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In this issue:

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IFBLS

INTERNATIONAL JOURNAL OF BIOMEDICAL LABORATORY SCIENCE

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The International Journal of Biomedical Laboratory Science (IJBLS) is an on-line peer-reviewed journal published bi-annually by International Federation of Biomedical Laboratory Sciences (IFBLS).

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Editorial

President’s Message



Hassan A. Aziz PhD, FACSs, MLS(ASCP)^{cm}
IFBLS President 2026 - 2028

Dear Colleagues, Friends, and Members of the Global Biomedical Laboratory Science Community,

It is a tremendous honor to write this message as the newly elected President of the International Federation of Biomedical Laboratory Science (IFBLS). I am deeply grateful for the confidence and trust placed in me by our member societies, and I look forward to working with colleagues around the world to advance our profession and strengthen the impact of biomedical laboratory science on patient care and global health.

As I assume this new leadership role, I am also privileged to serve as Editor-in-Chief of the International Journal of Biomedical Laboratory Science (IJBLS) during this period of transition. The journal remains a cornerstone of IFBLS's mission, providing an international platform for the dissemination of scientific knowledge, educational innovation, and best practices that advance our profession worldwide. Maintaining the quality, integrity, and international reach of IJBLS remains a priority as we continue to support authors, reviewers, and readers from across the globe.

On behalf of IFBLS and the editorial team, I would like to extend my sincere appreciation to Dr. Pat Tille for her outstanding service and dedication as Editor-in-Chief. Through her visionary leadership, commitment to scholarly excellence, and unwavering support of laboratory professionals around the world, Dr. Tille has helped strengthen the journal's reputation and impact. Her contributions have been invaluable, and we are profoundly grateful for the strong foundation she leaves behind.

I would also like to recognize and thank Marie Nora Roald for her tireless service as Technical Editor of IJBLS. Behind every successful journal is a dedicated individual whose attention to detail, professionalism, and commitment ensures the quality and consistency of each publication. Marie's hard work, often conducted behind the scenes, has been instrumental to the journal's success. Her efforts have supported authors, reviewers, editors, and readers alike, and her dedication to maintaining the journal's high standards is sincerely appreciated.

At the same time, it is my pleasure to welcome Dr. Indu Singh as the incoming Editor-in-Chief of IJBLS. Dr. Indu brings extensive experience as an educator, scholar, and leader within the profession. I am confident that under her leadership the journal will continue to flourish, expand its global influence, and further its mission of promoting excellence in biomedical laboratory science education, research, and practice. I look forward to working with her to ensure a smooth and successful transition in the months ahead.

This year also provided a remarkable opportunity for our profession to come together at the 36th World Congress of Biomedical Laboratory Science in Chiba, Japan. The Congress showcased the innovation, resilience, and global collaboration that define biomedical laboratory science today. The scientific program featured distinguished speakers from around the world, outstanding student participation, and valuable engagement from industry partners and vendors who continue to contribute to the advancement of laboratory medicine.

I would like to offer my heartfelt thanks and appreciation to the Japanese Association of Medical Technologists (JAMT) for their exceptional hospitality and for hosting an outstanding Congress. The meticulous planning, welcoming atmosphere, and commitment to excellence demonstrated by the organizing committee created an unforgettable experience for attendees. The Congress served not only as a forum for scientific exchange but also as a celebration of our shared commitment to improving health outcomes through laboratory science.

As we move forward, our profession faces both significant opportunities and important challenges. Advances in artificial intelligence, automation, molecular diagnostics, precision medicine, and digital health are transforming healthcare at an unprecedented pace. At the same time, workforce shortages, evolving educational needs, and increasing demands on healthcare systems require innovative solutions and strong international collaboration. IFBLS and IJBLS will continue to play vital roles in fostering dialogue, supporting professional development, promoting research, and advocating for the essential contributions of biomedical laboratory professionals worldwide.

I thank all of our members, volunteers, authors, reviewers, editors, and partners for their continued dedication to our profession. Together, we will continue to advance biomedical laboratory science, strengthen our global community, and improve the health and well-being of the patients and populations we serve.

Sincerely,

Hassan Aziz, PhD, MLS(ASCP)CM, FACSs
President – International Federation of Biomedical Laboratory Science (IFBLS)

Case Report

Esophageal Xanthoma: A Case Report with Immunohistochemical Findings Related to Pathogenesis

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Esophageal xanthoma (EX) is a rare, benign lesion composed of foamy macrophages beneath the squamous epithelium. We report a case of EX showing cytotoxic T cell-mediated inflammation in the overlying epithelium. Immunohistochemistry revealed CD8, granzyme B, and adipophilin cells, suggesting T cell-induced epithelial injury and lipid release. The accumulated macrophages scavenge epithelial debris, forming foamy histiocytes. These findings support that EX represents a reactive process rather than a neoplastic one.

Keywords: Esophageal xanthoma, Adipophilin, Immunohistochemistry, Pathogenesis

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Introduction

The first case report of xanthoma (synonym: xanthelasma) of esophagus and stomach was published by Vimala R et al in 2000[1]. The most common location of xanthoma in the upper gastrointestinal tract is the stomach (76%), followed by the duodenum[2]. Involvement of the esophagus is very rare. Only eleven cases of esophageal xanthoma (EX) have been documented from 1984 to 2013. EX may endoscopically appear as yellow granular spots, solitary or multiple nodules or plaque, with diameters across 2-10 mm. EX are asymptomatic and non-neoplastic lesions. Microscopically, they are composed of large foamy cells located just beneath the squamous epithelium. The large foamy cells are foamy histiocytes with abundant fat accumulation in their cytoplasm. The pathogenesis of xanthoma has been described in other sites, such as oral mucosa, skin, prostate, urinary bladder and GI, but not in the esophagus[3-8]. We recently encountered a typical case of EX with associated dramatic active inflammatory reaction of the overlying squamous epithelium. The impetus behind this study is to elucidate whether the inflammatory reaction plays a role in the pathogenesis of the EX.

Materials and Methods

Endoscopic finding

The patient was a 59-year-old man. He had a serial blood testing, urine routine and GI endoscopy for health examination in our hospital without any GI symptoms in his present or past history. The result of the urine test is normal. The results of blood tests, including complete blood counts, liver and renal function, serum cholesterol and triglycerides levels, as well as tumor markers, were within normal limit. However, upper GI endoscopy revealed a 0.1 cm tiny yellowish plaque over lower third esophagus, at 35 cm from incisors, and biopsy of the yellowish plague was performed.

Tissue specimens

The specimen consisted of two pieces of gray white and yellowish tissue, measuring up to 0.2 x 0.1 x 0.1 cm from the Department of Pathology and Laboratory Medicine of Kaohsiung Veterans General Hospital. The entire specimen was fixed in 10% neutral formalin and processed to paraffin-embedding using automatic tissue processor. Three micrometer thick sections were cut, mounted on slides, and incubated at temperature of 90◦C for 30 mins. The Institutional Review Board of Kaohsiung Veterans General Hospital approved the study protocol (approval code: KSVGH20-CT12-11).

