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– ORIGINAL PAPER –

# Clinical Diversity and Treatment Outcomes in IgM Monoclonal Gammopathy Associated with Cold Agglutinin Disease and Cryoglobulinemia: A Single Center Study

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***Abstract***

***Background****: Cold agglutinin disease (CAD) and cryoglobulinemia are rare immune-mediated complications of IgM monoclonal gammopathies, such as Waldenström macroglobulinemia (WM) and monoclonal gammopathy of undetermined significance (MGUS).*

***Methods:*** *We retrospectively analyzed 11 patients with CAD and/or cryoglobulinemia out of 159 cases of IgM monoclonal gammopathy diagnosed at Fundeni Clinical Institute between 2018 and 2024.*

***Results****: Median age was 66 years; 54.5% were female. All patients had IgM kappa monoclonal proteins. CAD was present in 63.6%, cryoglobulinemia in 36.4%, with renal involvement in all cryoglobulinemia cases. Common symptoms included anemia (median hemoglobin 8.5 g/dL), Raynaud's syndrome (45.5%), and neuropathy (27.3%). The majority of patients received rituximab-based regimens as part of their treatment. A hemoglobin increase ≥2 g/dL without transfusions was observed in 63.6% of patients after 2 cycles. Overall response rate ≥VGPR was 18.2%. Mortality was 63.6%, mainly due to infections and cardiovascular disease.*

***Conclusions:*** *Patients with CAD and cryoglobulinemia associated with IgM monoclonal gammopathy show heterogeneous clinical features and poor outcomes. Despite partial hematologic improvement, high mortality highlights the need for early intervention and optimized therapies.*

***Keywords:*** *Cold agglutinin disease (CAD), cryoglobulinemia, IgM monoclonal gammopathy, Waldenström macroglobulinemia (WM), MGUS, autoimmune hemolytic anemia (AIHA).*

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## Introduction

Cryoglobulinemia is a rare disorder
characterized by the presence of abnormal proteins in the blood known as cryoglobulins. These proteins, primarily immunoglobulins, sometimes with complement components, precipitate or clump together at low temperatures. Once precipitated, they can deposit in small and medium-sized blood vessels, leading to vasculitis, endothelial damage, and end-organ injury. Clinical manifestations include arthralgia (joint pain), purpura (skin rashes), neuropathy, and renal involvement such as glomerulonephritis. (1)

The Brouet criteria classify cryoglobulinemia into 3 subgroups, depending on their immunoglobulin composition. (2)

Type I: Type I cryoglobulinemia is characterised by monoclonal immunoglobulins, typically IgG or IgM, and can be found in lymphoproliferative or hematologic disorders of the B-cell lineage, such as chronic lymphocytic leukemia, multiple myeloma, Waldenström macroglobulinemia or protein-secreting monoclonal gammopathies such as monoclonal gammopathy of undetermined significance (MGUS). (3)

In type II cryoglobulinemia, cryoglobulins are composed of a mixture of monoclonal IgM (or IgG or IgA) with rheumatoid factor (RF) activity, along with polyclonal immunoglobulin, and are often associated with the following conditions: hepatitis C virus (HCV) infection, which is the most common causative factor of cryoglobulinemic vasculitis and mixed cryoglobulinemia (4), vaccines, hepatitis B virus (HBV) infection, HIV, autoimmune diseases, mainly systemic lupus erythematosus (SLE), Sjögren syndrome, and adult-onset Still disease. (1)

In type III cryoglobulinemia, the cryoglobulins consist of a mixture of polyclonal IgG and polyclonal IgM. This form is typically secondary to autoimmune disorders and is occasionally associated with infections, most commonly HCV infection. (1)

Clinically, cryoglobulinemia may be asymptomatic, but it can also present with a broad spectrum of clinical manifestations. These include skin lesions, arthralgia, peripheral neuropathy, and damage to single or multiple organs. (5)

To detect cryoglobulins in the laboratory, the patient's blood is collected and kept at 37 °C during processing, without adding anticoagulants. The blood is then centrifuged to separate the serum, which is subsequently refrigerated to allow cryoglobulins to precipitate. (1)

In mixed cryoglobulinemia, key laboratory findings often include a positive serum rheumatoid factor (RF) in 45%–95% of cases, low serum C4 levels in 65%–100% of cases, and low C3 levels in 20%–70% of patients. In type I cryoglobulinemia, which typically involves monoclonal IgG3 or IgG1, reduced levels of C4 and C3 may also be seen, although less commonly. (5)

