

Spatial Anemia and Osmotic Fragility of Erythrocytes in Microgravity Conditions: A Systematic Review

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Abstract—The study of the effects of microgravity on the human body has become increasingly relevant in biomedical research, particularly with regard to hematological changes. Therefore, the objective was to analyze the available scientific evidence on the impact of microgravity, both real and simulated, on erythrocytes with emphasis on osmotic fragility, cell membrane stability, and hemolysis. Likewise, 40 articles were selected using the PRISMA methodology, using the Scopus, PubMed, Web of Science, and IEEE Xplore databases, applying inclusion and exclusion criteria that had been previously established. Tools such as VOSviewer were also used, which facilitated the visualization of patterns of collaboration and scientific production. The results showed that microgravity produces remarkable changes in erythrocytes, such as an increase in hemolysis, alterations in the capacity for cell deformation, increased oxidative stress, and variations in the membrane. However, most research shows indirect information when it comes to osmotic fragility, with few applications of standardized measurements such as OFT or MCF-H50. In conclusion, severity influences the integrity and functionality of erythrocytes, leading to spatial anemia, although studies with greater standardization in their methodology are needed.

Keywords—Erythrocytes; hemolysis; microgravity; osmotic fragility; spatial anemia

I. INTRODUCTION

According to a study reported by NASA, technical reports served in 2024 indicated the effects of discharge on hematopoiesis and the subsequent life cycle of red blood cells evaluated at the resolution of the individual cell phone, where it indicates that prolonged exposure to microgravity causes the so-called spatial anemia. Because this phenomenon is associated with the absence of mechanical load, which alters erythropoiesis and can shorten the lifespan of erythrocytes, evidencing the key role of gravity in the regulation of the hematological system [1].

During the last decades, space exploration has been increasing, which has promoted the study of the effects of microgravity on the basis of the human body, in this way generating new challenges in the field of medicine. In this sense, according to the authors, they emphasized that one of the most relevant areas is the analysis of blood samples, due to its importance regarding the evaluation of physiological state; therefore, health monitoring and the diagnosis of diseases arise in spatial and terrestrial conditions [2]. In this way, microgravity produces significant alterations in the human body, such as the

distribution of fluids, changes in plasma volume, and modifications in the production and function of blood cells.

Thus, in this study, they emphasized that these variations can directly affect hematological and biochemical parameters, which can make it difficult to interpret the results obtained through conventional methods of clinical analysis. Specifically, erythrocytes play an important role in oxygen transport, and their stability depends on the integrity of their cell membrane. In this regard, osmotic fragility is presented as an essential indicator to evaluate such integrity, since it shows the ability of red blood cells to resist changes in the osmotic medium without undergoing hemolysis [3]. Therefore, different studies have indicated that microgravity conditions can alter these properties, increasing the sensitivity of erythrocytes to destruction.

In this way, due to the limitations to carry out studies in space, tools have been developed, such as the clinostat, allowing to simulate microgravity conditions in the laboratory through the constant rotation of samples, facilitating experimental research in controlled environments, analyzing and identifying the effects of microgravity on human cells without requiring an off-planet study [4]. Likewise, the use of simulated microgravity models has allowed to expand knowledge based on the cellular response with respect to the alteration of the gravitational vector; however, there are still some evidence-based limitations in relation to specific hematological parameters [5].

In order to be able to carry out studies in microgravity, simulated microgravity models have been implemented, for example, the clinostat, which allows similar conditions to be developed in the laboratory by continuously rotating the samples. In this way, they help research into the effects of microgravity in a controlled way and have also contributed to the development of their own studies and scientific training [6]. Several studies have shown that microgravity produces important changes in the body's homeostasis, including alterations in fluid distribution, lower plasma volume, and alterations in blood cell production or function. Within this context, spatial anemia has been made known as one of the physiological strategies adopted in the course of a prolonged space mission. Spatial anemia affects the growth of the erythrocyte mass, maintaining an increase in the destruction of red blood cells [7]. This shows the complex nature of human adaptation to the space environment.

In this context, erythrocytes are essential for oxygen transport and their stability depends on the integrity of their cell

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membrane. Osmotic fragility appears as a possible marker to assess such integrity, since it evaluates the ability of red blood cells to resist changes in the osmotic environment without undergoing hemolysis. Recently, there is data that points to how the structural and, if not functional, properties of erythrocytes can change under microgravity conditions, which can increase the risk of destruction and contribute to the picture of spatial anemia [8]. Therefore, the importance of the present study is to understand how simulated microgravity conditions can affect the stability of erythrocytes, which is why it is significant both for aerospace medicine and for biomedical research. In this way, it allows the use of methodologies accessible in the laboratory to be enhanced, contributing to the generation of knowledge applicable in contexts where it is possible to access real conditions of microgravity.

Despite the advances made, scientific information on the effects of microgravity on hematological indicators, such as osmotic fragility of erythrocytes, remains limited and scattered in the literature. In particular, there is no systematic synthesis that integrates the available findings on this phenomenon, which hinders a clear and comprehensive understanding of its implications on human health. Based on this problem, the research questions that guided this study are presented: What is the available scientific evidence on the effects of microgravity, real or simulated, on the osmotic fragility of erythrocytes? What methodologies have been used for its study? What are the main limitations and gaps in the current literature?

Therefore, the objective of this systematic review is to analyze and synthesize the available scientific evidence on the effects of microgravity on the osmotic fragility of erythrocytes, identifying the main findings, methodologies used, and limitations existing in the present studies. This study seeks to contribute to a better understanding of the hematological changes associated with microgravity, as well as to provide a solid theoretical basis to guide future research in the field of aerospace medicine and biomedical research.

The study is structured as follows: Section II describes in detail the literature review; Section III presents the materials and methods; then Section IV presents the results, Section V presents the discussion; Section VI presents the conclusion, and finally Section VII presents the recommendations and future work.

II. LITERATURE REVIEW

A. Background

Sickle cell anemia is a genetic disease whose clinical expression varies considerably between individuals, which has been attributed to the interaction between genetic and environmental factors. Recent literature highlights the importance of these factors in modulating disease severity, as well as in response to treatment. In this context, microgravity has been studied as a relevant experimental model, since it alters fundamental cellular processes. Various studies have shown that in these conditions, hemolysis and oxidative stress in erythrocytes are increased, key mechanisms in the pathophysiology of the disease. Likewise, changes in the structure and functionality of red blood cells have been observed, which could aggravate their characteristic alterations.

Taken together, these findings suggest that the study of extreme environments such as microgravity contributes to a better understanding of sickle cell anemia and offers new perspectives for the development of more effective therapeutic strategies [9].

The study presented by Agramont et al. [10] argues that osmotic fragility in erythrocytes is related to spatial anemia; that is, they evaluated in detail the behavior of erythrocytes in the face of variations in the osmotic environment, in such a way, it was evidenced that they can experience relevant alterations in their functionality and structure. In this way, the results showed that it is possible to be under conditions that manage to simulate extreme environments such as microgravity. Consequently, erythrocytes are more susceptible to hemolysis, which has an essential impact on cell stability, as well as on the accuracy of hematological analyses. The study was able to highlight these modifications, as they can influence the interpretation of laboratory results, that is, directly in contexts where physical conditions differ from those on land. Therefore, the research provided significant evidence on the need to consider the effects of the environment in the analysis of blood samples, thus contributing to a better understanding of the physiological changes associated with microgravity.

