	19 (3.4%)	**0.040**
Renal disease	12 (7.5%)	14 (2.5%)	**0.006**
Anemia	8 (5.0%)	9 (1.6%)	**0.028**
Osteoporosis and bone fractures	8 (5.0%)	10 (1.7%)	**0.037**
Two or more of the above diagnoses	11 (6.9%)	69 (12.5%)	0.067
Hematological diseases	6 (3.8%)	12 (2.2%)	0.399
Inflammatory rheumatic diseases	11 (6.9%)	34 (6.2%)	0.892
Disorders of thyroid	5 (3.1%)	35 (6.4%)	0.163
Malignancy	6 (3.8%)	32 (5.8%)	0.430
Diseases of the skin	4 (2.5%)	6 (1.1 %)	0.347
General and non-specific problems	9 (5.6%)	57 (10.3%)	0.092
Other diagnoses*	16 (10.0%)	134 (24.4%)	NA

*Other diagnoses occurring in less than ≤2.5%: infections, asthenia and weakness, asthma, shortness of breath, fatigue, headache, diarrhea, vomiting, adenopathy, abnormal liver function test, syncope, abdominal pain, overweight, benign prostate hyperplasia, hair loss, weight loss, allergies, losing appetite, etc.

The results from this study are consistent with those provided by other authors: 1) MGUS frequency depends on age and gender, 2) IgG is the most common type of immunoglobulin,

3) Kappa is the most common serum light chain, and 4) the majority of patients with MGUS have a normal FLC-ratio (0.26-1.65) (1, 12-16). The results from this study observed a greater discrepancy in the IgM and IgA immunoglobulin isotype (19.3% and 9.2% respectively) and are similar to the results provided by some authors such as Kyle et al. (1) (IgM: 17.2%, IgA: 10.8%), Gregersen et al. (17) (IgM: 18.5%, IgA: 9.9%), and Schaar et al. (18) (IgM: 18.6%, IgA: 8.5%), but they are quite different from those provided by other authors such as Han et al. (13) (IgM: 8.8%, IgA: 22.43%), Iwanaga et al. (14) (IgM: 7.5% and IgA: 17.6%), Onwah et al. (19) (IgM: 1.5%, IgA: 21.5%), and Steingrimsdottir et al. (20) (IgM: 5.5% and IgA: 33.4%). This variation observed between publications has not been fully explained to date, but it seems that several factors such as racial, genetic, environmental, or geographic factors may influence it, as well as factors related to the study design, study population, and the testing techniques used (21). In this study, it was observed that 49.3% of patients with MGUS present a low risk of progression to malignant lymphoproliferative diseases, which correlates with what has been reported by other authors, who found that 50% of patients with MGUS are low risk (22).

Anemia, renal failure, and an increase in total protein are some of the reasons why the presence of a monoclonal component must be ruled out (23). Therefore, this study found, as expected, that GP patients with MGUS present with significantly higher protein, creatinine acid, and urea values, and lower hemoglobin values. Likewise, since chronic inflammation is present in patients with MGUS (24), it was expected that significantly higher values of blood parameters, characteristic of the inflammatory response, were found, such as leukocytes, neutrophils, monocytes, and low albumin, as well as high values of the NLR and MLR indices and low AGR, which are also considered indicators of a systemic inflammatory response (25, 26).