The treatment of cryoglobulinemia is guided by the underlying primary disorder, as well as the severity and extent of organ involvement. In cases of symptomatic mixed cryoglobulinemia, management focuses on treating the associated autoimmune or infectious conditions, such as hepatitis C or systemic autoimmune diseases. (1)

In primary cold agglutinin disease (CAD), autoimmune hemolytic anemia is caused by monoclonal IgMκ cold agglutinins that bind erythrocyte antigens optimally at 4°C, leading to agglutination and complement activation. Pathogenic antibodies active above 28°C result in mostly extravascular hemolysis in the liver and, in severe cases, intravascular hemolysis. (6)

A significant proportion of CAD cases is secondary to clonal B-cell disorders, particularly IgM monoclonal gammopathies such as Waldenström macroglobulinemia (WM) and monoclonal gammopathy of undetermined significance (MGUS). CAD typically presents with chronic anemia, fatigue, acrocyanosis, and Raynaud's phenomenon. (7)

## Objective

This single-center descriptive study aimed to highlight the diversity of patients with CAD and cryoglobulinemia associated with IgM MGUS/Waldenström's macroglobulinemia.

## Methods

Between 2018 and 2024, a total of 159 patients with IgM monoclonal gammopathy were diagnosed at the Fundeni Hematology Clinic in Bucharest, Romania. Among these, 68 patients (42.8%) were diagnosed with Waldenström macroglobulinemia, 13 patients (8.2%) had smoldering Waldenström macroglobulinemia, 36 patients (22.6%) had IgM MGUS, 18 patients (11.3%) had IgM monoclonal gammopathy of clinical significance, 13 patients (8.2%) had IgM light chain amyloidosis, and 11 patients (6.9%) had CAD and/or cryoglobulinemia associated with IgM monoclonal gammopathy. (Figure 1)

Clinical data were retrospectively extracted from patient charts and included demographics, laboratory results, immunological markers (including cold agglutinin titers),

and evidence of organ involvement such as renal lesions or neurologic symptoms.

The hematologic response was assessed according to International Workshop on Waldenström's Macroglobulinemia (IWWM) criteria, with outcomes such as very good partial response (VGPR), partial response (PR), stable disease (SD), or not evaluable (NE) recorded.

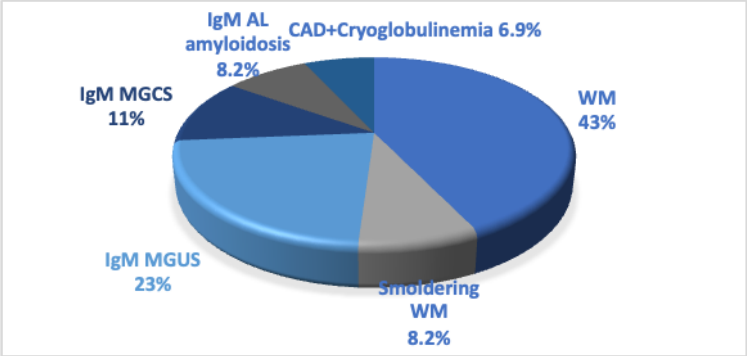


***Figure 1**. Spectrum of IgM-Related Disorders in Patients Diagnosed at Fundeni Clinical Institute*

## Results

### Cohort characteristics

The median age at diagnosis within this subgroup was 66 years, and 54.5% of the patients were women. The median diagnostic delay from symptom onset was 12 months. From a clinical perspective, 7 patients (63.6%) presented with cold agglutinin disease alone, while 2 patients (18.2%) had both CAD and cryoglobulinemia, and the remaining 2 patients (18.2%) had cryoglobulinemia alone. (Figure 2)

Five patients (45.5%) were classified as having IgM MGUS, and six patients (54.5%) had Waldenström macroglobulinemia.

All patients were found to express monoclonal IgM kappa light chains. Five patients with CAD had cold antibody titers greater than 1:1.000.000.

Laboratory evaluations showed a median monoclonal protein peak of 1.8 g/dL, a median involved free light chain concentration of 371 mg/L, and a median hemoglobin level of 8.5 g/dL at diagnosis.

Renal involvement was present in all cases of cryoglobulinemia and was characterized by membranoproliferative glomerulonephritis (GNMP type I), with one patient also displaying signs of thrombotic microangiopathy. Additional clinical manifestations included Raynaud's phenomenon (45.5%) and peripheral neuropathy (27.3%).