Therefore, a study by Manis et al. [11] emphasizes that the behavior of human erythrocytes under simulated microgravity conditions showed that these cells undergo structural changes. Thus, according to the research, a decrease in antioxidant capacity, increased oxidative stress and alterations in the lipid composition of the cell membrane were obtained as a result. Therefore, modifications in the shape and stability of erythrocytes were identified, suggesting that microgravity can directly affect the integrity of the cell membrane. Thus, these results are relevant, since the stability of the cell membrane is related to the osmotic fragility of erythrocytes.

Thus, Murali and Sarkar [12] studied the behavior of erythrocytes under different gravity conditions, demonstrating that the variation of the gravitational field influences cell shape, deformability and dynamics. The results showed that microgravity generates changes in the structure of erythrocytes, affecting their stability and interaction with the environment, which could increase their susceptibility to hemolysis processes.

However, according to a study by Manis et al. [13], they analyzed human erythrocytes under simulated microgravity conditions, evidencing significant alterations in the lipid composition of the cell membrane. The results showed the presence of oxidized lipids and changes in phospholipids, indicating cellular stress and structural modifications in erythrocytes. These changes directly affect membrane stability, which is related to a possible increase in osmotic fragility.

In this sense, the authors emphasize that hemolysis is a determining factor in the development of anemia during long-duration spaceflight. The authors point out that, under conditions of microgravity, there is a sustained increase in the destruction of red blood cells, which shows that anemia is not only a temporary adaptation, but an active physiological process. The authors also highlight that the high presence of by-products of hemoglobin degradation confirms the persistence of hemolysis during the space mission. They also stress that some of these effects continue even after return to Earth, suggesting a

prolonged impact of the space environment on blood physiology. In this regard, the study concludes that environmental factors, such as microgravity, play a key role in the regulation and survival of red blood cells [14].

In this sense, the authors point out that erythrocytes are not a uniform population, but rather present a remarkable heterogeneity in their structure, function and biochemical properties. The authors point out that these differences may be caused by factors such as cell age, physiological environment and metabolic conditions. The authors also highlight that this variability directly influences the ability of red blood cells to carry oxygen and respond to stressful situations. In this sense, they stress that some erythrocytes may be more susceptible to processes such as hemolysis, which has important implications in the development of various hematological diseases. Similarly, they emphasize that erythrocyte heterogeneity is not only a normal biological phenomenon but can also contribute to the progression of pathologies, affecting the stability and functionality of the blood system [15].

However, in this study, they emphasized exposure to microgravity since it generates multiple physiological alterations at the systemic level, in such a way that the hematological system being one of the most affected. Likewise, they mention that during space missions, a progressive reduction in the mass of erythrocytes was observed, which directly contributes to the development of space anemia. In this way, this phenomenon does not manifest itself in isolation, but is accompanied by changes in the distribution of body fluids, which can mainly mask the real decrease in red blood cells. They also indicate that these changes are linked to the body's adaptive mechanisms in a space environment, in addition to producing a decrease in erythropoietin production and an increase in erythrocyte destruction. It is highlighted that microgravity alters oxygen homeostasis, which forces the body to modify its transport capacity [16].

According to the authors, erythrocytes undergo significant metabolic alterations during spaceflight, demonstrating that microgravity has a direct impact on their biochemical functioning. Thus, changes in essential metabolic pathways, such as energy metabolism, glycolysis, and antioxidant systems, were identified. This has the potential to jeopardize the production of ATP (Adenosine Triphosphate) and the ability of erythrocytes to maintain their structures. In addition, they emphasize that oxidative stress is elevated as a result of the accumulation of reactive oxygen species, causing damage to the lipids and proteins of the cell membrane. This damage caused erythrocytes to be more fragile and to produce hemolytic processes; likewise, they propose that these metabolic transformations could change the deformability of erythrocytes, since it is a fundamental element for their transit through capillaries. In other words, they suggest that the spatial environment not only decreases the number of erythrocytes but also affects their quality and functioning [17].

Therefore, evidence suggests that erythrocyte fragility is closely related to physiological stress conditions. Thus, a study carried out by the authors showed that even mild systemic inflammation can significantly increase the osmotic fragility of erythrocytes. The authors reported that inflammatory processes

alter the structural integrity of the erythrocyte membrane. Likewise, the authors reported that inflammatory processes alter the structural integrity of the erythrocyte membrane, making red blood cells more susceptible to hemolysis, this finding is very pertinent, because it reveals how barely perceptible changes in the internal environment can condition the stability of erythrocytes. As a consequence, the results obtained also suggest that external factors such as microgravity can cause similar alterations in the membrane and increase the sensitivity of erythrocytes in response to osmotic stress.

B. Theoretical Basis

1) *Erythrocytes*: Erythrocytes are specialized blood cells whose main function is the transport of oxygen from the lungs to the tissues and the return of carbon dioxide. Therefore, their biconvex structure allows them a high capacity for formation, facilitating their passage through narrow capillaries; therefore, the integrity of their cell membrane is essential to maintain their functionality and survival in the bloodstream [18].

2) *Erythrocyte membrane*: The erythrocyte membrane is composed of a lipid bilayer and structural proteins that ensure its flexibility, stability, and mechanical adaptability. Alterations in their composition, either due to oxidative stress or external factors, can affect cell deformability and increase the probability of hemolysis [19].

3) *Osmotic fragility of erythrocytes*: Osmotic fragility is a parameter that assesses the resistance of erythrocytes to changes in the osmotic concentration of the medium. Therefore, it is measured by observing the degree of hemolysis when cells are exposed to hypotonic solutions, i.e., an increase in osmotic fragility indicates a lower stability of the erythrocyte membrane, which implies greater susceptibility to cell rupture [20].

4) *Microgravity*: Microgravity is a physical condition characterized by a significant reduction in gravitational force; in this sense, it occurs in space or in simulated laboratory models. This condition generates physiological changes in the human body, including fluid redistribution, metabolic alterations, and modifications in cellular function, especially in the hematological system [21].

5) *Oxidative stress*: Oxidative stress occurs when there is an imbalance between the generation of reactive oxygen species and the antioxidant capacity of the body. In erythrocytes, this phenomenon can cause damage to membrane lipids and proteins, compromising their stability and increasing their fragility [22].

6) *Hemolysis*: Hemolysis is the process of destruction of erythrocytes, which can occur due to mechanical, chemical, or physiological factors. In conditions such as microgravity, an increase in hemolysis has been observed, which contributes to the decrease in erythrocyte mass and the development of anemia [23].

7) *Erythrocyte deformability*: Erythrocyte deformability is the ability of red blood cells to change shape without breaking through capillaries. This property depends on the integrity of the membrane and the cell cytoskeleton. Likewise, its alteration

can affect blood circulation and promote hemolytic processes [24].

III. MATERIALS AND METHODS

In order to analyze in a structured way the scientific evidence regarding the effects of simulated microgravity on the osmotic fragility of erythrocytes, the present work was carried out under a systematic review of the literature. This methodology was chosen because of the way in which it evaluates, organizes and synthesizes the scientific information it has, in a rigorous and reproducible way and in which the minimum bias in the selection of studies intervenes. It should be noted that the prism methodology was used as a set of guidelines to be followed in the preparation and presentations of meta-analysis and systematic review, with the main purpose of this method being to ensure that the search and selection treatment of studies is done in a transparent and orderly manner. Likewise, the methodology allows to describe in detail how the search for the information has been done, as well as the criteria that were used to include/exclude the studies that were retrieved and which studies were finally analyzed, since it includes a flow chart that allows you to see the entire process of selecting the articles. In this way, the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) methodology increases the reliability and quality of systematic reviews and meta-analyses, since other researchers can understand and replicate the procedure followed [25].