Histochemistry

The slides were stained with hematoxylin & eosin (HE), Periodic Acid-Schiff (PAS), diastase-PAS (d-PAS) and mucicarmine.

Immunohistochemistry

Immunohistochemical (IHC) stains were performed using commercially available antibodies and processed in an automated Leica Bond Max Immunohistochemistry stainer (Leica Microsystems Inc, Buffalo Grove, Illinois). Primary antibodies directed against the following proteins were used: CD3 at a 1:100 dilution (clone LN10, Leica Biosystems), CD4 at a 1:50 dilution (clone 4B12, Leica Biosystems), CD8 at a 1:100 dilution (clone 4B11, Leica Biosystems), CD20 at a 1:100 dilution (clone L26, Genemed Biotechnologies, Inc.), CD56 at a 1:50 dilution (clone 1B6, Leica Biosystems), CD68 at a 1:1200 dilution (clone KP1, Leica Biosystems), Granzyme B at a 1:100 dilution (clone 11F1, Leica Biosystems), Brain factor-1 (BF-1) at a 1:200 dilution (clone 8A3, Thermo Fisher Scientific Inc), C4d at a 1:50 dilution (polyclonal, Zytomed Systems GmbH), and CKAE1/3 at a 1:300 dilution (monoclone AE1/AE3, Genemed Biotechnologies, Inc.). Heat-induced antigen retrieval was performed using Leica's Epitope Retrieval solutions and anti-goat biotinylated secondary antibody (Vector Laboratories Inc, Burlingame, California) at a 1:1000 dilution was used in the Bond Polymer Refine detection system (Leica).

Results

Under light microscopy, the EX was composed of aggregation of foamy histiocytes in lamina propria just beneath the squamous epithelium.

The overlying squamous epithelium showed focal minor injury of surface epithelial cells, and active inflammatory reaction composed of intraepithelial small lymphocytes and occasional neutrophils, with associated dilated intercellular spaces and cytoplasmic vacuolar degeneration of the basal part of the squamous epithelium (Figure1A and 1B). The cytoplasmic content in the foamy histiocytes were negative for PAS, d-PAS and mucicarmine (Figure 1C, 1D and 1E). The intraepithelial lymphocytes were positive for CD3 (Figure 2A), granzyme B (Figure 2B) and BF-1 (Figure 2C); and negative for CD56 and CD20. A few CD68 (+) histiocytes were also observed within the basal part of the squamous epithelium (Figure 2D). The foamy histiocytes of the EX were immunoreactive for CD68, adipophilin (Figure 2E) and negative for CKAE1/3 (Figure 2F). The result of C4d IHC stain was negative.

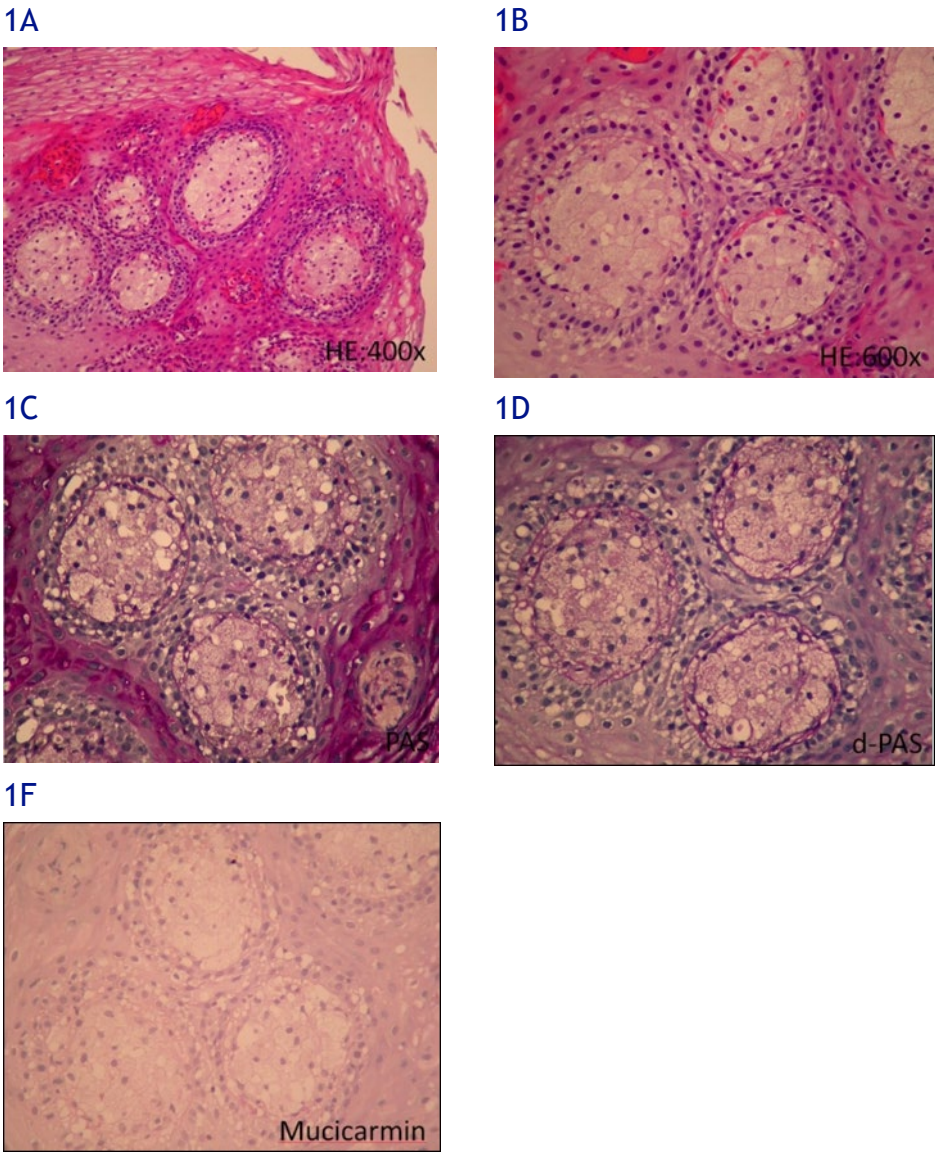


Figure 1. Esophageal xanthoma composed of aggregation of foamy histiocytes in lamina propria immediately beneath the squamous epithelium (HE stain, 1A:400x; 1B:600x). The foamy content in the macrophages is negative for PAS, d-PAS and mucicarmine (1C, 1D and 1E, respectively 600x).

