MPe
Myeloma Patients Europe

REPORT

AL AMYLOIDOSIS DIAGNOSIS EXPERIENCES IN EUROPE

INVESTIGATING THE DIAGNOSTIC EXPERIENCES AND CHALLENGES OF AL AMYLOIDOSIS WITH EUROPEAN PATIENTS AND HAEMATOLOGISTS

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INTRODUCTION AND BACKGROUND

AL AMYLOIDOSIS IS A VERY RARE DISEASE THAT CAN SEVERELY IMPACT THE ORGANS SUCH AS KIDNEYS, LIVER AND HEART.

A timely diagnosis has crucial implications for minimising organ damage and improving survival. However, limited, existing literature suggests that AL amyloidosis patients are, more often than not, diagnosed late, with some patients waiting for over a year.

To explore the challenges in achieving a timely diagnosis, MPE conducted a pan-European study to explore patient diagnostic experiences and the impact of a delayed diagnosis, and discuss potential solutions to improving diagnosis. Whilst the sample size was small (see methodology section for further details), necessitating the need for additional research, the findings serve as the basis for understanding the key challenges and identifying potential solutions to improving diagnosis.

WHAT IS AL AMYLOIDOSIS?

AL amyloidosis (also known as light chain amyloidosis) is a very rare disease, yet it is the most common type of amyloidosis. AL amyloidosis occurs when abnormal plasma cells in the bone marrow produce misfolded proteins instead of normal antibodies (proteins responsible for fighting infections). The misfolded proteins are called amyloid proteins they accumulate and deposit in vital organs, causing damage and eventual organ failure, and death. While AL amyloidosis can affect most organs except the brain, it often impacts the heart (75-80%), kidneys (65%), liver (15%), nervous (10%) and gastrointestinal systems (5%).[1,2]

AL amyloidosis is not a cancer. However, there are many similarities between myeloma and AL amyloidosis:

- Both diseases arise out of bone marrow plasma cell abnormalities.
- Up to 30% of patients with a new myeloma diagnosis may have asymptomatic deposits of amyloid proteins in their organs.[3]
- 12 - 15% of patients with myeloma may develop symptomatic AL amyloidosis.[3]
- 8% of patients with AL amyloidosis may also have the distinctive “CRAB” symptoms (calcium elevation, renal insufficiency, anaemia and bone lesions).[3]

INTRODUCTION AND BACKGROUND

THE CHALLENGE WITH DIAGNOSING AL AMYLOIDOSIS

Early diagnosis of AL amyloidosis is key to prevent further worsening of organ function, and improving survival and post-treatment quality of life.[4,5] Yet, AL amyloidosis is often not diagnosed or recognised until irreversible organ damage has occurred, usually when a patient shows signs of heart or kidney failure. The rarity of AL amyloidosis, the non-specificity of symptoms (such as unexplained weight loss, fatigue, oedema and shortness of breath on exertion[6]) and the average age of patients being over 64, collectively mean it is a very difficult disease to diagnose for general practitioners (GPs, i.e. primary care doctors).[2,6,7,8] Patients commonly report presenting at their GP numerous times before referral and convoluted pathways to diagnosis such as being referred to a non-haematology secondary care department (such as cardiologists or renal clinics).

A literature review undertaken by MPE confirmed patient testaments and found the following:

- Research has shown that 20% of patients with AL amyloidosis are not correctly diagnosed until two years or longer after the first symptoms.[2] Other research has shown that the median time from the first consultation to diagnosis is 441 days.[9]
- It can take more than five physicians before a patient receives a diagnosis of AL amyloidosis.[10]
- Most patients are diagnosed at specialised amyloidosis centres of excellence.[11]
- Many patients report a delay in diagnosis of greater than or equal to six months.[12]

Across the board, there is limited research on early detection methods for AL amyloidosis, and screening in the general population is discouraged given the rarity of the disease and the lack of very sensitive or specific measurements to detect the disease.[12] In the future however, as we learn more about AL amyloidosis, being able to identify the patients most likely to develop the disease is essential for improving the diagnosis of AL amyloidosis. In the interim, we need non-screening solutions to improve the diagnosis experience of AL amyloidosis patients.