The bibliometric analysis was carried out in order to identify trends, research patterns and scientific collaboration networks in the study of spatial anemia and erythrocyte alterations under microgravity conditions. To this end, the VOSviewer software was used, which allowed the generation of graphical representations of keyword co-occurrence, co-authorship between researchers and collaboration between countries, using bibliographic data obtained from Scopus, IEEE Xplore, PubMed and Web of Science (WoS). This analysis facilitated the identification of the main lines of research and the structure of scientific production in the area [26].

A. Study Design

The research was based on a process of research and analysis of scientific research related to the effect of microgravity on hematological parameters, especially in terms of the stability and osmotic fragility of erythrocytes. Decision and experimental studies that focused on microgravity models, such as the clinostat or other simulation devices, were also noted.

B. Data Sources

In order to identify the relevant articles, an exhaustive bibliographic search was carried out in scientific databases of great international recognition, such as ScienceDirect, Scopus, PubMed, IEEE Xplore, which were selected for the bibliographic search due to the high level of coverage in the biomedical field for the indexing of scientific journals also of high impact.

C. Search Strategy

To search for the relevant studies, a combination of keywords such as microgravity, erythrocytes and osmotic fragility was carried out, in order to have a better coverage,

synonyms and alternatives of the most frequent terms in the scientific literature were used. To this end, the four databases most used in the various scientific studies were used, such as WoS, Scopus, PubMed and IEEE. In addition, studies were collected during the period from 2021 to 2025, to obtain the most recent information from the literature and have a better outlook. For this purpose, Boolean operators such as (AND, OR) were used in the aforementioned databases. The strategies used are detailed below:

1) *Web of Science*: TS=((microgravity OR weightlessness OR "spaceflight" OR "simulated microgravity") AND (erythrocyte* OR "red blood cell*" OR RBC) AND (anemia OR hemolysis OR "red cell turnover" OR "osmotic fragility" OR "membrane stability" OR deformability))

2) *Scopus*: TITLE-ABS-KEY((microgravity OR weightlessness OR "spaceflight" OR "simulated microgravity") AND (erythrocyte* OR "red blood cell*" OR RBC) AND (anemia OR hemolysis OR "red cell turnover" OR "osmotic fragility" OR "membrane stability" OR deformability))

3) *PubMed*: ((microgravity[Title/Abstract] OR "simulated microgravity"[Title/Abstract] OR spaceflight[Title/Abstract] OR weightlessness[Title/Abstract]) AND (erythrocyte*[Title/Abstract] OR "red blood cell*" [Title/Abstract] OR RBC[Title/Abstract]) AND (anemia[Title/Abstract] OR hemolysis[Title/Abstract] OR "red cell turnover"[Title/Abstract] OR "osmotic fragility"[Title/Abstract] OR "membrane stability"[Title/Abstract] OR deformability[Title/Abstract] OR "space anemia"[Title/Abstract])) AND (ffft[Filter]) AND ("2021/01/01"[Date -Publication] : "2025/12/31"[Date -Publication])

4) *IEEE Xplore*: (("Publication Title": microgravity OR "Publication Title": "simulated microgravity" OR "Publication Title": spaceflight OR "Publication Title": weightlessness) AND ("Abstract": erythrocyte OR "Abstract": "red blood cells" OR "Abstract": RBC) AND ("Abstract": anemia OR "Abstract": hemolysis OR "Abstract": "red cell turnover" OR "Abstract": "osmotic fragility" OR "Abstract": "membrane stability" OR "Abstract": deformability))

D. Inclusion and Exclusion Criteria

In order to ensure the validity, relevance, and updating of the works that are recognized, specific inclusion and exclusion criteria have been determined.

- Inclusion criteria:
 - Articles published in indexed journals.
 - Scientific articles published in the last 5 years.
 - Publication in English.
 - Investigations that include analysis of osmotic fragility, erythrocyte membrane stability or hemolysis.
 - Investigations that evaluate erythrocytes, spatial anemia or hematological parameters.

- Investigations related to simulated or real microgravity.
- Studies that use experimental models of microgravity, such as the clinostat.
- Exclusion criteria:
 - Studies with insufficient information or unclear methodologies.
 - Studies without access to full text.
 - Duplicate Articles Across Databases.
 - Publications that do not address the specified topics.

E. PRISMA Methodology

The strategy used for the selection of the review articles presented below was the one found in the protocol, which made possible the orderly and reproducible structures of each of the review phases. Therefore, in the identification phase, the search for these articles from the databases and using the Boolean operators mentioned above was carried out. As can be seen in Fig. 1, in the first instance in the Scopus database, a number of 41 articles were obtained, in IEEE Xplore 178, in PubMed 200 and in Web of Science 228, obtaining a total of 745 articles to be later analyzed. Then, in the filtering phase, duplicate records and those that did not meet the inclusion and exclusion criteria were eliminated, such as those that were not related to the topic of the study, year of publication, as well as those that were not available in full text, leaving a total of 75 articles.

On the other hand, in the screening phase, another evaluation was carried out, but this time the titles and abstracts of the articles were verified, according to the direct relationship, taking into consideration the subject of study in this specific case, in order to determine the effect of microgravity on the behavior of erythrocytes, leaving a total of 42 articles. Therefore, in the inclusion stage, a conscientious reading of the differently selected articles was carried out, where duplication was found in two articles; therefore, a total of 40 articles were finally left. In this phase, its scientific relevance and methodological relevance were critically assessed, also adding that the reading of the articles from which the set of studies carried out subsequently for qualitative research was ultimately elaborated, as well as in short, this procedure allowed to gradually reduce the number of studies initially selected and also to guarantee the selection of appropriate and updated research related to qualitative research line of the objectives of this study [27].

F. Analysis of Information

In this section, the research selection process that underpins the systematic review that was carried out according to the PRISMA diagram model is detailed, in which the phases of identification, filtering, screening, and inclusion of the studies formed in a logical sequence are organized. In the first stage of identification, a total of 745 of the records were obtained from the 4 selected databases and were collected: Scopus (41), IEE Xplore (178), PubMed (200), Web of Science (226). In this

sense, this phase aimed to obtain a high number of publications that could be relevant in terms of microgravity and its effects on erythrocytes in order to configure a broad initial base for the analysis. Thus, in the second phase of filtering, the inclusion and exclusion criteria were established in order to purify the records obtained. Likewise, in this phase, criteria were established such as the type of document taken as a basis, with preferable those investigations that are aligned with the original article, as well as the direct relationship with the topic of study pointed out in terms of the conditions of microgravity or spaceflight, anemia, impact on erythrocytes and their implications.

However, specific variables such as hemolysis, anemia, osmotic fragility, membrane stability, and deformability were evaluated. It should be noted that only studies published in the period of 2021-2025 were included, corresponding to articles available in English and, likewise, with access to the full text. As a result of this process, around 75 articles were obtained in the eligibility phase: Scopus (28); IEEE Xplore (24); PubMed (4); Web of Science (19). In the screening phase, the titles and abstracts of the articles obtained were meticulously analyzed. In this phase, 42 investigations were obtained that were taken into consideration for subsequent analysis. In this phase, 33 studies were excluded since they did not meet the methodological or thematic criteria that we had established. Therefore, in the inclusion phase, only 2 duplicate articles were detected; therefore, they were eliminated to avoid content redundancies. Therefore, a set of 40 articles was obtained that make up the database of this systematic review, which were organized systematically in order to facilitate the analysis.

