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Received: 25/07/24
Accepted: 02/09/24
Online: 10/09/24

REVIEW ARTICLE

Cryoglobulin interference in laboratory tests: analytical error or diagnostic clue?

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Keywords:
cryoglobulins; cryoglobulinemia; laboratory test; diagnosis; interference; immunoglobulins (Source: MeSH - NLM).

ABSTRACT

Cryoglobulins are immunoglobulins that precipitate at low temperatures and redissolve upon reheating the sample. They are also a well-known source of laboratory test errors, potentially compromising medical diagnosis. This review aimed to analyze cryoglobulin interference in clinical laboratory tests to determine whether it represents merely an analytical error or a valuable diagnostic clue. A literature review was conducted using scientific databases from 2020 to 2024. Notably, their presence has often been crucial in identifying pathologies that are difficult to diagnose. In conclusion, the detection of cryoglobulins in clinical samples should not be regarded solely as an analytical error but also as a valuable diagnostic indicator of underlying diseases that are often challenging to detect by other means.

Interferencia de crioglobulinas en pruebas de laboratorio: ¿error analítico o pista diagnóstica?

Palabras clave:
crioglobulinas; crioglobulinemia; prueba de laboratorio; diagnóstico; interferencia; inmunoglobulinas (Fuente: DeCS - BIREME).

RESUMEN

Las crioglobulinas son inmunoglobulinas que precipitan a temperaturas bajas y se disuelven al recalentar nuevamente la muestra; además, constituyen una fuente conocida de errores en resultados de pruebas de laboratorio, afectando así al diagnóstico médico. El propósito de esta revisión fue analizar la interferencia de las crioglobulinas en pruebas de laboratorio clínico, a fin de determinar si representa únicamente un error analítico o una valiosa pista diagnóstica. Se realizó una revisión de la literatura disponible en bases de datos científicas entre 2020 y 2024. Cabe destacar que su presencia ha sido clave para la identificación de patologías de difícil diagnóstico. En definitiva, la detección de crioglobulinas en muestras clínicas no debe verse únicamente como un error analítico, sino también como una valiosa pista diagnóstica de enfermedades subyacentes, muchas veces difíciles de detectar por otros medios.

Cite as: Pandashina-Masabanda AI. Cryoglobulin interference in laboratory tests: analytical error or diagnostic clue?. Rev Peru Cienc Salud. 2025; 7(4):368-74. doi: https://doi.org/10.37711/rpcs.2025.7.4.3

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INTRODUCTION

Cryoglobulins are a group of serum immunoglobulins that, *in vitro*, reversibly precipitate at low temperatures and dissolve upon rewarming the blood sample [1-6]. The presence of cryoglobulins in the blood is referred to as cryoglobulinemia [4,7,8], which usually arises as a consequence of hematological disorders (multiple myeloma and lymphoproliferative disorders), chronic infections, or autoimmune diseases and, in other cases, in the absence of any apparent disease, of essential cause [2-4]. Although these proteins are clinically relevant due to their association with multiple disease entities, they also have practical implications in the clinical laboratory and, therefore, in medicine, where their precipitation may interfere with obtaining reliable results.

Current knowledge about this interference is limited and, in many cases, underestimated. There are reports of diagnostic errors resulting from the precipitation of cryoglobulins during the analytical and pre-analytical phases of sample processing, leading to erroneous results in hematological, immunological, and biochemical tests [3,9,10]. However, an analytical error may become an important clinical finding, since the identification of unexplained abnormalities in these tests may represent a diagnostic clue to an underlying cryoglobulinemia.

Although many available articles address cryoglobulinemia from a clinical or immunopathological perspective, few references report its interference in laboratory tests and its impact on the diagnosis of different clinical entities. For this reason, this review analyzes the role of cryoglobulins as a source of interference and as a diagnostic clue, contributing to a better interpretation of laboratory results and preventing errors that may delay the treatment of potentially serious underlying diseases.