METHODS

A MIXED-METHODS RESEARCH METHODOLOGY WAS CHOSEN STARTING WITH A PAN-EUROPEAN SURVEY AND FOLLOWED BY PATIENT AND HAEMATOLOGIST INTERVIEWS. IN TOTAL, 63 PATIENTS AND 16 HAEMATOLOGISTS COMPLETED THE SURVEY. TWO PATIENTS AND NINE HAEMATOLOGISTS TOOK PART IN THE INTERVIEWS.

Table 1: Country-specific patient and haematologist demographics

	Patients		Haematologists	
Country	Survey	Interviews	Survey	Interviews
Belgium	1		2	
Czech Republic				1
Denmark	8			
Finland	5			
France	1			2
Germany	1			
Greece				1
Israel	9			1
Italy			3	1
North Macedonia				1
Netherlands	6		1	
Norway	4			
Other	2		1	
Poland	3		1	1
Romania			3	
Slovenia	1			
Spain	19	2	3	
Sweden			1	
Turkey	1			
United Kingdom	2		1	1
Total	63	2	16	9

KEY FINDINGS

THE RESULTS OF THE SURVEY AND INTERVIEWS WERE GROUPED AND ANALYSED THEMATICALLY. THE KEY FINDINGS ARE SUMMARISED BELOW AND PRESENTED IN MORE DETAIL IN THE ASSOCIATED FIGURES

TIME TO DIAGNOSIS AND LOCATION:

MPE's research found that many AL amyloidosis patients experience delays in receiving a diagnosis due to the complex nature of the disease. In addition, they also often wait too long before presenting to the GP with symptoms, which further delays a patient entering the healthcare system.

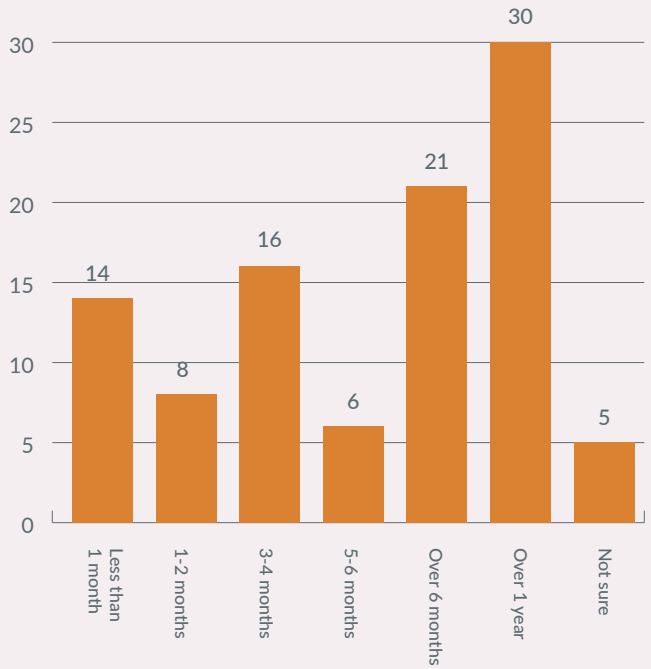
- 73% of patients waited 3 months or more before seeking medical help.
- 68% first presented with their symptoms or received abnormal blood results at their GP and 11% at an emergency hospital department.
- Approximately 47% of patients waited 5 months or more to get a diagnosis and 22% waited over a year.
- In contrast, 62% of haematologists stated it took their patients 5 months or more to get a diagnosis.