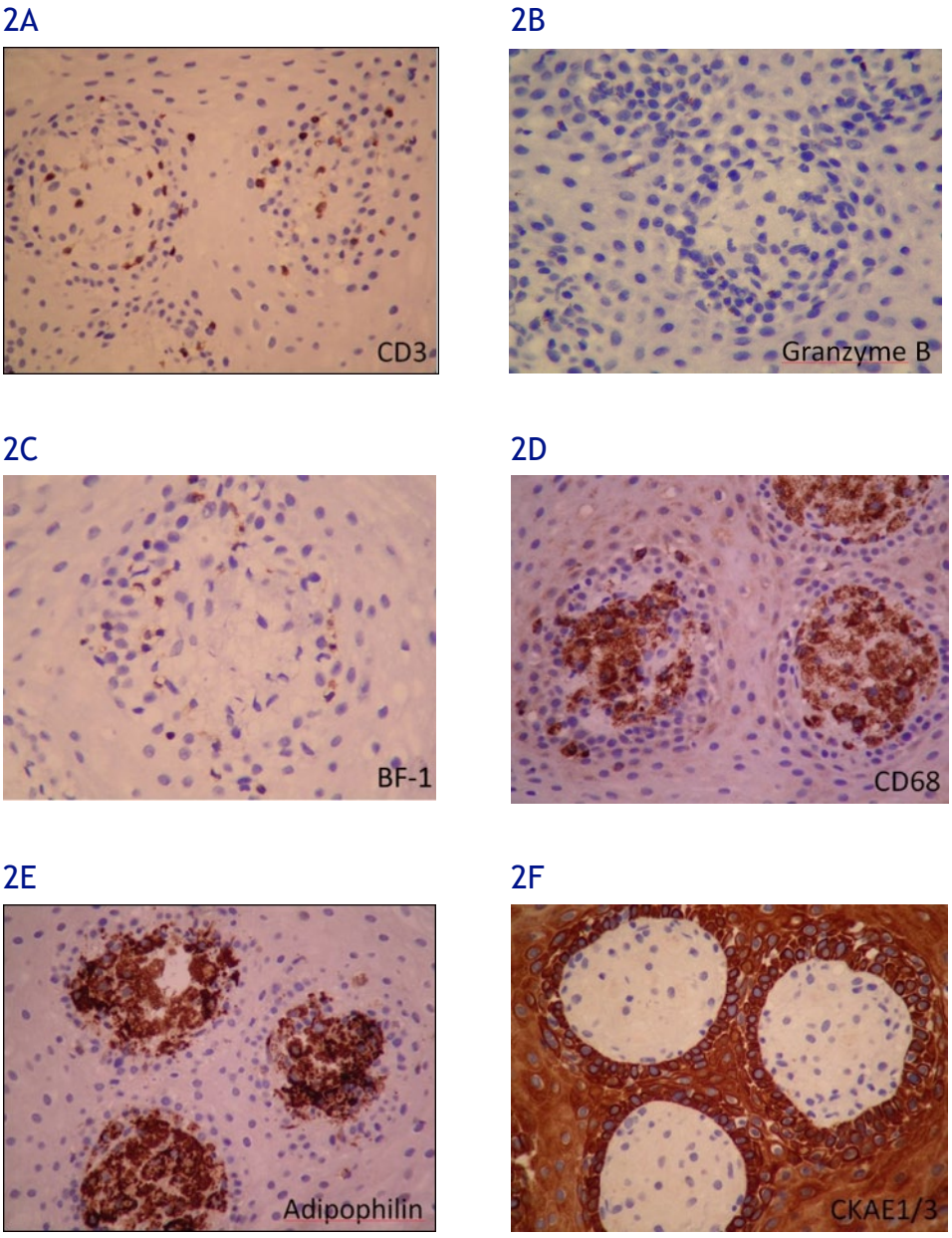


Figure 2. Positive immunocytochemistry for CD3 in some small T lymphocytes (2A: 600x).T cells showing immunoreactivity for granzyme B (2B: 600x). T cells showing immunoreactivity for BF-1 (2C: 600x). The macrophages are immunoreactive for CD68. Note that CD68 (+) are also present in the basal part of the squamous epithelium which shows vacuolar degeneration (2D: 600x). Positive immunoreactivity for adipophilin confirming the presence of lipid (2E: 600x). Negative immunoreactivity for for CKAE1/3 (2F: 600x)

Discussion

The result of this study first demonstrates that in addition to the typical appearance of the EX, which is composed of aggregation of CD68(+) lipid-laden foamy histiocytes in lamina propria just beneath the squamous epithelium, there are also intraepithelial T lymphocytes (CD3+) and occasional neutrophils and macrophages infiltration resulting in dilated intercellular spaces and cytoplasmic vacuolar degeneration of the basal and suprabasal part of the squamous epithelium. The majority of the T cells are of CD8(+) and show immunoreactivity for granzyme B and BF-1, and negative for CD56, indicating that the T cells are of cytotoxic T lymphocytes instead of natural killer cells. Since C4d is a marker of antibody-mediated complement activation[9], the negative

result of CD20 (B cell) and C4d may probably exclude the possibility of antibody-mediated injury.

The results of the IHC study suggest a T cell-mediated reaction. In response to minor trauma and/or exposure to the causative agent, the specific CD8(+) and CD4(+) T cells can be activated by antigen-presenting cells with the cognate antigen and associated MHC molecules. Once activated, these T cells migrate into the squamous epithelium. The CD8(+) cytotoxic T cells may damage the squamous cells using their perforin/granzyme B, leading to cell destruction and release of cytoplasmic content. Perhaps, CXCL8, a potent neutrophilic cytokine, is also involved during the inflammatory response, leading to the chemotaxis of neutrophils into the squamous epithelium. As a role of scavenger, macrophages are recruited to the site of inflammatory reaction and cell damage.

The presence of dilated intercellular spaces may change epithelial permeability and lead to a permissive microenvironment that enhances antigen presentation, which in turn leads to activation of the T cells and persistent recruitment of the macrophages. Another explanation for the persistent recruitment of the macrophages is the possibility of neoantigens or molecular mimics released from the damaged epithelial cells. The neoantigens or molecular mimics may be recognized and regarded as 'foreign' by the sensitized T lymphocytes, resulting in an autoimmune response and persistent recruitment of the macrophages. It is presumed that under certain circumference, persistence of the causative agent exposure over this particular site or release of neoantigens or molecular mimics from the damaged epithelialcells with altered microenvironment may eventually results in the accumulation of the macrophages and formation of the EX.

Adipophilin is a lipid droplet-specific marker and the foamy content in the macrophages showed particularly strong immunopositivity for adipophilin, confirming the presence of lipid droplets in the macrophages. It has been shown that intracellular lipid droplets are not static but rather dynamic and tightly regulated cell organelles for the storage of energy-rich fats; and formation of the lipid droplets is regulated by structural proteins of the PAT/perilipin family which includes adipophilin [10].