METHODS

A bibliographic review of the available literature on the interference of cryoglobulins in laboratory test results, as well as their diagnostic value, was conducted. Inclusion criteria comprised original studies, systematic reviews, and case reports published between 2020 and 2024, the latter mainly focused on clinical situations in which the presence of cryoglobulins altered laboratory results and led to findings relevant for diagnosis.

Information was obtained from three databases: PubMed, Google Scholar, and Scopus. DeCS/MeSH terms and keywords such as "cryoglobulins", "cryoglobulinemia", "interference", and "laboratory test" were used, combined using Boolean operators (AND, OR), applying filters by language (English and Spanish) and year of publication.

The article selection process is summarized in Figure 1 using the PRISMA flow diagram. In the identification phase, 8 articles were found in PubMed, 23 in Google

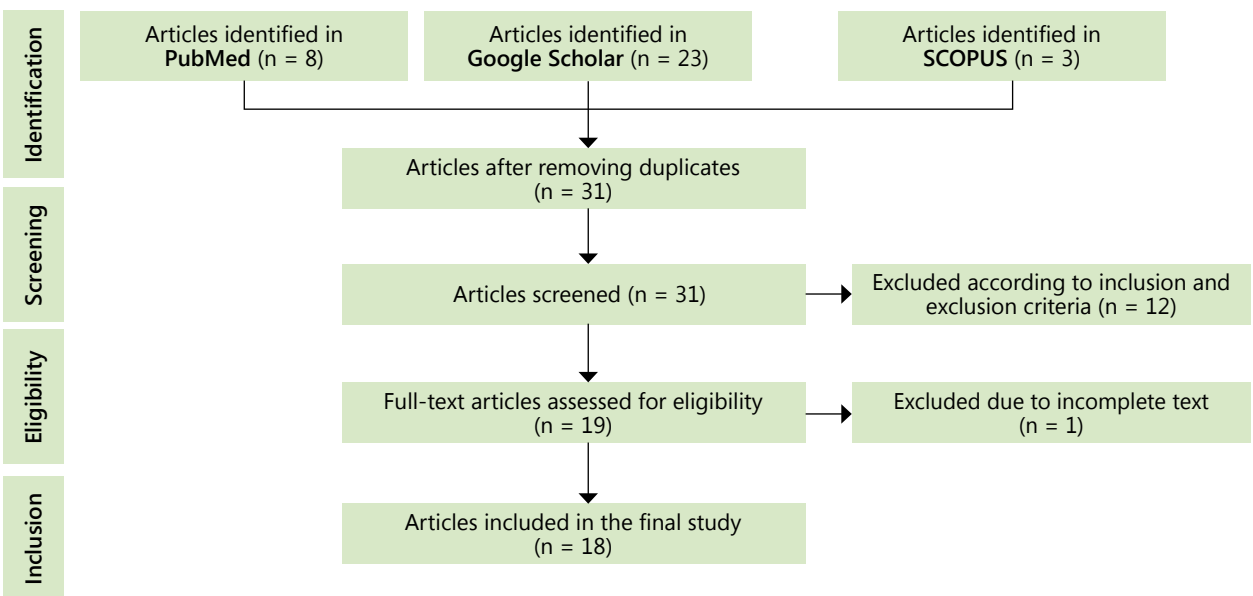

Figure 1. PRISMA flow diagram of the literature review

Scholar, and 3 in Scopus. After removing duplicates, 31 articles were screened, of which 12 were excluded for not meeting the inclusion and exclusion criteria. In the eligibility stage, 19 full-text articles were assessed, with 1 excluded for being incomplete. Finally, 18 articles were included in the study.