> *"When they ask me how long I had symptoms for, I couldn't answer. Now that I think about it from a distance, I remember that the first feeling was that I got tired going up hills, but since we were in a pandemic, I thought that I had lost the habit of exercising. Before the pandemic, I walked at least between eight and ten kilometres. Then I went on to walk half an hour a day. That's why, at first, I blamed the lack of exercise."*
>
> – AL AMYLOIDOSIS PATIENT, SPAIN

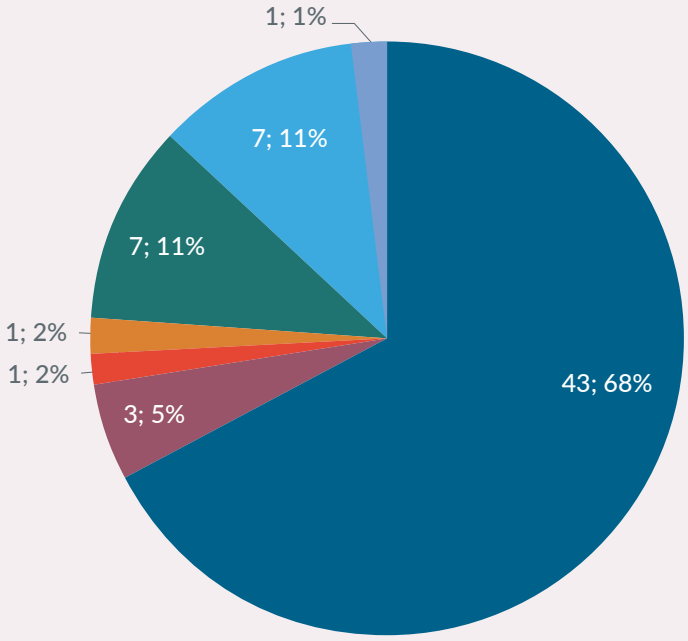
> *The symptoms are insidious. It's not like you wake up in the morning and you suddenly have shortness of breath. When you ask the patients, in retrospect, then they would say that symptoms started two, three, four years ago sometimes. Most patients will not know to pinpoint when the exact time was that the symptoms started. So usually, it takes about half a year or a year for the symptoms to become evident enough."*
>
> – HAEMATOLOGIST, ISRAEL

Patient responses

Fig 1. Percentage of responses for how many months patients experienced symptoms before seeking medical help.



KEY FINDINGS



Patient responses

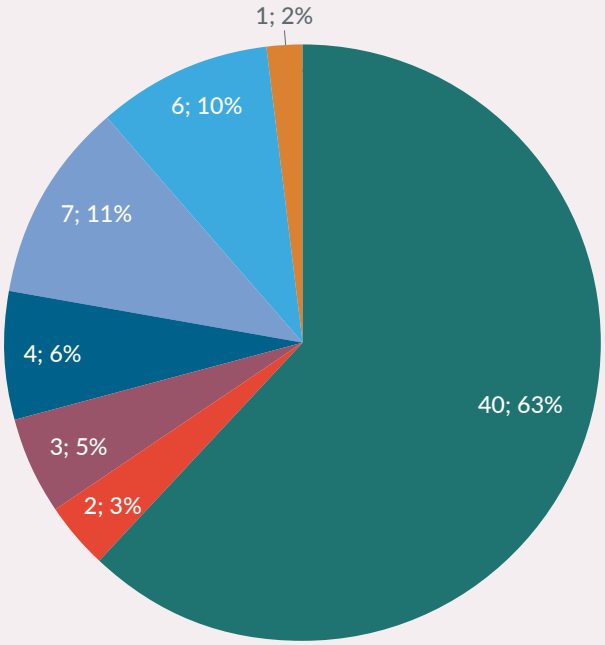
Fig 2. Number and percentage of responses (n; %) for where patients first presented with symptoms or first received abnormal blood results.

- General practitioner (GP) or family doctor
- General haematology department
- General oncology department
- Specialist AL Amyloidosis department
- Emergency hospital department
- Other specialist department
- Not sure

Patient responses

Fig 3. Number and percentage of responses (n; %) for where patients had their diagnosis confirmed.