For each collection study, information was collected based on relevant bibliographic data, such as the year of publication, authors, source of origin, which allowed it to be structured in an orderly manner, facilitating the analysis of the different approaches used in research on erythrocyte alterations in conditions of microgravity, spatial anemia, as well as the possibility of contrasting the methods in the different articles. However, for the organization and management of the articles, specialized tools such as bibliographic managers were used, in which it was very useful, since they allowed storing the records, identifying duplicate articles and thus optimizing the review process, likewise, the VOSviewer software was used for the elaboration of bibliometric maps and collaboration networks between authors and countries, allowing a visual analysis of scientific production to be carried out.

Together, the selection method applied to the literature made it possible to reduce a large amount of scientific literature until a final set of relevant studies was obtained. It should be noted that the rigorous application of the inclusion and exclusion criteria in each phase made it possible to guarantee the coherence of the selected articles, building a solid database for the analysis of erythrocyte alterations under microgravity conditions and the analysis of spatial anemia. In this way, the included studies provide an up-to-date view of the state of research in this field, as well as a starting point for future scientific research (see Fig. 1).

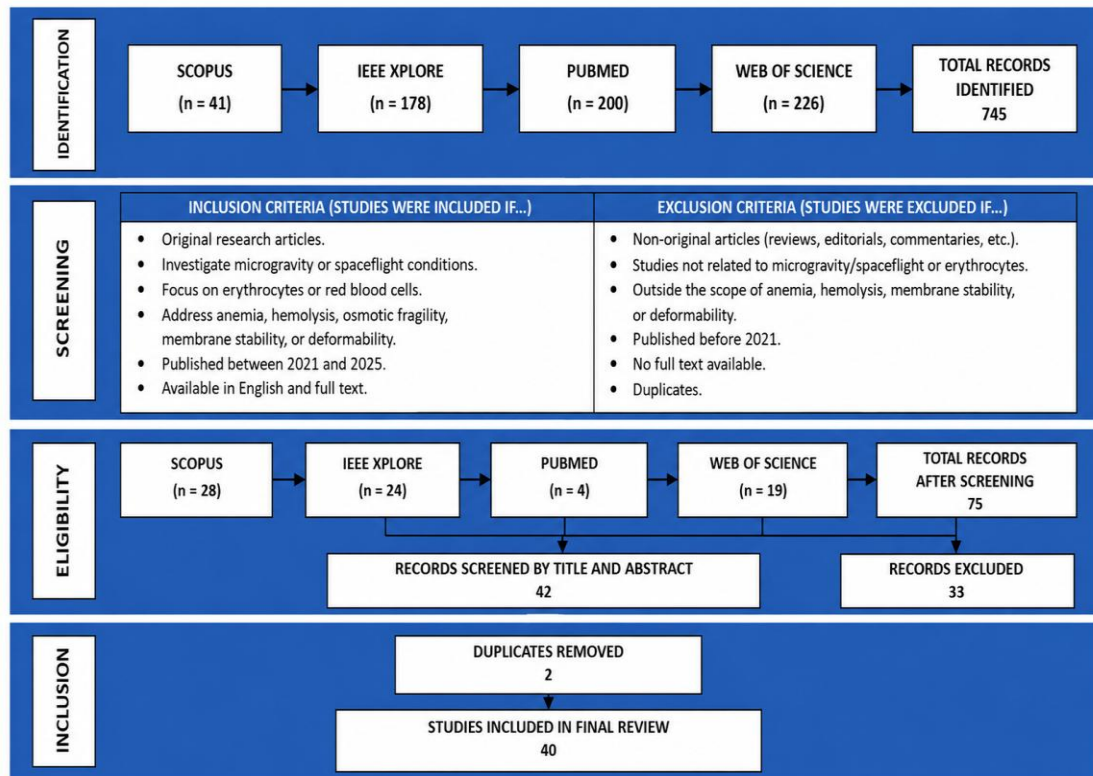


Fig. 1. PRISMA methodology

IV. RESULTS

In this section are the results of the systematic review. There was an increase in scientific interest in researching the effects of microgravity on erythrocytes, with a particular focus on problems such as hemolysis, spatial anemia and alterations in the mechanical characteristics of red blood cells. In this sense, the information based on the analyzed literature shows how this field has been consolidating itself as a relevant area within aerospace biomedical research, due to its impact on the health of astronauts during their prolonged missions.

In general terms, the studies reviewed show an inclination towards the use of experimental models, both in real and simulated microgravity conditions, as well as including places such as the International Space Station and devices designed for simulation on Earth. These approaches allow the analysis of physiological changes in erythrocytes such as osmotic fragility, membrane stability, deformability and in general the fundamental aspects in order to understand the appearance of the so-called spatial anemia, in this way, the results allowed to identify variations in the methods used, as well as the type of samples analyzed and the level of evidence achieved by the studies. An unequal geographical distribution of scientific production is also observed, these findings offer a current view of the state of research and serve as the basis for the bibliometric analysis developed below.

A. Keyword Co-occurrence Map

In this section, an analysis of keyword co-occurrence was carried out with the 40 selected articles, using the VOSviewer

tool, with the aim of determining the most important thematic lines in research on microgravity and erythrocytes. Therefore, in Fig. 2, you can see the map produced where he identified an extensive network of interrelated terms, organized in multiple clusters. In this sense, in this representation, the size of nodes indicates the frequency of occurrence of each keyword, however, the thickness of the links reflects the intensity of the relationship between the terms and the colors, since they facilitate the distinction of different thematic groups [28].

Likewise, several central nuclei were identified that are clearly delimited. Therefore, the concepts "spaceflight" "microgravity", "erythrocyte", and "hemolysis" are the ones that stand out the most, which constitute the main axis of the research, and demonstrate that most of the studies are carried out in space conditions or simulated microgravity. Likewise, terms such as "ISS" or "international space station" emphasize the importance of the experimental spaces used in this field. In addition, a group focused on "RBC", "erythrocyte", and "erythrocytes" is seen. Therefore, this confirms that erythrocytes are the most important biological center of the literature analyzed. This set is strongly linked to physiological variables such as hemolysis, which is presented as one of the most essential terms and thus shows interest in the process of damage or destruction of red blood cells in microgravity conditions.