RESULTS

General characteristics and pathogenic mechanisms of cryoglobulins

According to Stoyanov et al. [11] and Smit et al. [12], cryoglobulins are immunoglobulins that precipitate from serum at temperatures below 37 °C and become soluble again upon rewarming. These rare immunological abnormalities exhibit a wide variety of morphological patterns under the microscope, including "clusters of dense, amorphous particles or pools, and the appearance of more or less pink crystals or globules" [13]; in other cases, more frequently, they are translucent and colorless, being identified mainly by a characteristic morphological defect in erythrocytes (spiculated erythrocyte surface) [14]. According to other reports, they may also present as thin, shiny deposits [2] or as phagocytosed neutrophilic inclusions [9].

Cryoglobulins are produced when B lymphocytes begin to produce abnormally large quantities of immunoglobulins, as a consequence of a response to prolonged stimulation of the immune system; for example, in chronic infections or autoimmune diseases, or also due to more severe disorders, such as certain types of cancer that affect these cells [3–5].

Cryoglobulin-associated tissue damage may occur through two main mechanisms: accumulation and precipitation in the microcirculation, or the formation of immune complexes that generate inflammation and tissue damage in the walls of blood vessels [4,8]. All organs in the human body may be affected; however, combined involvement of several organs is rare, although it can be fatal [15].

Types of cryoglobulins and associated diseases

Three types of cryoglobulins are recognized according to their characteristics and immunochemical composition (see Figure 2): type I (monoclonal immunoglobulins), type II (a mixture of monoclonal and polyclonal immunoglobulins), and type III (polyclonal immunoglobulins) [4,16].