It has been shown that uptake of modified lipoprotein by macrophages through scavenger receptors results in intracytoplasmic lipid droplets accumulation, a process that can be stimulated and accentuated by adipophilin. Macrophage adipophilin expression is also a consequence of lipid accumulation and contributes to further accumulation of lipids by inhibiting cellular cholesterol efflux, eventually resulting in foamy cells formation[11]. In order to maintain water barrier, the activity of fatty acid synthase is elevated in mainly the epidermal keratinocytes of the lower stratum spinosum and the stratum basale by local inflammation[12], which may also contribute to the increased lipid of the microenvironment. The damaged squamous epithelium with presumed abundant fatty acid (lipid) content is then scavenged by the macrophages and leads to the aggregation of foamy histiocytes and eventually formation of the EX beneath the squamous epithelium. In our case study, the presence of adipophilin positive granules and CD68(+) macrophages in the lower stratum spinosum and stratum basale of the squamous epithelium support the hypothesis. The aggregated foamy histiocytes are negative for ki-67 (a proliferating cell marker), indicating that they are recruited from the circulation and differentiate into macrophages instead of in situ proliferation.

Since all EXs were incidental and endoscopically- found lesions, there is no data how long they will persist or resolve; and what is the survival and retention signals for their persistence if they do persist like persistence of a chronic inflammatory lesion, which fibroblast plays a critical role[13].

In summary, we propose that in response to minor trauma and/or exposure to the causative agent, the inflammatory reaction or T cell-mediated hypersensitivity targeting the causative agent or damaged esophageal squamous

epithelium may result in recruitment of the monocytes/macrophages. Neoantigens or molecular mimicry from the damaged epithelial cells can also lead to an autoimmune reaction responsible for the persistent recruitment of the monocyte/ macrophage. Formation and aggregation of the large foamy macrophages containing the lipid released from the damaged epithelial cells eventually result in the endoscopically visible EX. The result of this study strongly suggests that EX seems to be a reactive rather than a neoplastic process. Proposed pathogenesis of the EX is demonstrated as cartoon (Fig 3A) and flowchart illustrations in figure 3A and 3B, respectively; however, what triggers the localized T cell-mediated hypersensitivity is still a mystery and more studies are needed to elucidate the etiopathogenesis of the EXs.

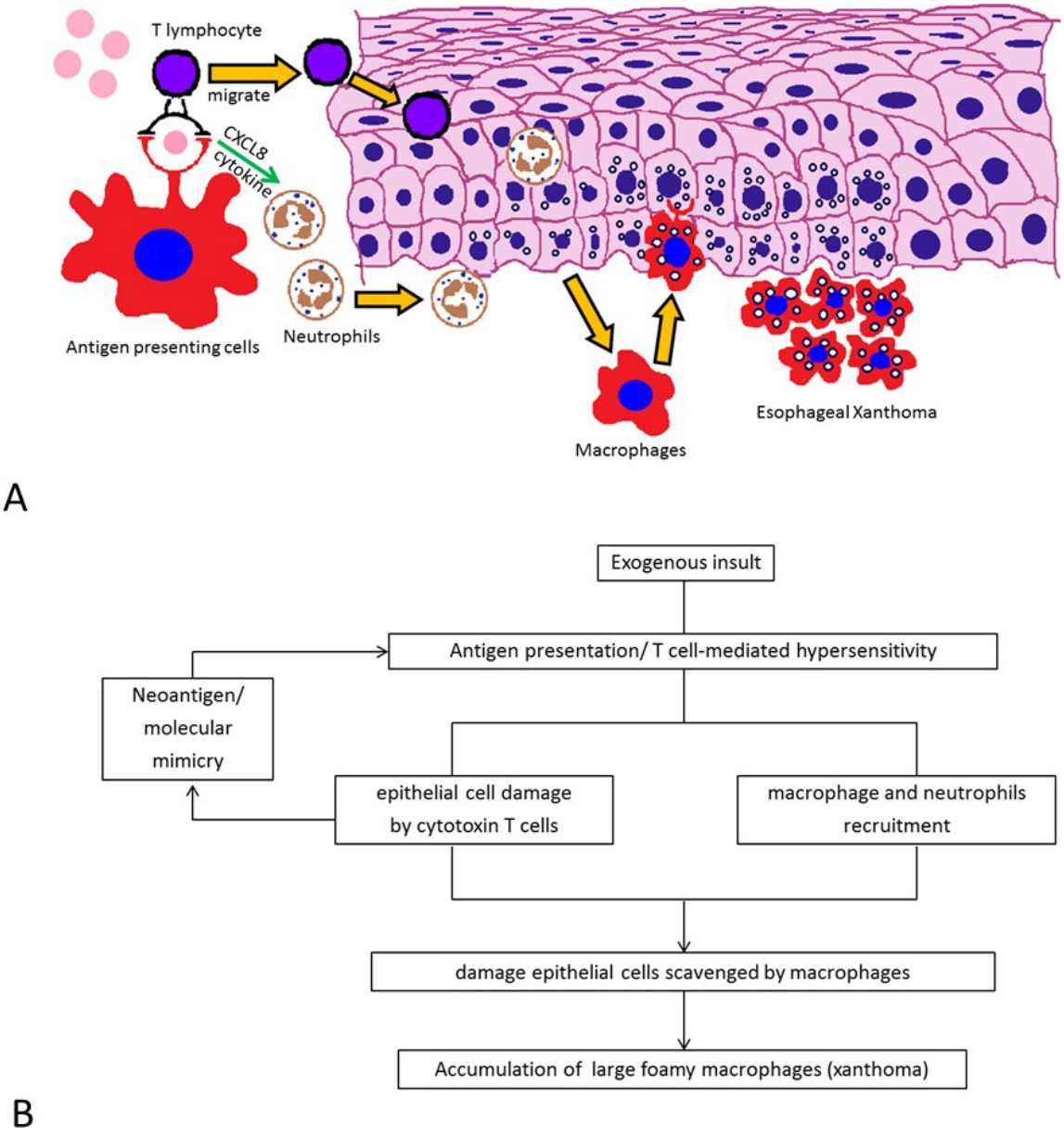


Figure 3. Proposed pathogenesis of the esophageal xanthoma.
3A Cartoon illustration, 3B Flowchart illustration.