In this sense, terms related to biochemical and cellular processes are identified, such as "function", "oxidative stress", "membrane", "lipidomic", which indicate that a significant part of the research is focused on understanding the underlying mechanisms that explain the functional and structural alterations of erythrocytes [29]. Therefore, the presence of terms related to

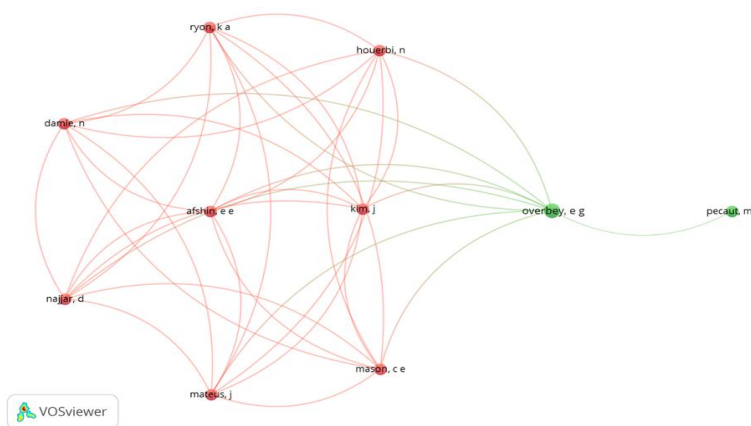


Fig. 3. Co-authorship map

C. Map of Co-authorship by Country

In this section, the graphical representation facilitates the analysis of international collaboration between countries within a set of selected studies, as can be seen in Fig. 4. Two main groups were identified that were distributed in five countries and are linked by several co-authorship links. Thus, in this type of map, each node represents a country in the same way the lines indicate the existence of publications made by a group of authors from different nations [33].

In this sense, the network shows that international collaboration is limited, due to the fact that there are few countries that have co-authorship links, which indicates that most of the research is carried out in small teams and is also developed in national contexts. However, Austria is a point of

connection between the European group (Austria, Germany, Switzerland) and the Asian group (China and Japan), allowing for intercontinental interaction [34]. On the other hand, closer ties are observed in each of the groups, especially in the European bloc, indicating more consolidated regional cooperation. In Asia, cooperation and collaboration are mainly concentrated in Japan and China, the latter being an important node because it maintains relations not only within its geographical area but also with Europe; therefore, the analysis of co-authorship reveals a sparse network with concrete links, which evidences a specialized field of research. This indicates that, despite international cooperation efforts, there is still room to strengthen cooperation between countries and to promote joint research that broadens the scope and also the robustness of research in this area (see Fig. 4).

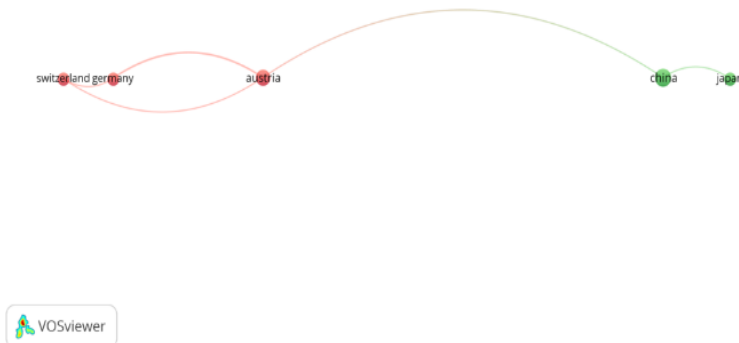


Fig. 4. Co-authorship map by country.

D. Annual Evaluation of Scientific Production

Fig. 5 shows how the annual scientific production linked to research into microgravity and its impacts on erythrocytes has changed. The review was carried out based on the 40 selected articles. Thus, the vertical axis of the graph shows how many articles were published in each period, while the horizontal axis shows the representation of the years of publication, in general terms, between 2021 and 2025. Scientific production represents a variable behavior. Consequently, 9 publications were registered in 2021, but the production dropped to 7 articles in 2022. Subsequently, in 2023, the lowest value of the entire period (3 publications) is appreciated. This indicates a temporary decrease in the number of studies reported on this topic.

Since 2024, a significant increase in scientific production has been observed, reaching its peak in the period with 12 investigations. This increase indicates a more recent interest in investigating alterations in erythrocytes that occur in microgravity, such as spatial anemia, hemolysis, and variations in red blood cell function and stability. In 2025, production remains at a high level with 9 articles, which supports the permanence of this line of research. In general, the trend observed despite the fact that production was not constant during all years, in the most recent periods there was a significant increase. This allows us to infer that research on microgravity and its impacts on erythrocytes has established itself as an emerging area of interest, with a projection to continue developing in future research [35].

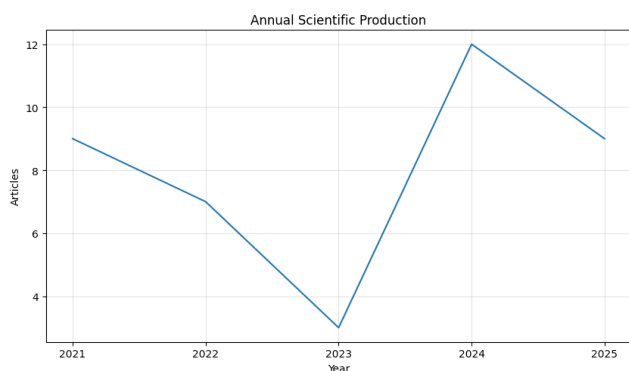


Fig. 5. Annual scientific production

E. Distribution of Publications by Journal

This section refers to the distribution of publications by scientific journals, as can be seen in Fig. 6. It allowed us to identify the most relevant sources within the field of study related to microgravity and erythrocytes. Therefore, with the results obtained from 40 articles, it was identified that the journal *Studies in Health Technology and Informatics* concentrates the largest number of publications, with a total of 5 articles, positioning itself as the main source of dissemination in this field. Therefore, this result indicates that it is of utmost importance in research that integrates technology and health, especially in innovative contexts such as microgravity.

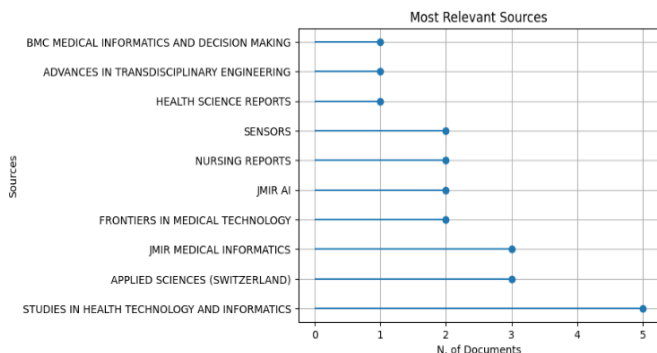


Fig. 6. Most relevant sources

Consequently, the journals *Applied Sciences (Switzerland)* and *JMIR Medical Informatics* stand out, with 3 publications each, which shows their significant contribution to the dissemination of studies related to computational and technological analysis applied to biological phenomena. Likewise, several journals with an intermediate production are identified, such as *Frontiers in Medical Technology*, *JMIR AI*, *Nursing Reports* and *Sensors*, each with 2 published articles. These sources reflect the thematic diversity of the field, spanning approaches from biomedical engineering to clinical applications.

On the other hand, journals such as *Health Science Reports*, *Advances in Transdisciplinary Engineering* and *BMC Medical Informatics and Decision Making* have a lower participation, with 1 article each, which indicates a more specific contribution within the analyzed set. Overall, the observed distribution shows that scientific production is not concentrated in a single journal, but is dispersed in various sources, which confirms the

interdisciplinary nature of the research topic. In addition, this diversity favors the dissemination of knowledge and the development of new lines of study in the field of microgravity and its effects on erythrocytes [36].