- General haematology department
- General practitioner (GP) or family doctor
- General oncology department
- Specialist myeloma department
- Specialist AL Amyloidosis department
- Emergency hospital department
- Other specialist department



KEY FINDINGS

Patient responses

Fig 4. Percentage of patient responses for how long it took them, from first medical consultation, to get a diagnosis versus the percentage of clinician responses for how long it takes on average for a patient to have a diagnosis confirmed in their country.

NUMBER OF CONSULTATIONS:

Given the non-specific symptoms related to AL amyloidosis (e.g., fatigue, kidney, heart-related problems etc), patients may be misdiagnosed with more common conditions at first or be referred to different specialities, such as general practice, cardiology or nephrology, before finally seeing a haematologist and/or AL amyloidosis specialist.

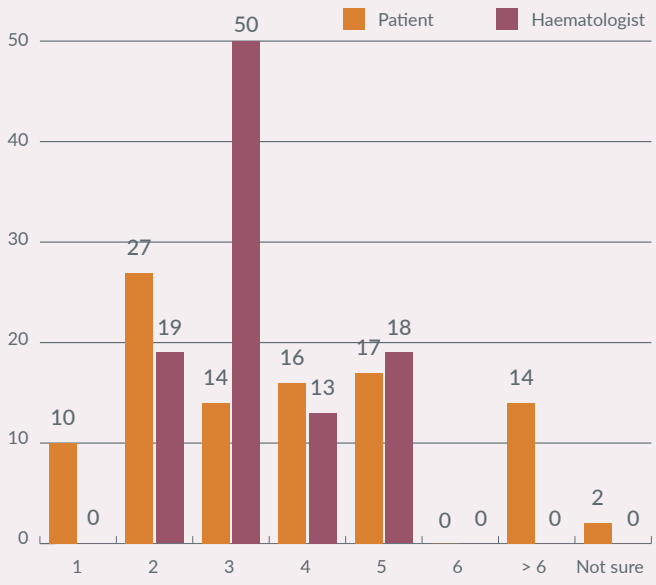
- 51% of patients saw up to three different specialists (e.g., primary care, renal, cardiologist) before receiving a diagnosis and 47% of patients saw more than three.
- 32% of haematologists stated their patients saw more than three specialists.
- 56% of patients had more than four medical consultations and 43% had more than six.
- 37% of haematologists reported that their patients typically had more than four medical consultations and 25% stated they had six or more.

> *For amyloidosis, patients may go to a specialist for heart or kidney problems, but the specialist doesn't treat the characteristics of amyloidosis, so we may lose time there. In amyloidosis, there are amyloid deposits in the tissues and, if this increases, then this cannot be removed. And so, every damage that happens is there, we cannot do anything. I think we need to make the cardiology and the nephrologist more aware of the disease.*
>
> – HAEMATOLOGIST, GREECE

KEY FINDINGS

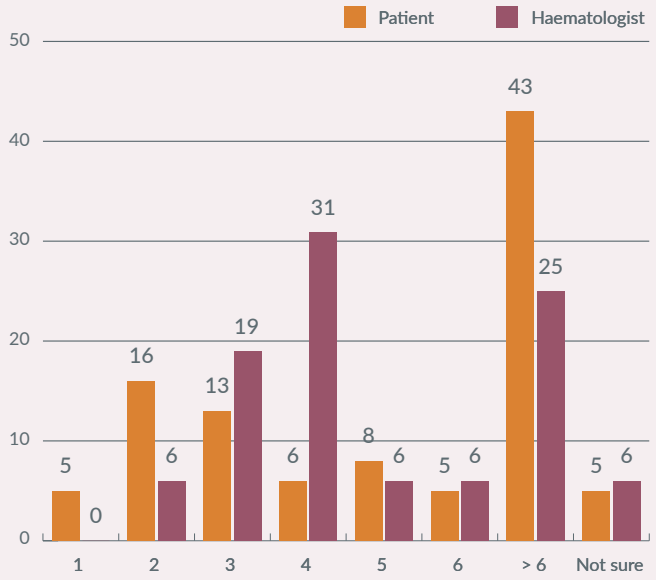
Patient and haematologist responses

Fig 5. Percentage of patient responses for how many specialists they approximately saw before being diagnosed versus the percentage of clinician responses for how many specialists they think a patient sees before being diagnosed.