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Review article

Antiphospholipid Syndrome as a Complicating Factor for INR Testing: A Review of the Literature

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Antiphospholipid syndrome is an autoimmune disorder associated with recurrent arterial and venous thrombosis requiring long-term anticoagulation, most commonly with warfarin. Monitoring warfarin therapy relies on accurate INR measurement; however, antiphospholipid antibodies may interfere with phospholipid-dependent coagulation assays, resulting in inaccurate INR values. This literature review summarizes current evidence regarding the impact of APS on INR testing methodologies, with emphasis on discrepancies between POC INR testing and venipuncture-based laboratory methods. A non-systematic review of the literature was conducted using PubMed and Web of Science to identify studies evaluating INR measurement accuracy, methodology, and anticoagulation monitoring in APS populations. The reviewed literature demonstrates that APS is a significant source of variability in INR testing due to interactions between antiphospholipid antibodies and thromboplastin reagents. POC INR testing appears most susceptible to interference, frequently producing falsely elevated INR results compared with laboratory-based methods. Quick's method also demonstrates increased sensitivity to lupus anticoagulant interference, whereas Owren's method appears less affected due to differences in thromboplastin composition and assay design. Alternative approaches, including chromogenic factor X assays and individualized correction strategies, may improve anticoagulation monitoring accuracy in APS patients. Overall, the findings highlight important limitations of phospholipid-dependent coagulation assays in APS and underscore the need for increased awareness among laboratory professionals and clinicians regarding assay-specific interference. Recognition of these limitations is essential to support accurate anticoagulation management, appropriate confirmatory testing practices, and improved patient safety.

Abbreviations: Antiphospholipid syndrome (APS); international normalized ratio (INR), point-of-care (POC)

Keywords: Antiphospholipid syndrome; international normalized ratio; point-of-care testing; warfarin monitoring; coagulation assays.

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Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by venous and arterial thrombosis associated with a persistent hypercoagulable state.[1] Given the elevated thrombotic risk, long-term anticoagulation is the standard therapeutic approach for patients with APS.[1] While initial therapy may involve parenteral anticoagulants, most patients transition to long-term treatment with a vitamin K antagonist, most commonly warfarin. The effectiveness of warfarin therapy is monitored using the international normalized ratio (INR). INR measurements require accurate laboratory assessment to ensure safe and effective therapy, because warfarin dosing must be individualized based on careful interpretation of INR results and numerous variables.

INR is derived from prothrombin time (PT), which is a laboratory test that measures the length of time for plasma to form a fibrin clot.[2,3] PT is the time, measured in seconds, to clot formation after citrated plasma is combined with thromboplastin, a reagent composed of calcium, phospholipids, and tissue factor. This assay is used to assess the factors in the extrinsic and common coagulation pathways. Clotting through the extrinsic pathway requires the activation of factor VII by tissue factor (factor III). The thromboplastin reagent used in PT provides this tissue factor, allowing formation of the tissue factor-factor VIIa complex. In the presence of calcium, this complex forms the extrinsic tenase complex on negatively charged phospholipid surfaces, which are essential for activation of the coagulation cascade.[4] PT results are converted to INR values using the formula $\mathrm{INR} = (\mathrm{Patient\ PT}/\mathrm{MNPT})^{\mathrm{ISI}}$. The INR was developed by the World Health Organization to standardize PT results by accounting for variability in analyzers, methodologies, and reagent sensitivities.[3]

However, in patients with antiphospholipid antibodies, the antibodies can interact with the reagent phospholipids, leading to prolongation of the PT, which subsequently affects the INR, despite the correction factors incorporated into the INR calculation.[5] This interference may lead to inaccurate assessment of anticoagulation status in this patient population. Given these clinical and laboratory challenges, a thorough understanding of current therapeutic and monitoring strategies for the use of warfarin in APS is essential, particularly as warfarin remains the preferred anticoagulant in most patients.[6] Although the limitations of coagulation assays in APS have been described, discrepancies between point-of-care (POC) INR testing and standard laboratory-based measurements remain underrecognized in routine clinical practice.

This gap has important implications for anticoagulation management as POC INR testing has become more commonplace in recent years. As such, the potential for inaccurate POC INR results may lead to inappropriate dosing adjustments and increased risk of thrombosis or bleeding. Because laboratory professionals play a central role in test selection, result interpretation, quality assurance, and clinician consultation, awareness of this potential interference is critical for ensuring accurate patient monitoring and minimizing adverse clinical outcomes. However, the effect of antiphospholipid antibodies on INR methodologies, particularly in POC testing systems, remains relatively underrecognized despite its potential clinical significance. Increased reliance on POC INR testing in outpatient anticoagulation clinics further underscores the need for heightened awareness among medical laboratory professionals. Therefore, this literature review aims to summarize current literature on the impact of antiphospholipid syndrome on coagulation testing, with a specific focus on INR measurement.

Methods

A non-systematic review was conducted to evaluate INR testing methodologies in patients with APS, with emphasis on comparisons between venipuncture-based laboratory testing and POC INR testing. The literature search was

developed and conducted in collaboration with a health systems librarian.

Electronic searches were performed in PubMed and Web of Science in October 2025. Two searches were conducted in PubMed (one narrow and one broader), along with one search in Web of Science to identify potentially relevant publications. Searches incorporated both Medical Subject Headings (MeSH) and keyword terms related to APS, INR testing, and POC methodologies. Searches used limits to exclude any article written in a language other than English. Search terms included combinations of APS-related, INR-related, POC, and anticoagulation management terms. The keyword searches included:

- ("Antiphospholipid Syndrome"[Mesh] OR "antiphospholipid syndrome" OR "APS" OR "Hughes' syndrome" OR "lupus anticoagulant") AND ("International Normalized Ratio"[Mesh] OR "international normalized ratio" OR "INR" OR "prothrombin time" OR "Prothrombin Time"[Mesh]) AND ("Point-of-Care Testing"[Mesh] OR "point of care")
- ("Antiphospholipid Syndrome"[Mesh] OR "antiphospholipid syndrome") AND ("International Normalized Ratio"[Mesh] OR "international normalized ratio" OR "INR") AND ("Point-of-Care Testing"[Mesh] OR "point of care" OR (("warfarin" OR "oral anticoagulant*") AND (monitor* OR manag*)))
- (antiphospholipid syndrome AND "international normalized ratio" AND "point of care").

Additional searches incorporated anticoagulation monitoring terminology to broaden the retrieval of literature addressing INR management in APS populations. No filters or date restrictions were applied during the database searches to ensure comprehensive identification of potentially relevant articles.

The librarian compiled citations identified from the database searches and provided a consolidated list of articles considered potentially relevant, along with publication dates and search documentation. Articles were screened for inclusion by two faculty with expertise in anticoagulation and clinical laboratory science. Articles were included if they evaluated INR measurement accuracy, methodology, or clinical interpretation in APS populations. Articles not addressing INR testing in APS or lacking relevance to anticoagulation monitoring were excluded. Full-text review was conducted when necessary to make an inclusion or exclusion determination.

All articles meeting inclusion criteria were reviewed for data related to influence of antiphospholipid antibodies on INR testing, with key data on INR testing methods and factors influencing accuracy in APS extracted and summarized by article. Upon completion of article review, all findings were synthesized narratively, with common data themes grouped for clarity. In this summary, studies focusing on discrepancies between POC and venipuncture-based INR methods were prioritized.

Results

A total of 119 articles were identified across all searches. 30 articles were reviewed in detail to inform the narrative synthesis; of these, 14 were used to contribute to the narrative summary.