F. Content Analysis

With respect to content analysis, the selected articles allowed the identification of the main methodological, thematic and conceptual approaches present in the literature in relation to microgravity and its effects on erythrocytes. Therefore, this analysis was carried out based on the review of the 40 studies, which made it possible to organize the information into important categories. It should be noted that a significant part of the research was identified focused on the study of the physiological alterations of erythrocytes under the conditions of both real and simulated microgravity. In this sense, the scientific articles analyzed highlight changes in the stability, structure and functionality of red blood cells, evidencing their impact on processes such as spatial anemia and hemolysis. Therefore, with respect to the analysis of the osmotic fragility of erythrocytes, it is considered as a key indicator of the integrity of the cell membrane. Therefore, several studies agree that exposure to microgravity can increase the susceptibility of erythrocytes to rupture, which causes an alteration in their mechanical and biochemical properties [37].

On the other hand, research aimed at the study of molecular and cellular mechanisms, including oxidative stress, is identified; therefore, the factors are frequently related to the decrease in erythrocyte stability and the increase in hemolytic processes. As for the methodological approaches, the use of experimental models of simulated microgravity, such as the clinostat, as well as studies carried out in real environments such as the International Space Station, is evidenced. Therefore, these methods make it possible to analyze the effects of the space environment on blood cells in a controlled manner. Likewise, the content analysis identified that the studies present a diversity of interdisciplinary approaches, thus integrating areas such as biomedicine, biochemistry, physiology, and engineering. In this way, this reflects the difficulty of the phenomenon studied and also the need to address it from different perspectives. Thus, the results regarding the content analysis showed that research in this field of development has made important advances in the understanding of the effects on microgravity on erythrocytes. However, gaps in the literature are also identified, especially in relation to long-term clinical studies and the standardization of methodologies, which suggests the need to continue deepening this line of research [38].

G. Distribution of Journals on Microgravity and Erythrocyte Studies

Fig. 7 shows the distribution of the scientific articles analyzed according to the journals in which they were published, which allows us to identify the main sources of dissemination when investigating microgravity and its impacts on erythrocytes. Therefore, from the 40 articles selected in this systematic review, it is observed that the journal *Studies in Health Technology and Informatics* concentrates the largest number of publications with a total of 5 articles, positioning itself as the most relevant source in the field. Thus, this result shows the focus on research that integrates

health and technology, especially in innovative contexts such as microgravity. It should also be noted that the journals (Switzerland), JMIR Medical Informatics and Applied Sciences with 3 publications each, reflect their significant contribution to

the dissemination of studies related to the analysis of biological phenomena through computational and technological approaches.

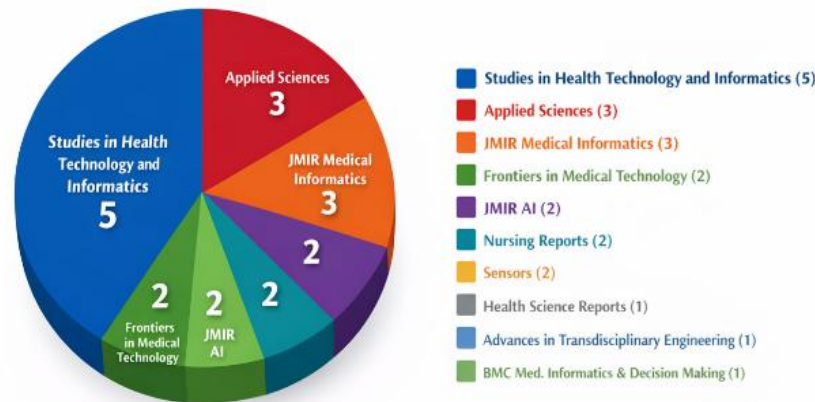


Fig. 7. Content analysis

Likewise, several journals with an intermediate production are identified, including Frontiers in Medical Technology, JMIR AI, Nursing Reports and Sensors, each with 2 published articles. These journals reflect the diversity of approaches present in the literature, ranging from biomedical engineering to clinical applications related to the analysis of erythrocytes in microgravity conditions. On the other hand, journals such as Health Science Reports, Advances in Transdisciplinary Engineering and BMC Medical Informatics and Decision Making have a lower participation, with 1 article each, which indicates a more specific contribution within the analyzed set.

Thus, the observed distribution shows that the scientific production is dispersed in various journals, which confirms the interdisciplinary nature of the study of erythrocytes and microgravity. Therefore, this diversity favors the dissemination of knowledge and also contributes to the development of new lines of research in the field of biochemistry and aerospace medicine [39].

H. Comparison of Studies on the Effects of Microgravity on Erythrocytes and Their Relationship with Osmotic Fragility

As can be seen in Table I, of the 40 articles that were selected, only 8 studies were taken into account for a comparative analysis, because only this small group of articles provided quantitative or qualitative information directly associated with erythrocyte osmotic fragility, hemolysis, membrane stability, or equivalent indicators associated with the adaptation of erythrocytes to microgravity conditions. Likewise, these studies had a more complete description of the experimental protocols used and reported results that facilitated comparisons between the different methodological approaches. It should be mentioned that the remaining studies were considered during the general synthesis of the systematic review evidence, but did not provide sufficient information about the specific variables analyzed in this table. To this end, they were distributed by authorship, year, title, experiment-protocol (brief), metrics (main findings) and limitations, likewise, it is evident that most of the studies analyzed coincide in

microgravity conditions, both simulated and real, which can generate important alterations in erythrocytes. Therefore, these modifications are not always directly evaluated by classic tests such as the OFT (Osmotic Fragility Test) or MCF/H50 (Mean Corpuscular Fragility-H50) tests, but they do manifest themselves through functional, biochemical and structural changes that affect cell stability. Therefore, firstly, some studies, such as that of Agramont et al. (2023), directly report an increase in osmotic fragility and also in susceptibility to hemolysis, suggesting a lower resistance of erythrocytes to changes in the osmotic environment. This type of evidence is especially relevant, as it allows a more direct relationship to be established between erythrocyte damage and microgravity.

Therefore, a large part of the studies provides indirect evidence, since research such as that of Manis (2022, 2023) indicates an increase in oxidative stress, alterations in the composition of the membrane and metabolic changes, factors that are closely related to the loss of cell stability. Therefore, Murali and Sarkar (2025) analyze changes in the deformability and behavior of erythrocytes, which may affect their ability to resist adverse situations and increase their susceptibility to hemolysis. In studies carried out in real microgravity, such as Trudel et al. (2022), there are evidence of a sustained increase in hemolysis during prolonged space missions, which supports the notion that the destruction of red blood cells is an active process in this context, which favors the emergence of the so-called spatial anemia. In this sense, according to Hinge et al. (2024) they show morphological and functional alterations in erythrocytes both under simulated conditions and in reality, which indicates that experimental models on the ground can partially replicate the effects seen in space. Finally, certain studies considered as additional support according to Stuart et al. (2024) and Kashirina et al. (2022), offer evidence from a physiological and molecular perspective. These studies indicate that elements such as inflammation or molecular stress may increase the fragility of erythrocytes, thus contributing to a better understanding of the underlying mechanisms, even if they are not directly related to microgravity.