In addition to the risk of MGUS being able to progress into a malignant lymphoproliferative process, the M-protein has been reported to cause organ damage through various mechanisms, such as deposition in organ tissues, interaction with the complement system, or through direct autoantibody activity of the monoclonal immunoglobulin itself, leading to diseases such as recurrent infections, heart and kidney disease, neuropathy or skin manifestations (5). In this sense, we observed that the comorbidities most frequently associated with GP patients with MGUS are cardiac, renal, and bone disorders, anemia, and hyperlipidemia. The higher frequency of these comorbidities in patients with MGUS has already been highlighted by other authors (8, 9, 10, 27, 28). The relationship between MGUS and renal failure called "monoclonal gammopathy of renal significance" is well known; the mechanisms include monoclonal immunoglobulin deposition disease, proliferative glomerulonephritis resulting from monoclonal IgG deposition, and light chain proximal tubulopathy (8). Patients with MGUS have a higher risk of osteoporosis and bone fractures, which seems to be related to alterations in bone metabolism and decreased bone mineral density (8, 27). Anemia is common in these patients, due to an erythropoietin deficiency caused by the renal failure that they may suffer, and a decrease in erythropoietin production as a consequence of bone marrow infiltration by the malignant cells of the M-protein (28). Several studies report an increased risk of developing deep venous thrombosis, coronary artery disease, cerebrovascular disease, or pulmonary embolism in MGUS patients; there is an increased risk of cardiovascular disease in patients with MGUS; an increase in factor VIII and von Willebrand factor levels has also been observed in these patients, which contributes to an increase in arterial thrombosis. Hyperlipidemia is a rare condition in MGUS (mainly IgA); the M-protein could bind to lipoproteins, LDL receptors, or lipoprotein lipases, resulting in reduced lipid degradation (27).

We cannot forget that the majority of patients (160 patients out of 201: 80%) with MGUS are elderly (≥60-year-old) and, since it is after 65 years of age that chronic diseases such as hypertension, arthritis, type II diabetes, coronary and renal disease, anemia, etc., appear (29), it would not be surprising if these chronic pathologies coexist with MGUS without being related. For this reason, the same study was carried out on ≥60-year-old patients, and practically the same results were found. The challenge with these M-protein disease associations is demonstrating causality, given that most patients being tested for M-protein are older and are more likely to have pre-existing medical diagnoses, leading to inherent bias in these studies (30). However, as epidemiological evidence continues to accumulate, it becomes increasingly important to initiate a thorough investigation into the possible biological causes of MGUS-associated morbidity. It would be necessary to approach the problem from a multidisciplinary point of view (hematology, dermatology, nephrology, neurology, etc.) given the great heterogeneity of organs affected and the clinical manifestations that can occur in this type of patient. It would be necessary for GP doctors to have clear guidelines from specialized care doctors, mainly hematologists, to optimize the management and monitoring strategies for these patients, since there is evidence that monitoring and treatment of serious complications in patients with MGUS lead to an increased survival rate (2, 5-9).

It is critical to highlight some of the limitations in the present study that should be considered: 1) the size of the evaluated population may not be sufficient to represent the entire population of patients who go to GP. 2) The method used in this study (SPE followed by IFE in cases of suspected M-protein) does not detect all patients, like the case of non-secreting myeloma or the disease that produces a single FLC. 3) A percentage of MGUS cases could be transient; Murray et al. (31) found that 16% of MGUS patients who presented with small concentrations of the monoclonal component disappeared over time. 4) Since this study focuses on patients who go to GP and who are diagnosed with MGUS for the first time, it is difficult to conclude which of these comorbidities appeared before or after MGUS. 5) It is possible that the diagnoses indicated in each patient are not the definitive ones or the only ones since these patients did not undergo a more in-depth review by specialized care doctors, who could change or increase the pathologies initially indicated by the GP doctor.

Despite these limitations, this study is important for three reasons. Firstly, and as far as the authors of this study are aware, this research is the first of its type to be carried out in Spain. Secondly, the higher presence of MGUS in patients who attend GP compared to the general population is notable. Thirdly, in this study, a series of blood parameters and comorbidities associated with MGUS has been made clear, which supports the opinions provided by other authors regarding the need to implement a program for the early detection and monitoring of MGUS (5-9).

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CONFLICT OF INTEREST
The authors state no conflict of interest.

AUTHORS' CONTRIBUTIONS
FJH: Literature review, contribution to study conception and design, supervision, interpretation of data, writing of the paper. MF: acquisition and treatment of data, contribution to study conception and design, critical revision of paper.

ETHICAL BACKGROUND

Institutional Review Board statement: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Permission was obtained from the Committee for Ethical Review at the Hospital Clínico Universitario de Santiago de Compostela for conducting this study (JHAGMSI-2023-01).

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Data availability statement: The authors are accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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