The detailed clinical and biological characteristics of the cohort, including laboratory findings, organ involvement, and treatment outcomes, are summarized in the attached Table 1.

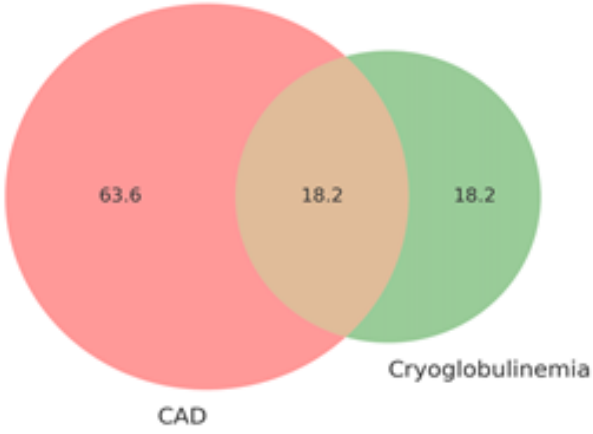


***Figure 2.** Clinical Overlap of CAD and Cryoglobulinemia*

| Clinical/biological feature | CAD (n=7) – no. (%) | Cryoglobulinemia (n=2) – no. (%) | CAD + Cryoglobulinemia (n=2) – no. (%) |
|---|---|---|---|
| **Cutaneous vasculitis** | 2 (28%) | 2 (100%) | 1 (50%) |
| **Raynaud phenomenon** | 4 (57%) | 1 (50%) | 0 |
| **Acrocyanosis** | 2 (28%) | 0 | 1 (50%) |
| **Splenomegaly** | 1 (14.2%) | 2 (100%) | 1 (50%) |
| **Arthralgia / arthritis** | 1 (14.2%) | 2 (100%) | 0 |
| **Peripheral neuropathy (PNP)** | 1 (14.2%) | 2 (100%) | 0 |
| **Renal insufficiency** | 2 (28%) | 1 (50%) | 0 |
| **Nephrotic syndrome** | 0 | 2 (100%) | 0 |

***Table 1***. *Clinical and biological characteristics of patients with CAD and cryoglobulinemia*

**Treatment details**

Therapeutic regimens included rituximab-based therapies in the majority of cases (90.9%) : R-Bendamustine (36.4%), R-CVP (45.5%), R-Cyclophosphamide (9.1%), and CVP alone (9.1%). (Figure 3)

**Outcomes**

Hematologic response rates were modest, with only two patients (18.2%) achieving VGPR, and two additional patients achieving PR. In two other patients, the disease remained stable,

while in five patients, the response could not be evaluated due to early complications or incomplete follow-up. (Figure 4)

A clinically meaningful improvement in anemia, defined as an increase in hemoglobin of at least 2 g/dL after two cycles of treatment without transfusions, was observed in seven patients (63.6%).

Estimated overall survival, based on Kaplan-Meier analysis, further reflects the poor long-term prognosis of these patients, highlighting the clinical impact of both disease- and treatment-related complications. (Figure 5)

Mortality during the follow-up period was high. Seven of the eleven patients (63.6%) died, with the main causes of death being infectious complications (27.3%) and cardiovascular events (27.3%). One death (9.1%) was attributed to disease progression

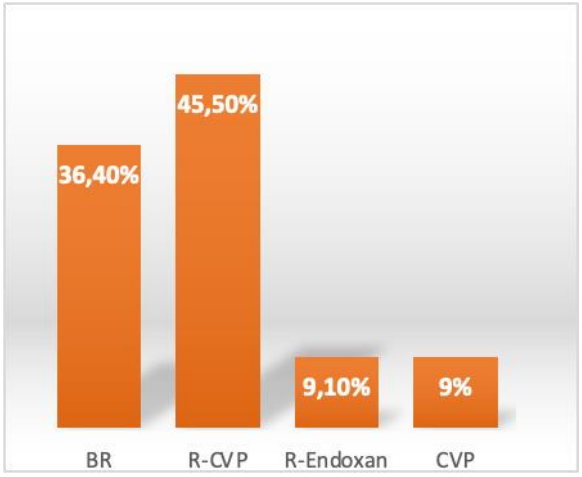


***Figure 3 :*** *Distribution of First-Line Treatment Regimens in Patients with IgM Monoclonal Gammopathy and CAD/Cryoglobulinemia. Abbreviations: R-Bendamustine: Rituximab + Bendamustine. R-CVP: Rituximab + Cyclophosphamide + Vincristine + Prednisone. CVP: Cyclophosphamide + Vincristine + Prednisone*