Effects of APS on INR Methodologies

There is general agreement in the literature that APS represents an independent source of variability in INR measurement, contributing to labile INR values and increased uncertainty due to phospholipid-dependent disease-assay interactions, particularly at higher INR levels.[5, 7-12] While three studies reported statistical agreement between venous and POC INR values, each also identified INR thresholds at which concordance deteriorated, contributing to ongoing inconsistency in the literature.[13-15] Furthermore, the literature remains inconsistent regarding the optimal approach for anticoagulation monitoring in APS patients. Proposed strategies include avoiding POC INR testing in favor of venous laboratory-based testing,[5,6] applying individualized correction factors based on paired POC and venous INR

results,[9] and utilizing phospholipid-independent assays such as chromogenic factor X for anticoagulant monitoring.[16]

Differences in APS-associated interference appear to vary by INR methodology. There are three common methods for performing PT/INR testing: Quick's, Owren's, and POC INR, each demonstrating varying degrees of sensitivity to APS-related interference. The phospholipid composition of the thromboplastin reagents used in these methods varies and can be derived from recombinant or tissue-based sources.[2] In plasma-based methods (e.g., Quick's and Owren's), the addition of thromboplastin to the patient's citrated plasma activates the extrinsic coagulation pathway, leading to clot formation. Mechanical or optical endpoint methods are most often used to detect fibrin clot formation. POC INR methods use whole blood with a thromboplastin-embedded testing strip.[17] Electromechanical endpoints are used to detect clot formation in these assays. The presence of APS has a variable impact on the accuracy of these three methods.

Most impacted: Point-of-Care Testing

POC INR devices provide rapid turnaround of INR results; however, they use thromboplastin reagents with variable sensitivity to lupus anticoagulation interference. POC INR testing has been shown to be the most susceptible to antiphospholipid antibody-related interference.[5] This procedure uses testing strips containing recombinant thromboplastins, as seen in the Quick's method. Several studies have found POC INR values to be significantly higher than laboratory-based plasma methods, observing the largest differences at higher INR values.[5,11,18]

Intermediate impact: Quick's method

Quick's method is the standard methodology for PT/INR measurement worldwide.[11]

This method uses laboratory-made recombinant thromboplastin reagent and is more sensitive to antiphospholipid antibodies compared with tissue-derived thromboplastins.[5] The increased sensitivity prolongs time to clot formation, producing falsely elevated results that may not reflect the patient's true anticoagulation status. Moreover, INR measurements using recombinant thromboplastins have been shown to exhibit greater variability, even in the absence of antiphospholipid antibodies.[5]

Least impacted: Owren's method

The use of Owren's method is limited to a few countries, including those in Scandinavia.[11] This methodology uses thromboplastin extracted from animal or human tissues and has been proven to be less sensitive to interference by antiphospholipid antibodies. It has been postulated that the differences in sensitivities between Quick's and Owren's methods are due to the differences in plasma dilutions used in these methodologies (1:3 for Quick's method and 1:20 for Owren's method).[5,11] However, Gehlen et al. (2024) found Owren's method to be insensitive to lupus anticoagulant interference even at low dilutions.[18] This study also showed that it is unlikely that the differences in testing sensitivities are related to the presence of added factor V and fibrinogen.

Exploratory methods

One alternative method for monitoring anticoagulation therapy in patients with APS is the chromogenic factor X assay, a phospholipid-independent test that measures factor X activity without interference from reagent phospholipids.[10] Although its availability is currently limited, broader access could improve its clinical utility. Another alternate approach involves the development and validation of individualized correction factors to adjust POC INR values, allowing continued use of POC testing while improving accuracy in the presence of antiphospholipid antibodies.[9] Such strategies have the potential to improve test reliability and support more informed anticoagulation management.

Summary

Collectively, the literature demonstrates that APS may significantly affect the reliability of INR measurements, particularly in POC testing platforms. This effect is largely attributed to

phospholipid-dependent assay interference and varies by thromboplastin composition and methodology. Importantly, this interference has considerable interpatient variability and remains largely unpredictable. As a result, INR values may not accurately reflect the patient's true anticoagulation status, leading to over- or under-anticoagulation in patients with APS. These findings highlight a critical limitation in standard anticoagulation monitoring strategies in APS patients.

Discussion

The findings from this review support the clinical observation that patients with APS may demonstrate unexpected variability in INR results, creating challenges for anticoagulation monitoring and laboratory interpretation. Inconsistent agreement among INR methodologies suggests that optimal approaches for warfarin dose adjustment and long-term anticoagulation monitoring in APS remain insufficiently characterized.

INR discrepancies in patients with APS should not be interpreted as random analytical error, but rather as a consequence of the interaction between antiphospholipid antibodies and phospholipid-sensitive thromboplastin reagents. As a result, elevated INR results may not accurately reflect true anticoagulation status, but instead represent an *in vitro* assay artifact associated with phospholipid-containing reagents. Additionally, fluctuations in antiphospholipid antibody titers and profiles may alter the degree of assay interference observed over time. Recognition of these disease-assay interactions is essential for laboratory professionals, as failure to identify reagent-dependent effects may contribute to inappropriate clinical interpretation and anticoagulation management.

Many institutions have implemented anticoagulation clinics utilizing POC INR testing to facilitate rapid clinical decision-making and immediate dose adjustment. These services are frequently operated by pharmacists, nurses, and other non-laboratory healthcare professionals. Most POC INR devices are classified as waived under the Clinical Laboratory Improvement Amendments (CLIA), reflecting their designation as simple tests with low risk of erroneous results under routine use conditions.[19,20] However, APS highlights an important limitation of this assumption, as POC INR assays remain susceptible to clinically significant phospholipid-related interference in this patient population. This creates a disconnect between regulatory classification and real-world analytical performance, particularly when testing occurs outside direct laboratory oversight.

In facilities where the laboratory maintains responsibility for the CLIA waiver, both laboratory personnel and interpreting healthcare professionals should recognize APS as a significant source of interference in POC INR testing. The Clinical and Laboratory Standards Institute (CLSI) POCT14 guidelines recommend at least 95% agreement between POC and venipuncture methodologies.[21] Although this benchmark is generally achievable in the broader patient population, APS-associated interference may reduce concordance, particularly at higher POC INR values. These findings underscore the importance of institution-specific validation, ongoing quality assessment, and clearly defined escalation strategies when INR results are inconsistent with the clinical presentation or confirmatory venipuncture testing. Laboratories overseeing POC INR testing should also play an active role in identifying at-risk patient populations, implementing confirmation testing protocols, and educating non-laboratory users regarding assay limitations in APS. Additionally assay selection and validation processes should consider phospholipid sensitivity and susceptibility to lupus anticoagulant interference.