Patient and haematologist responses

Fig 6. Percentage of patient responses for how many medical consultations they approximately had before being diagnosed versus the percentage of clinician responses for how many medical consultations they think a patient has before being diagnosed.



KEY FINDINGS

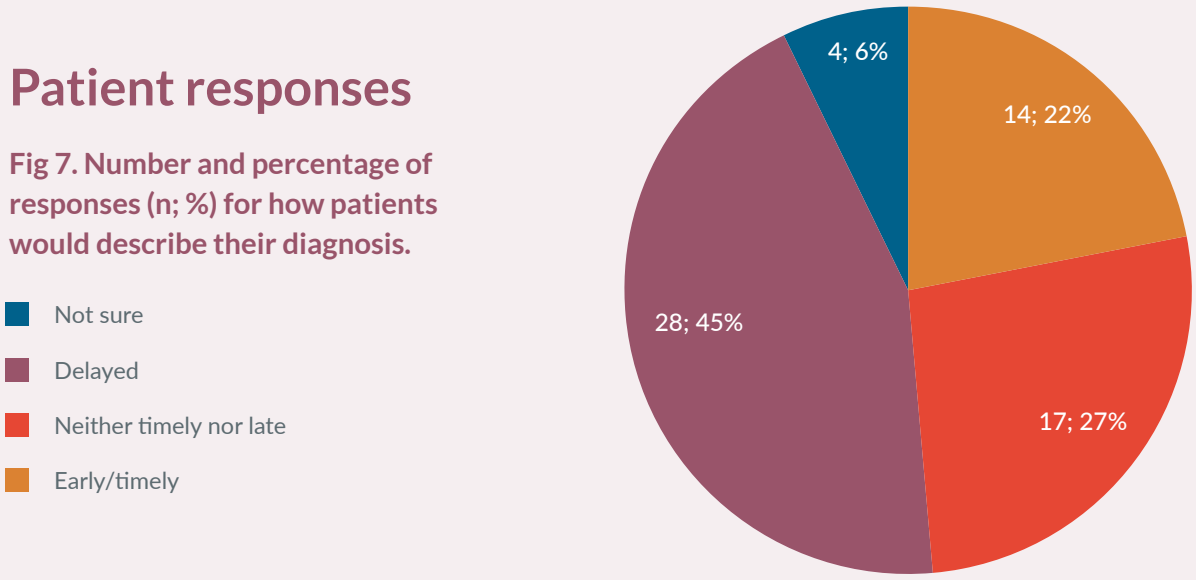
PERCEPTIONS OF DELAYS IN DIAGNOSIS:

Although, the location, timing and number of medical consultations and specialists suggests AL amyloidosis patients experience significant diagnostic delays, patients were asked to describe their diagnoses, while clinicians were asked to describe the timing of diagnosis in their country, with the following results:

- Approximately 45% of patients stated that their diagnosis was delayed.
- 63% of clinicians described the timing of diagnosis in their country as delayed.

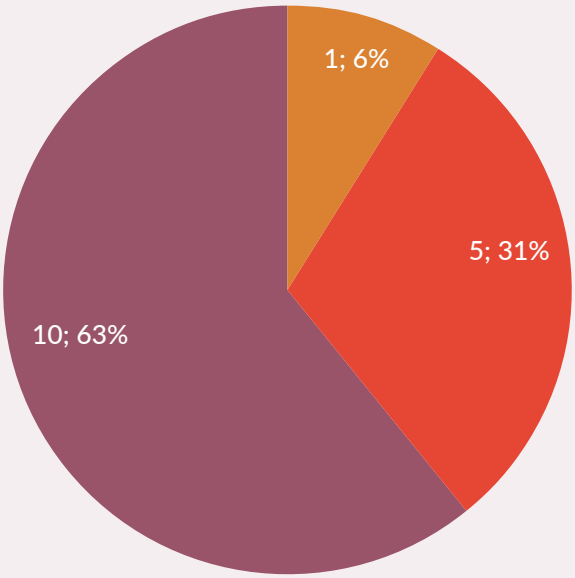
Patient responses

Fig 7. Number and percentage of responses (n; %) for how patients would describe their diagnosis.