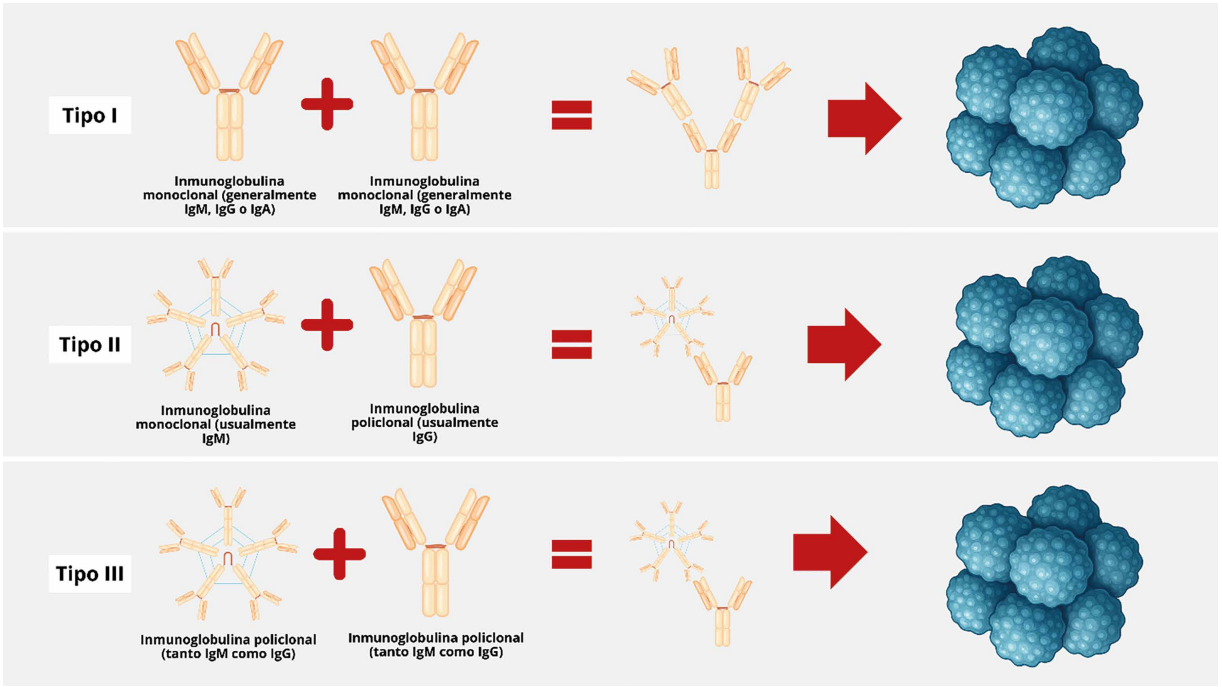

Figure 2. Formation, structure, and classification of cryoglobulins

Table 1. Cryoglobulins according to their composition and clinical associations

Type of cryoglobulin	Composition	Monoclonal/ Polyclonal	Clinical associations	Incidence
Type I (simple)	Monoclonal Ig (IgG, IgM, or IgA)	Monoclonal	Waldenström macroglobulinemia, multiple myeloma, monoclonal gammopathy associated with lymphoproliferative disease, light chain disease	10-15%
Type II (mixed)	Monoclonal Ig (IgM) with RF activity + polyclonal Ig (IgG)	Mixed (monoclonal + polyclonal)	Hepatitis C, Sjögren syndrome, rheumatoid arthritis, chronic lymphocytic leukemia, non-Hodgkin lymphoma	50-60%
Type III (mixed)	Polyclonal Ig of all types	Polyclonal	Sjögren syndrome, systemic lupus erythematosus, biliary cirrhosis, viral infections (hepatitis C virus, hepatitis B virus, cytomegalovirus, human immunodeficiency virus, Epstein–Barr virus), endocarditis, other bacterial infections	25-30%

***** Frequently reported immunoglobulins for each type of cryoglobulin have been included. Table adapted and reorganized from Rodríguez et al. [4] and Motyckova et al. [16].

The presence of cryoglobulins in the blood is associated with various diseases depending on their type (see Table 1). Type I, composed of a single class of monoclonal immunoglobulin (Ig) (IgM, IgG, or IgA), is associated with mature B-cell neoplasms, such as multiple myeloma, Waldenström macroglobulinemia, chronic lymphocytic leukemia, among others. Type II, the most frequent, consists of two classes of immunoglobulins: one monoclonal, usually IgM with rheumatoid factor (RF) activity, which binds to a polyclonal immunoglobulin (IgG), and is associated with mature B-cell neoplasms, as well as infectious and autoimmune diseases. Type III, composed of two or more classes of polyclonal immunoglobulins, is mainly linked to infectious diseases and autoimmune disorders [4,8,12,16-18].

Mechanisms of interference of cryoglobulins in laboratory tests

Three main mechanisms of interference caused by cryoglobulins in laboratory tests were identified (see Figure 3): first, upon precipitating in the sample, they sequester serum antibodies and cause false negatives [3,19], or form erroneous immune complexes, thus generating false positives in serological tests [20]; second, at low temperatures, they form protein aggregates that hematology analyzers mistakenly count as leukocytes or platelets, producing