To mitigate the risk of inaccurate INR interpretation, several strategies have been proposed, including conducting confirmation venipuncture INR testing when POC INR results exceed defined thresholds (e.g., >3.0) and avoiding POC INR testing altogether in patients

known to have APS.[5,18] Ultimately, collaboration between laboratory professionals and non-laboratory healthcare providers is essential to develop protocols that balance accessibility, testing reliability, and patient safety.

This review has several limitations. As a non-systematic literature review, relevant studies may have been missed despite structured database querying. Available evidence is largely limited to case reports, small cohorts, and expert opinion, with no randomized controlled trials addressing APS and INR measurement. Additionally, this review does not attempt to synthesize quantitative findings across study types and should therefore be interpreted cautiously. The heterogeneous nature of APS contributes to variability in reported findings and limits broad generalizability.

Future efforts should focus on developing standardized approaches to improve INR accuracy and anticoagulation monitoring in patients with APS. Medical laboratory professionals play a central role in advocating for practices that improve testing reliability, including avoiding POC INR testing in APS patients, utilizing antiphospholipid-insensitive laboratory methods, establishing lower thresholds for confirmatory testing, and ensuring discordant results prompt laboratory consultation. Exploration of alternative monitoring approaches may be valuable, as chromogenic factor X testing and individualized correction strategies may offer more reliable assessment of anticoagulation in this patient population.

Conclusion

Antiphospholipid syndrome represents a significant and underrecognized source of interference in phospholipid-dependent coagulation assays, particularly POC methodologies, where falsely elevated INR results may not accurately reflect true anticoagulation status. Increased awareness among medical laboratory professionals is essential to support appropriate result interpretation, confirmatory testing practices, and safe anticoagulation management in patients with APS.

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Research article

Scientific Profile of Medical Technologists Registered as Researchers in Peru

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Objective. **To describe the scientific profile of Medical Technologists registered as researchers in the National Registry of Scientific, Technological, and Technological Innovation (RENACYT) of Peru.**
Materials and Methods. **A descriptive cross-sectional study was conducted using secondary data from official databases, including RENACYT, CTI Vitae, and the National Registry of Academic Degrees and Professional Titles of the National Superintendence of Higher University Education (SUNEDU). Medical Technologists registered as researchers in RENACYT up to June 8, 2026, were identified. Academic, professional, and scientific characteristics were analyzed using descriptive statistics.**
Results. **Among 23,200 licensed Medical Technologists in Peru, 105 (0.5%) were identified as RENACYT researchers. Most researchers were male (64.8%), had a master's degree (41.9%) or doctoral degree (39.0%), and worked mainly in universities (63.7%). The most represented professional area was Clinical Laboratory and Anatomical Pathology (71.3%), followed by Physical Therapy and Rehabilitation (18.1%). Regarding RENACYT researcher classification, the highest proportion corresponded to Level VII (41.0%), whereas higher categories showed lower representation. Most researchers were active at the time of evaluation (88.6%).**
Conclusion. **Medical Technologists registered as RENACYT researchers represent a small proportion of the profession in Peru. Their scientific activity is mainly concentrated in university institutions and in the area of Clinical Laboratory and Anatomical Pathology. These findings highlight the need to strengthen research training, postgraduate education, and institutional opportunities to promote scientific development among Medical Technologists.**

Abbreviations: RENACYT=National Registry of Scientific Technological and Technological Innovation; CTI Vitae=Curriculum Vitae for Science Technology and Innovation; SUNEDU=National Superintendence of Higher University Education.

Keywords: Medical Laboratory Personnel, Biomedical Research, Research Personnel, Scientific and Technical Activities, Health Workforce.

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Introduction

The National Registry of Science, Technology, and Technological Innovation (RENACYT) is Peruvian's official system for identifying, classifying, and recognizing researchers in science, technology, and innovation, considering their academic background, scientific output, and research career. Registered researchers are categorized into levels established by the National Council for Science, Technology, and Innovation (CONCYTEC), making it an important tool for evaluating scientific activity, promoting the development of research capacities, and strengthening research in the country's institutions. [1-3]

In recent years, Peru has shown progressive growth in its scientific output. Between 2013 and 2022, publications indexed in Scopus increased from 1594 to 9391 articles, primarily due to policies strengthening research, the implementation of the amendment N° 30220, known as the university law, and actions promoted by CONCYTEC. However, despite this growth, the country's scientific participation remains limited compared to other countries in the region. Furthermore, the number of researchers per million inhabitants remains low, highlighting the need to strengthen the human capital dedicated to generating scientific knowledge.[4-8] Within this context, health sciences represent one of the main research fields in the country, accounting for a significant proportion of Peruvian scientific publications and showing sustained growth over the last few decades.[9] Internationally, innovation indicators show that Peru still faces challenges in consolidating its scientific and technological system. In 2025, the country ranked 80th out of 139 economies in the Global Innovation Index; moreover, investment in research and development (R&D) represented approximately 0.18% of gross domestic product, a figure lower than that of countries with greater scientific development. These limitations are related to the insufficient availability of highly specialized researchers and the unequal distribution of scientific capabilities in strategic areas, factors that condition knowledge generation and national innovation.[10,11] Similarly, bibliometric studies have shown that Peru's contribution to Latin American scientific production is still small compared to countries with more established research sectors.[12] According to CONCYTEC (2026), Peruvian scientific output continues to increase, reaching 11,220 publications in 2024, accompanied by an increase in national institutional leadership in research, which rose from 65.9% in 2018 to 75.6% in 2024, reflecting greater participation of Peruvian institutions in knowledge generation.[13] In the health sector, institutions such as the Edgardo Rebagliati Martins National Hospital of EsSalud and the Ministry of Health stand out for their contribution to national scientific production and the development of evidence for health decision-making.[14,15] In this context, Medical Technologists play a relevant role within the health system due to their participation in specialized areas related to diagnosis, treatment, prevention, and health research.

Scientific research is part of the professional responsibilities of Medical Technologists. The Code of Ethics of the Peruvian College of Medical Technologists (CTMP) recognizes doing research as an activity oriented toward the development of knowledge, under principles of scientific integrity, social responsibility, and respect for ethical standards in research.[16] However, despite the growth of scientific research in Peru and the strengthening of researcher evaluation systems, there is limited evidence regarding the incorporation of Medical Technologists into the RENACYT system. Currently, it is unknown how these professionals are distributed according to areas of specialization, categories, scientific output, and academic characteristics, which hinders understanding their contribution to national scientific development.

Therefore, this study aimed to describe the scientific profile of Medical Technologists registered in the National Registry of Science, Technology, and Technological Innovation of Peru through a cross-sectional study.