TABLE I. PROPOSED MODEL STUDIES

No.	Author	Year	Title	Experiment-Protocol (brief)	Metrics - Main findings	Limitations
[9]	Agramont N.; Carrasco M.; Flores B.; Quenta D.; Chávez G.	2023	Osmotic Fragility and its Relationship with Space Anemia	A study focusing on the osmotic fragility of erythrocytes and its relationship to space anemia under conditions associated with simulated microgravity	Osmotic fragility: increased. Hemolysis: increased susceptibility. MCF/H50: not reported. p-value: not reported	The abstract does not provide standardized quantitative values; there is limited numerical evidence in the available excerpt.
[10]	Manis C.; Manca A.; Murgia A.; Uras G.; Caboni P.; Congiu T.; Faa G.; Pantaleo A.; Cao G.	2022	Understanding the Behavior of Human Cell Types under Simulated Microgravity Conditions: The Case of Erythrocytes	Human red blood cells under simulated microgravity; analysis of structural and biochemical changes in the cell membrane	Oxidative stress: increased. Antioxidant capacity: decreased. Erythrocyte membrane: altered. Osmotic fragility: indirect evidence of an increase. MCF/H50: not reported. p-value: not reported	It does not directly assess OFT or MCF50 in the available content; the relationship to osmotic fragility is indirect
[12]	Manis C.	2023	Study of metabolic changes in human erythrocytes and plasma under simulated microgravity conditions	Metabolic study of erythrocytes and plasma under simulated microgravity	Erythrocyte metabolic changes: present. Cell stability: compromised. Osmotic fragility: indirect evidence of increased levels. MCF/H50: not reported. p-value: not reported.	The abstract does not include complete numerical results or a full description of the methodology; verification against the full text is required.
[11]	Murali A.; Sarkar R. R.	2025	Impact of gravitational forces on Red Blood Cell dynamics in biofluid suspension	Evaluation of erythrocytes under different gravitational conditions; analysis of shape, deformability, and cell dynamics	Erythrocyte deformability: altered. Cell dynamics: altered. Susceptibility to hemolysis: indirectly increased. Osmotic fragility: indirect evidence. MCF/H50: not reported. p-value: not reported	It does not report direct measurements of osmotic fragility in the study; the evidence is primarily mechanical and functional.
[13]	Trudel G.; Shahin N.; Ramsay T.; Laneuville O.; Louati H.	2022	Hemolysis contributes to anemia during long-duration space flight	Study of actual microgravity during long-duration spaceflight; analysis of hemolysis and space anemia.	Hemolysis: consistently elevated. Space-occupying anemia: associated with persistent red blood cell destruction. Osmotic fragility: not directly assessed. MCF/H50: not reported. p-value: not reported in the abstract.	The primary outcome is hemolysis, not direct OFT; in a real-world setting, there may be additional confounding factors related to spaceflight.
[5]	Hinge S.; Dixit J.; Vidyasagar P.; Kulkarni G.	2024	Comparative analysis of red blood cell under real and simulated microgravity conditions	Comparison of erythrocytes in real and simulated microgravity; structural and functional analysis	Red blood cell morphology: abnormal. Functional changes: present. Osmotic fragility: not directly reported in the abstract. MCF/H50: not reported. p-value: not reported	The exact quantitative results are not detailed in the abstract; a full review of the article is required for a detailed analysis.
[2]	Kashirina D. N. et al.	2022	Proteomic characterization of dry blood spots of healthy women during simulation the microgravity effects using dry immersion	Simulated microgravity model using dry immersion; proteomic characterization of blood samples	Hematological proteomic changes: present. Osmotic fragility: indirect evidence; not measured directly. Hemolysis: not reported directly. MCF/H50: not reported. p-value: not reported in the abstract.	It provides additional molecular evidence, but does not focus directly on OFT or quantified erythrocyte hemolysis.
[17]	Stuart C. M.; Jacob C.; Varatharaj A.; Howard S.; Chouhan J. K.; Teeling J. L.; Galea I.	2024	Mild Systemic Inflammation Increases Erythrocyte Fragility	Clinical study of erythrocyte fragility in the context of mild systemic inflammation; included as a complementary mechanistic basis	Erythrocyte fragility: increased. Microgravity: not directly assessed. MCF/H50: not reported in the abstract. p-value: not reported in the abstract	This does not correspond to direct microgravity; it should be interpreted as supplementary evidence rather than as a key spatial finding.

Thus, the findings suggest that although there is an evident tendency to increase the fragility and hemolysis of red blood cells in situations of microgravity, the information found is diverse and in many cases is indirect, likewise, there is a lack of standardization of the methodologies used, since few studies present specific quantitative parameters such as MCF/H50 (Mean Corpuscular Fragility-H50) or osmotic fragility curves, which complicates the direct comparison between the investigations [40].

V. DISCUSSION

The results of this systematic review show that there is a general consensus that microgravity affects erythrocyte stability, however, the mechanisms responsible for these alterations differ among the studies analyzed. While some studies attribute these changes mainly to membrane damage and oxidative stress, others suggest that metabolic alterations and reduced cell deformability play a relevant role. These differences may be related to the variability of the experimental models used and the duration of exposure to microgravity. It should be noted that, in

both simulated and real situations, they have a significant impact on the functional and structural stability of erythrocytes. Therefore, the research examined indicates that this environment favors alterations associated with hemolysis, membrane damage, metabolic variations and decreased cell deformability, thus all the processes related to the emergence of special anemia and a possible increase in the osmotic fragility of red blood cells. Although not all studies directly analyzed classical parameters such as OFT (Osmotic Fragility Test) curves or MCF/H50 (Mean Corpuscular Fragility-H50) values, the evidence collected suggests a clear trend towards deterioration of erythrocyte integrity when exposed to microgravity [41].

Overall, the results obtained support the notion that microgravity affects the red blood cell membrane and thus alters its ability to withstand variations in the osmotic medium. This is most clearly evidenced in the research of Agramont et al. [10], in which osmotic fragility is linked with spatial anemia and a greater predisposition to hemolysis. This discovery is particularly significant as it establishes a more direct relationship between microgravity conditions and reduced cell stability. Consequently, from a pathophysiological approach, this indicates that exposure to extreme situations can weaken the mechanical and osmotic resistance of the erythrocyte, in this sense, favoring its Destruction and altering the interpretation of hematological analyses in aerospace environments. However, this finding coincides with the results reported by Trudel et al., who also identified an increase in erythrocyte destruction during prolonged exposures to the space environment; however, Agramont et al. establish a more direct relationship related to osmotic fragility, while Trudel et al. highlight hemolysis as the main clinical manifestation. This difference reflects the diversity of approaches used to study spatial anemia.

However, several studies incorporated in this review presented indirect but consistent evidence of red blood cell deterioration. Therefore, studies by Manis et al. [13] showed that an increase in oxidative stress, modifications in the lipid composition of the membrane, reduction of antioxidant capacity, and alterations that directly impact the stability of red blood cells and homeostasis. Similarly, Murali and Sarkar [12] analyzed changes in the shape, deformability, and dynamics of erythrocytes under various gravitational conditions, emphasizing that gravitational field variation affects the physical properties crucial to erythrocyte survival. However, although these studies do not measure osmotic fragility uniformly through a standardized parameter, they reinforce the idea that microgravity causes changes that favor hemolysis and the loss of membrane integrity. Overall, these studies suggest that erythrocyte damage induced by microgravity is multifactorial. On the contrary, the absence of standardized methodologies makes it difficult to establish which mechanism has the greatest influence on osmotic fragility. In short, this limitation makes it impossible to determine whether oxidative stress is the primary cause of damage or a secondary consequence of other cellular alterations.