Haematologist responses

Fig 8. Number and percentage of responses (n; %) for how clinicians describe the timing of diagnosis in their country.



BARRIERS TO A TIMELY DIAGNOSIS AND THE IMPACTS OF DELAYS

Based on the literature review and research findings, patients experience confusing and convoluted pathways to diagnosis. Therefore, it is crucial to understand why patients are experiencing these delays and how they impact their lives and treatment outcomes, in order to identify and implement solutions to improve diagnosis.

BARRIERS TO TIMELY DIAGNOSIS

In the survey, haematologists were asked to identify the primary barriers to a timely diagnosis. Haematologists and patients further discussed these barriers in the interviews, with the following being the key issues:

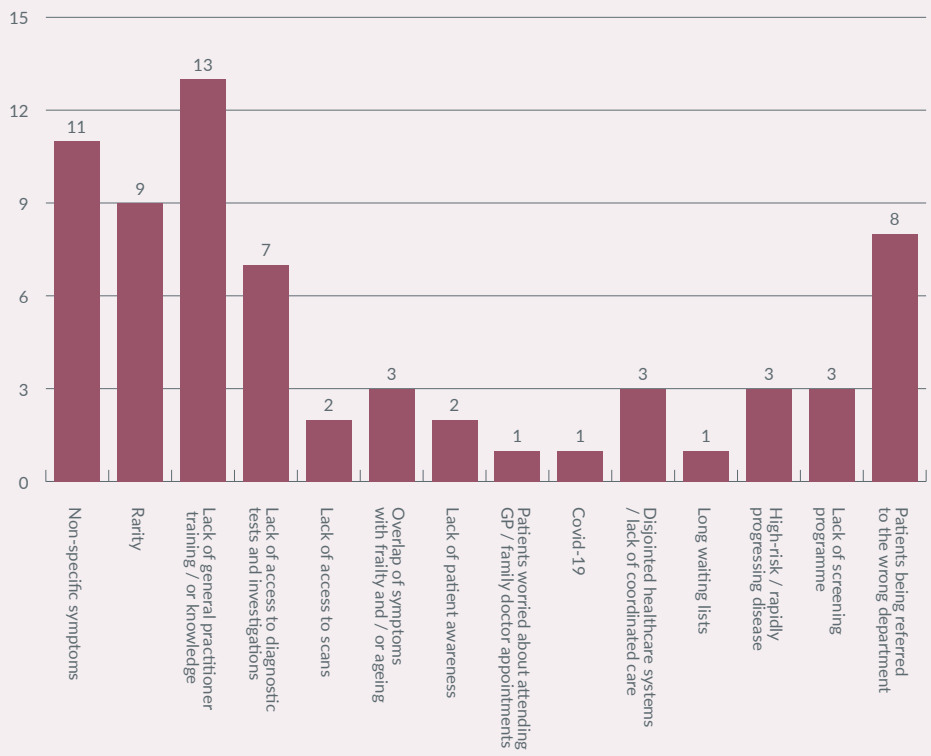
- Rarity of AL amyloidosis and non-specificity of symptoms.
- Referral to wrong departments.
- Health systems source and structure.
- Access to tests and investigations.