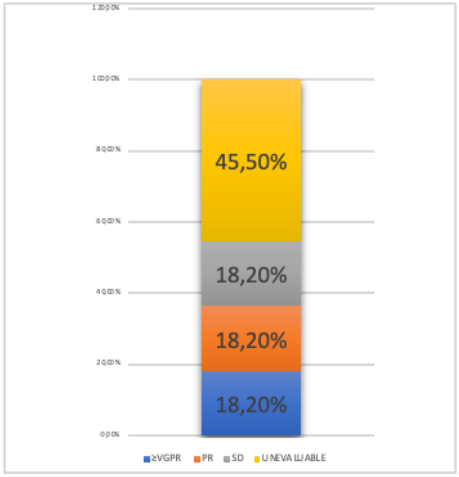


***Figure 4.*** *Hematologic Response Distribution*

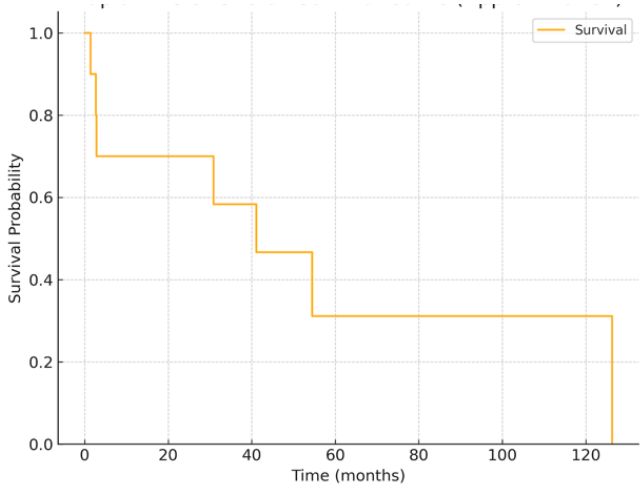


***Figure 5.*** *Kaplan-Meier Overall Survival Curve of Patients with IgM Monoclonal Gammopathy and CAD/Cryoglobulinemia*

## Discussions and Conclusions

This study highlights the significant clinical heterogeneity and diagnostic complexity of cold agglutinin disease and cryoglobulinemia in the context of IgM monoclonal gammopathies. Although some patients demonstrated hematologic improvement, including hemoglobin recovery, deep and sustained responses were uncommon. The overall response rate ≥VGPR was low (18.2%), and mortality remained high (63.6%), underscoring the limited efficacy of current therapeutic strategies.

A major limitation in response assessment was the inability to evaluate hematologic outcomes in nearly half of the patients. This was largely due to early mortality caused by infectious or cardiovascular complications, or loss to follow-up.

Given the modest response to standard therapies, there is growing interest in alternative approaches, such as complement inhibitors or BTK inhibitors, particularly for patients with relapsed/refractory disease or poor tolerance to immunochemotherapy. (8)

The improvement in anemia seen after treatment initiation is encouraging, but the limited number of deep responses highlights the need for further research.

Cryoglobulinemia was uniformly associated with renal involvement, typically GNMP type I, consistent with cryoglobulinemic vasculitis. This organ damage is known to confer a poor prognosis and warrants prompt, clone-directed or immunosuppressive interventions. (3)

Our Kaplan-Meier analysis demonstrated limited overall survival, with most deaths attributed to infections and cardiovascular events, rather than disease progression.

These findings reinforce the need for comprehensive supportive care, including infection prevention and cardiovascular risk management.

Although IVIG is not a disease-modifying treatment in Waldenström macroglobulinemia, it can be beneficial in selected patients with severe hypogammaglobulinemia and recurrent infections. Once hematologic disease is under control and the risk of IgM flare is minimized, immunoglobulin replacement may improve infection-related outcomes. (9,10)

Our findings underscore the vulnerability of this patient population, often affected by delayed diagnosis, complex disease manifestations, and comorbid conditions. These factors collectively contribute to poor overall prognosis.

**Ethics Statement and Conflict of Interest Disclosures**

Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.

**Ethics Consideration**

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by all participants in this study.

**Conflict of interest:**

No known conflict of interest correlated with this publication.

**Availability of data and materials**

The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.

**Competing interest**
The authors declared that they have no competing interests.

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