Therefore, research conducted in microgravity conditions provides an extra level of clinical significance. Trudel et al. [14] documented that hemolysis plays an ongoing role in anemia during prolonged spaceflight, indicating that erythrocyte

destruction is not just a transient adaptive response, but a long-lasting active process. Next, the result challenges the traditional hypothesis that spatial anemia is only a transient adaptive response to the redistribution of body fluids. Meanwhile, the persistence of observed hemolysis suggests the existence of active biological mechanisms capable of compromising erythrocyte survival during prolonged missions. Therefore, this finding supports the hypothesis that the spatial environment influences erythrocyte longevity through various pathways, including oxidative stress, metabolic changes, and cellular membrane variations. In summary, spatial anemia should be considered a multi-factor phenomenon, in which the fragility of the erythrocyte plays a major role along with other system adaptation mechanisms.

It is worth highlighting that a crucial aspect that emerges from this review is the methodological variability of the studies analyzed, studies carried out in real microgravity, simulated models such as clinostat or dry immersion and molecular or biochemical approaches aimed at detailing alterations in membrane, proteomics in blood, or metabolism. This variety shows that the analysis of the erythrocyte in microgravity is a clearly interdisciplinary area, but at the same time highlights one of its main weaknesses: the lack of standardization, while certain studies examine the hemolysis, or others focus on deformability. Likewise, some prioritize molecular biomarkers and only a small fraction focus directly on osmotic fragility. This diversity complicates comparison between studies and thus restricts the ability to reach quantitative conclusions that are more important [42]. Importantly, not all studies reported the same magnitude of erythrocyte alteration. However, some studies documented significant changes in hemolysis, membrane stability, and deformability; others found more moderate effects. Consequently, these discrepancies can be attributed to differences in the experimental models used, as well as the exposure conditions, the assessment methods used and the exposure conditions, the duration. Therefore, direct comparison between studies should be made with caution.

From this perspective, one of the discoveries that is significant of this review is that most of the existing studies offer indirect evidence rather than direct measurements of osmotic fragility. This does not dismiss their contributions, but it does require interpreting the results with caution. By entering the modification of the erythrocyte membrane, the increase in oxidative stress, the existence of damaged lipids and also the alterations in energy metabolism are indications of greater cellular vulnerability, although it does not always correspond to an accurate diagnosis through standardized osmotic tests. Therefore, the findings of this review indicate that there is a strong biological basis linking microgravity to increased erythrocyte susceptibility, although research assessing this phenomenon in a direct and comparable way is still needed.

Similarly, the data analyzed indicate that microgravity influences not only the structure of the erythrocyte but also its physiological function. Therefore, decrease in the mass of red blood cells, biochemical alterations, and an increase in hemolysis. Findings in several studies support the notion that oxygen transport can be affected during prolonged exposures to the space environment. This has significant relevance for aerospace medicine, as it indicates that hematological

surveillance in astronauts must take into account not only the erythrocyte count, but also their functionality, stability, and vulnerability to destruction. That is, erythrocyte research in microgravity should not focus solely on quantitative analysis, but also include mechanical, biochemical and osmotic factors to understand more fully the phenomenon of anemia in space [43].

In addition, this review facilitates the identification of obvious gaps in the literature; there are few studies that present standardized quantitative values on osmotic fragility MCF-H50 (Mean Corpuscular Fragility-H50), OFT (Osmotic Fragility Test) curves, or percentages of hemolysis under similar protocols. Therefore, numerous studies show small samples, as well as varied experimental designs or methods focused on indirect variables. However, research remains fragmented among several disciplined models, which complicates the creation of a coherent framework of interpretation. These restrictions indicate that, although studies have increased considerably in recent years, still there is not enough methodological uniformity to make direct comparisons solid between investigations.

Thus, the trend presented in this review is Coherent: Microgravity promotes changes in erythrocytes that increase cellular susceptibility and contribute to hemolytic processes linked to spatial anemia. However, the evidence you have found is stronger. Still, in the case of structural, functional and metabolic markers rather than direct osmotic evidence, the key contribution of this analysis focuses on bridging the scattered evidence and demonstrating that osmotic fragility can be seen as an important explanatory axis in erythrocyte pathophysiology in microgravity, although it is important to understand the importance of the Osmotic Pathophysiology. They need studies to be more concrete to validate it more accurately.

In other words, these findings suggest that the hematological monitoring of astronauts should incorporate additional functional indicators beyond the conventional erythrocyte count. That is, the evaluation of biomarkers related to hemolysis, membrane stability, and oxidative stress could contribute to an earlier detection of hematological alterations during prolonged space missions. In addition to this, the findings of this review indicate that future research should focus on creating experimental studies with standardized protocols, samples more extensive and also evaluations simultaneous of hemolysis, deformability, biomarkers of membrane damage, and osmotic fragility. A strategy of this type would make it easier not only to compare between studies, but also to enhance the understanding of the mechanisms that cause spatial anemia. Therefore, the osmotic fragility of erythrocytes is presented as an area of attractive interest for biomedical research and aerospace medicine, as it can be a marker of functional adaptation and cell damage under microgravity conditions.

VI. CONCLUSION

It is concluded, according to the analysis carried out, that microgravity in both simulated and real environments causes significant alterations in erythrocytes that impact functional and structural stability. Therefore, these variations are mainly expressed by an increase in hemolysis, as well as alterations in the cell membrane and changes in oxidative and metabolic processes that together favor the emergence of the so-called

spatial anemia. Thus, the evidence analyzed in detail indicates that there is a connection between these alterations and a possible increase in the osmotic fragility of red blood cells. However, this connection has not always been examined directly, since most of the research reviewed is based on indirect indicators such as cellular elasticity, oxidative stress, or the lipid composition of the membrane.

In this sense, despite the constant phenomenon, there is still not enough research that applies standardized methods to evaluate osmotic fragility in a specific way. On the other hand, considerable variability was detected in the methods used, covering research in true microgravity, molecular analysis, and simulated models, which manifests the interdisciplinary nature of the field. However, this variety also implies a restriction, because it complicates the direct comparison of the results and the elaboration of the most accurate quantitative conclusions.

Taken together, the findings suggest that microgravity has a significant influence on the physiology of red blood cells, impacting not only their quantity but also their capacity and functional quality. Thus, osmotic fragility appears as a useful indicator to analyze the integrity of erythrocytes, although its investigation still needs further investigation.

Finally, this research helps to unite the existing evidence and also to point out the gaps present in the literature, underlining the urgency of further investigating this phenomenon through more consistent studies and with comparable methodologies, as they facilitate a better understanding of the mechanisms involved and their effect on human health in microgravity situations.

VII. RECOMMENDATIONS FOR FUTURE STUDIES

Based on the results in the literature, the following recommendations are proposed to guide future research on the impacts of microgravity on red blood cells. For example, create and use standardized techniques to assess osmotic fragility, incorporating the use of OFT curves and parameters such as MCF/H50 (Mean Corpuscular Fragility-H50), which will allow an objective comparison between the multiple investigations. Evaluate research that includes various variables, such as erythrocyte deformability, hemolysis, oxidative stress, and membrane changes, in order to understand the most comprehensive form of the mechanisms involved. Promote the standardization of experimental protocols and reporting criteria, as well as the use of larger and more varied samples, to support the validity and replicability of the results. To carry out experimental and longitudinal research that facilitates the evaluation of variations in erythrocytes over time in order to deepen the evolution of hemolysis and cellular vulnerability in microgravity environments. Finally, increase the number of studies in conditions of true microgravity, as well as carry out direct comparisons with simulated models, in this sense to be able to corroborate the validity of the results obtained in the laboratory.

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