> *Primary medicine fails a lot because it doesn't know what amyloidosis is. My doctor kept insisting for a long time that what I had was digestive, and that delayed the diagnosis.*
>
> – AL AMYLOIDOSIS PATIENT, SPAIN

> *There are many tests the GP cannot do because of our public health system, they're not allowed to test it. For example, they can make the blood test of the proteins, but aren't allowed to do the immune fixation test. So not all the tests can be done by a GP.*
>
> – HAEMATOLOGIST, POLAND

Haematologist responses

Fig 9. Number of clinician responses for what they consider to be the biggest barriers to early diagnosis.



BARRIERS TO A TIMELY DIAGNOSIS AND THE IMPACTS OF DELAYS

IMPACTS OF A DELAYED DIAGNOSIS

Patients and haematologists were asked to identify the consequences of delayed diagnosis, with the following areas having the largest impact:

- Long-term symptoms and complications.
- Impact on daily activities, quality of life and emotional well-being.
- Impact on family members and carers.
- Impact on career and finances.
- Treatment options and survival.

> *If you get the right diagnosis quickly, you can get all treatments that you need. If you have a delayed diagnosis and the organ damage is advanced, you can't get all possible treatment approaches. And this could be a reason of symptom complications and it could also have an impact on your survival."*
>
> – HAEMATOLOGIST, ITALY

> *All aspects of quality of life are affected. The disease limits all of your activity, to the point that you don't feel like moving or you can't. Regarding the psychosocial aspect, I have had great family support that has helped me a lot on an emotional level."*
>
> – AL AMYLOIDOSIS PATIENT, SPAIN

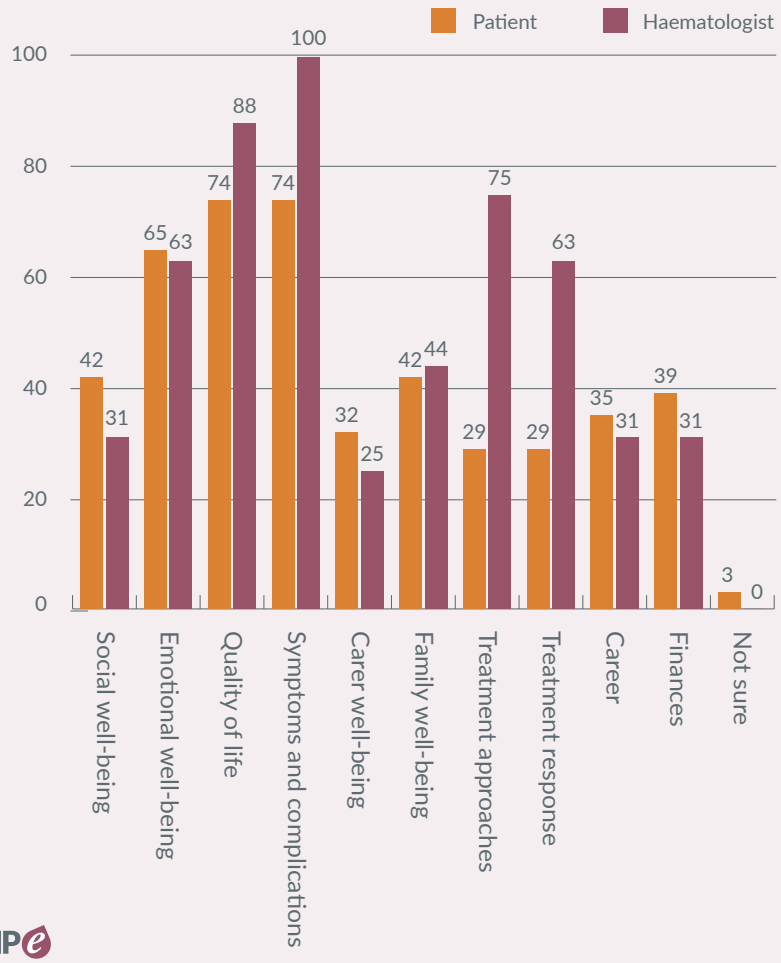


Fig 10. Percentage of patient responses for which areas of their lives were impacted by a later diagnosis versus the percentage of clinician responses for which areas/domains are impacted by a patient's delayed diagnosis.