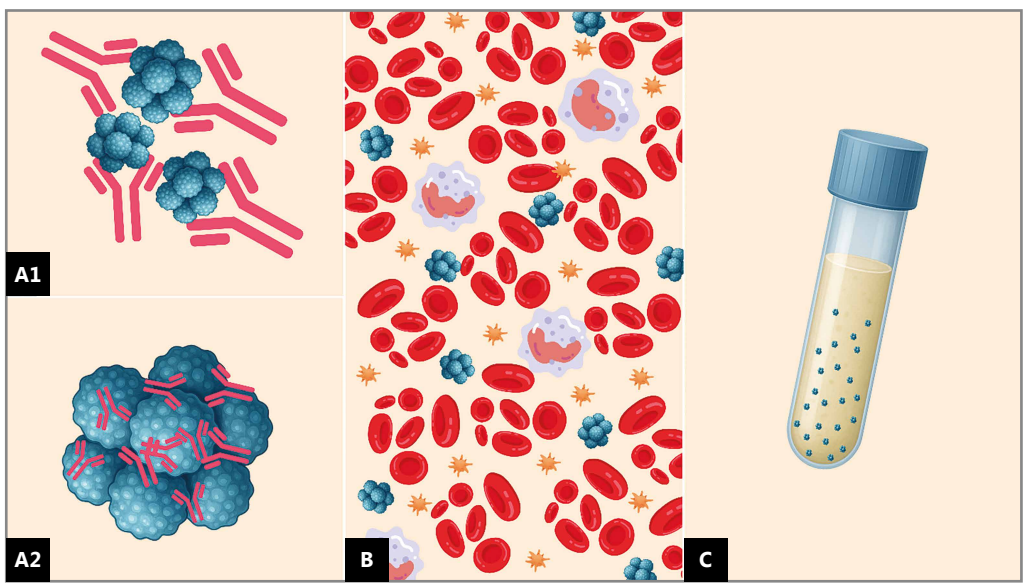

Figure 3. Main mechanisms of interference caused by cryoglobulins

*** A1.** Cryoglobulins bound to antibodies, forming erroneous immune complexes, which may generate false positives in serological tests. **A2.** Immunoglobulins trapped by cryoglobulins, which may cause false negatives by interfering with the detection of specific antibodies. **B.** Cryoglobulins in blood smear, which may resemble platelets and leukocytes, leading to misinterpretation in automated hematology analyzers. **C.** Cryoglobulins causing turbidity in samples, which may hinder interpretation of laboratory test results.

pseudoleukocytosis or pseudothrombocytosis [9,12,14]; and third, the precipitate increases serum turbidity, altering spectrophotometric readings and leading to inaccurate results in photometric determinations such as bilirubin quantification [21].

Factors contributing to cryoglobulin precipitation

It has been documented that preanalytical conditions play a decisive role in the precipitation of cryoglobulins [4,9,22], compromising the validation stage of laboratory results. Thus, it has been noted that this precipitation is favored when samples remain exposed to room temperature or refrigeration for approximately 24 hours, as well as by inadequate handling during transport or storage [13,22,23]. Another aspect to consider is the analytical phase, since the time required for performing serological tests, complete blood count, determination of total proteins, among others, without adequate thermal control, significantly increases the risk of precipitate formation [9,21-23].

Cryoglobulin interference and its relevance for clinical diagnosis

The presence of precipitates or turbidity in serum has usually been considered an analytical error in the processing of biological samples or the cause of unusual results that are not compatible with the patient's clinical presentation. Nevertheless, various studies suggest that, in some cases, this finding may represent a diagnostic clue for detecting underlying diseases that are difficult to diagnose [2,3,9,12,13,21].

Among the factors that may cause these anomalies are cryoglobulins, which can interfere with a wide range of laboratory tests, especially in the fields of immunology, biochemistry, and hematology [3,9,10]. Cryoglobulins have been described to cause interference in automated hematology analyzers, leading to pseudoleukocytosis, pseudothrombocytosis, abnormal histograms, and alterations in scatter plots [14,24–26]; in another case, true thrombocytopenia was masked by cryoglobulins [27]. Similarly, cryoglobulins have been reported to interfere in serological tests, affecting the detection of infections such as hepatitis C and the detection of anti-glomerular basement membrane antibodies (anti-GBM), causing false negatives [3,28]. In another reported case, elevated total bilirubin levels were associated with cryoglobulinemia [21].

These interferences suggest that discrepancies in cell counts between different measurements should alert laboratory personnel to the possible presence of cryoglobulins, justifying manual review of the blood smear [2,9]. In fact, cases have been reported where these findings were key to suspecting and confirming cryoglobulinemia, allowing early diagnosis of underlying diseases such as lymphoproliferative disorders [9,24].

A relevant example is that of a patient with lymphoplasmacytic lymphoma/Waldenström (LPL/WM), in whom the interference observed in automated hematological tests was the starting point for identifying cryoglobulinemia and subsequently the hematological malignancy [29]. Similarly, in three documented cases, the identification of hematological abnormalities and artifacts constituted the first clue for the diagnosis of cryoglobulinemia and, consequently, the underlying hematological malignancy [9]. In addition, other reports have described alterations in serological and biochemical tests associated with the presence of cryoglobulins [3,21]. These findings constitute reliable evidence that cryoglobulins represent an interference that must be considered in the clinical analysis of samples, as they may interfere with many other laboratory tests, which remain currently unknown.

To minimize these interferences, authors such as Recio et al. [3], Dave et al. [9], and King et al. [10] suggest processing samples immediately, maintaining adequate thermal control, warming samples to 37 °C for 60 minutes prior to analysis, and confirming atypical results using specific techniques such as immunofixation.

DISCUSSION

Cryoglobulins, although considered rare immunological abnormalities [13], constitute an important source of interference in different clinical laboratory tests [12], which play a fundamental role in patient diagnosis [3,19].

During clinical analysis, different types of interference may arise, such as hemolysis, lipemia, icterus, the presence of antibodies, as well as external factors such as medications or technical problems involving laboratory equipment and reagents [30]. Therefore, the timely identification of these interferences is an essential skill for the clinical laboratorian, since it helps avoid diagnostic errors and, consequently, the application of unnecessary treatments in patients [12,13]. In this context, false-negative results represent a greater clinical risk than false-positive ones, since they

prevent timely identification of the patient's condition and delay the initiation of appropriate treatment [3]. On the other hand, a false-positive result may give rise to discrepancies with the clinical manifestations and, in this way, lead to incorrect treatments.

Cryoglobulinemia is one of the conditions that should be considered in this context, since, as a complex and heterogeneous entity, it may occur secondary to a long list of diseases that represent a significant risk to patients' lives [5]. Hence the importance of timely identifying these "errors" during sample processing in the clinical laboratory.

It is necessary to emphasize that, although cryoglobulin precipitation is a phenomenon known to a significant number of laboratorians, in most cases it is not adequately addressed in clinical practice because of the lack of standardized protocols for the thermal handling of blood samples, from collection to analysis [4,31]. In this regard, especially in low-complexity healthcare facilities with limited resources, the ideal conditions of a constant temperature of 37 °C are often not fully maintained, which favors precipitate formation and, therefore, alteration of results. This situation is alarming, since it may lead to a false diagnosis, creating the impression of diseases that do not exist or, conversely, masking true diseases that require urgent treatment.

Therefore, it is essential that laboratory professionals not only identify cryoglobulin interference, but also report it promptly to the physician when unusual alterations in results are detected [13]. This information is essential so that the physician can thoroughly investigate the possible underlying causes and make sound decisions. Thus, cryoglobulins, typically considered a source of interference, may become a valuable tool that, when properly used, contributes to a more accurate diagnosis and more effective treatment [32].

Finally, to improve the accuracy of results, especially in low-resource settings, it is recommended to establish clear and rigorous protocols for the thermal handling of samples [31]. The use of water baths at a constant temperature of 37 °C immediately after sample collection, as well as detailed documentation of possible abnormalities (turbidity, sediment formation, color changes, or the presence of clumps), constitute simple but effective measures to significantly reduce alterations in laboratory test results.

Conclusions

In conclusion, the presence of cryoglobulins in clinical samples should not be viewed solely as an analytical error, but also as a valuable diagnostic clue. This phenomenon, if recognized and properly managed, may offer key clues about underlying diseases, often difficult to detect by other means. Therefore, a more comprehensive view of cryoglobulins is proposed, not only as an analytical obstacle, but as a tool that, when properly interpreted, may enrich the clinical process and significantly contribute to more accurate and timely patient care.

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Funding sources

This research was conducted with the author's own resources.

Conflict of interest statement

The author declare no conflicts of interest.