CONCLUSION AND RECOMMENDATIONS

Diagnosing a rare disease with non-specific symptoms is challenging and depends on a multitude of factors. Patients themselves may find it difficult to know when to seek medical attention in the first place, attributing their symptoms to other issues such as general aging. Additionally, disparities in availability of GP appointments, overburdened and under-resourced healthcare systems, and access to testing can result in a patient waiting for months to receive a diagnosis.

A delayed diagnosis can impact treatment options and response as well as overall survival, sometimes leading patients to undergo palliative care. Further, the symptom complications associated with a delayed diagnosis of AL amyloidosis have a significant impact on mental and emotional health, and physical fitness, and extend beyond the patient to affect family members and financial stability. However, a timely diagnosis can improve a patient's outcomes and quality of life.

MPE's data only represents a snapshot of patient and haematologist perspectives on diagnosis. Further country-specific data needs to be generated to inform advocates, policy makers, clinicians, government officials and other stakeholders, and to develop solutions that address the larger systemic barriers to diagnosis, such as limited access to testing and specialists.

However, our research and existing data show there are actions that can be implemented now to improve education, training and awareness, addressing a significant barrier to a timely diagnosis. Based on our findings, MPE recommends the following focused actions:

- Development of decision-making aides for primary care and related specialists (cardiac and renal) to raise awareness of AL amyloidosis and assist doctors to conduct the relevant tests and investigations, as appropriate.
- Continued professional development for GPs and specialists through accredited online learning modules on AL amyloidosis.
- Haematologists to present on AL amyloidosis (or more broadly on the symptoms of rare haematological diseases) at congresses aimed at GPs and internal medicine specialists.
- Government-funded public health campaigns which promote GP attendance, if health changes.

> *Awareness is always a key issue. A family physician who had one [AL amyloidosis] patient will be more aware. But if they haven't seen any, or if it's been years since the last patient, they are not aware of it.*
>
> – HAEMATOLOGIST, ISRAEL

> *Share knowledge at some big internist conferences. In Poland, there are two big conferences for all internists so cardiologists, nephrologists, endocrinologists, gastrologists. A haematologist could have a lecture about amyloidosis. Then the awareness will be greater.*
>
> – HAEMATOLOGIST, POLAND

> *One thing we can do to make the diagnosis process easier is to prepare some algorithm specifically for each country's public health system. What the GP should do when he sees this symptom, i.e. he should do this test and transfer the patient to a specialist, to the nephrologist or haematologist. And so an easy algorithm with some easy tests that are accessible by the GP. I think that it would be very helpful to get the diagnosis earlier.*
>
> – HAEMATOLOGIST, POLAND

LIMITATIONS

SURVEY

The survey received a low number of responses, resulting in limited data. In addition, more patients responded than haematologists, therefore we cannot accurately compare the results between the two groups. Finally, responses across the countries were variable and not all European countries were represented.

INTERVIEWS:

The patient interviews only included two patients from Spain and therefore did not capture the diagnostic experiences and challenges patients have across Europe. Further, in the patient and haematologist interviews, participants were from similar demographics and therefore certain county-specific socioeconomic issues may not have been raised. MPE also acknowledges the lack of representation from central and eastern European countries may have skewed certain discussions surrounding access issues.

ACKNOWLEDGEMENTS

MPE would like to extend a special thank you to the patients and haematologists that took part in this study. We are grateful for your time and generosity in sharing your experiences. MPE also appreciates the efforts of our member organisations who supported the project with patient recruitment and dissemination. Thank you for making this research possible.

APPENDICES

Appendix 1: Survey on myeloma and AL amyloidosis diagnosis.

Appendix 2: AL Amyloidosis Patients Interview Guide

Appendix 3: Interview guide doctors – Myeloma and AL amyloidosis

Appendix 4: AL Amyloidosis Patients Early Diagnosis Pre-reads

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