Materials and Methods

Study Design

A cross-sectional descriptive study was conducted using information from secondary registries: a) the Registry of Natural Persons Conducting Science, Technology, and Innovation Activities (RENACYT) in Peru, administered by the National Council for Science, Technology, and Technological Innovation (CONCYTEC); b) the CTI Vitae platform (https://ctivitae.concytec.gob.pe/appDirectorioCTI/), used for the identification and review of researcher profiles; and c) the National Registry of Academic Degrees and Professional Titles of the National Superintendency of Higher University Education (SUNEDU), used to verify the academic qualifications of the identified professionals(https://www.sunedu.gob.pe/registro-nacional-de-grados-y-titulos/).

Study Population

The study population consisted of Medical Technology professionals registered as researchers in RENACYT as of June 8, 2026. Participants were identified through an initial search in the CONCYTEC CTI Vitae Directory, using the filter for researchers. To locate Medical Technology professionals, terms related to their main areas of professional practice were used.

For the Clinical Laboratory and Anatomical Pathology areas, the terms “clinical laboratory” and “laboratory technician” were used. In the areas of Physical Therapy and Rehabilitation, Occupational Therapy, and Speech Therapy, the terms “physical therapy,” “therapist,” “physiotherapy,” “occupational therapy,” and “speech therapy” were used. For Radiology, the terms “radiology,” “radiology imaging,” and “tomography” were considered; while for Optometry, “optometry” and “optometrist” were used. The identified records were subsequently verified on the RENACYT researcher search platform using each researcher's corresponding code to confirm their official registration. Likewise, academic degrees and professional titles were corroborated through the consultation platform of the National Superintendency of Higher University Education (SUNEDU).

After the search, review, and refinement process of the identified records, profiles that did not correspond to Medical Technology professionals or that lacked sufficient information for confirmation were excluded. Finally, a study population of 105 Medical Technologists registered as researchers in RENACYT was obtained.

A coded database without personal identifiers was created, incorporating variables related to the academic, professional, and scientific characteristics of the Medical Technologists registered in RENACYT. These variables allowed for the characterization of the academic, professional, and scientific distribution of Medical Technologists participating in research within the national science, technology, and innovation system. Data Collection Procedure

Information was obtained through individual review of the profiles available in CTI Vitae and RENACYT. For each identified researcher, data related to academic background, professional specialty, institutional affiliation, active status, and researcher category were recorded.

The collected information was organized into a structured database and subsequently reviewed to verify the consistency of the records. The data was anonymized before statistical analysis, preventing the inclusion of information that could individually identify participants.

Statistical Analysis

The database was initially organized in Microsoft Excel 2016® (Microsoft Corporation, Redmond, WA, USA) and subsequently exported for statistical analysis using IBM SPSS Statistics version 30.0® (IBM Corp., Armonk, NY, USA). A descriptive analysis of the characteristics of the Medical Technologists registered in RENACYT was performed. Categorical variables were expressed using absolute and relative frequencies. To assess associations between categorical variables,

Pearson's chi-square test or Fisher's exact test was used, as appropriate.

Ethical considerations

The study used secondary data from public records managed by CONCYTEC and SUNEDU. Because no direct contact was made with participants and no personal identifiable information was used, informed consent was not required. Data handling was conducted in accordance with the principles of confidentiality, scientific integrity, and responsible use of data for research purposes.

Results

As of April 23, 2026, the Peruvian College of Medical Technologists registered 23,200 professionals with current licenses. Through a search and verification of records in the National Registry of Science, Technology, and Technological Innovation (RENACYT), 105 (0.5%) Medical Technologists registered as researchers were identified, comprising the population analyzed in this study.

Table 1. Academic and professional profile of Medical Technologists registered in RENACYT, Peru (N=105)

Characteristic		n (%)
Sex		
	Female	37 (35,2)
	Male	68 (64,8)
Master's Degree		
	No	61 (58,1)
	Yes	44 (41,9)
Doctoral Degree		
	No	64 (61)
	Yes	41 (39)
Second Professional Specialization		
	No	85 (81)
	Yes	20 (19)
Employee's Institution according to CTI Vitae		
	University	67 (63,7)
	Health Institution	19 (18,1)
	Research Institute	17 (16,2)
	Other	2 (2,0)

Among the Medical Technologists registered in RENACYT, academic and professional characteristics related to gender, postgraduate training, second specialization, and employment institution were described, revealing a greater presence of male professionals and those affiliated with university institutions (Table 1).

Regarding the scientific and professional characteristics of the Medical Technologists registered in RENACYT, the researcher category, professional area, activity status, and region of the Peruvian College of Medical Technologists were described. The largest representation corresponded to researchers classified in RENACYT category VII, predominantly from the professional areas of Clinical Laboratory and Anatomical Pathology; likewise, most were active and belonged to Region I of the CTMP (Table 2).

Table 2. Scientific and professional characteristics of Medical Technologists registered in RENACYT, Peru (N=105)

Characteristic	n (%)
Researcher Category according to RENACYT	
Distinguished Researcher	6 (5,7)
Level I	2 (1,9)
Level II	8 (7,6)
Level III	13 (12,4)
Level IV	12 11,4)
Level V	9 (8,6)
Level VI	12 (11,4)
Level VII	43 (41)
Medical Technology specialty	
Clinical Laboratory	75 (71,3)
Physical Therapy and Rehabilitation	19 (18,1)
Radiology	6 (5,7)
Occupational Therapy	3 (2,9)
Speech Therapy	1 (1,0)
Optometry	1 (1,0)
Activity Status as of June 8, 2026	
Active	93 (88,6)
Expired	12 (11,4)
Registered in RENACYT by CTMP Region*	
I	98 (93,2)
II	3 (2,9)
IV	2 (1,9)
VIII	1 (1,0)
XI	1 (1,0)

* Medical Technological College of Peru, Y: Lima, Callao and Ica; II: Lambayeque, Amazonas, Cajamarca and San Martin; IV: Junín, Huancavelica and Ayacucho; VIII: Loreto; XI: Tacna and Moquegua

Table 3. Bivariate analysis of the academic and professional characteristics of Medical Technologists according to sex and grouped category of the RENACYT researcher (N=105)

Characteristic	Male n (%)	Female n (%)	Valor p	Group 1 n (%)	Group 2 n (%)	Valor p
Master's Degree						
No	24(64,9)	37(54,4)	0,300	18(62,1)	43(56,6)	0,610*
Yes	13(35,1)	31(45,6)		11(37,9)	33(43,4)	
Doctoral Degree						
No	22(59,5)	42(61,8)	0,817	18(62,1)	46(60,5)	0,885*
Yes	15(40,5)	26(38,2)		11(37,9)	30(39,5)	
Works at a University						
No	16(43,2)	22(32,4)	0,267	11(37,9)	27(35,5)	0,819*
Yes	21(56,8)	45(67,6)		18(62,1)	49(64,5)	
Second Specialization						
No	29(78,4)	56(82,4)	0,620	23(79,3)	62(81,6)	0,791*
Yes	8(21,6)	12(17,6)		6(20,7)	14(18,4)	
Activity Status						
Inactive	5(13,5)	7(10,3)	0,620	12(41,4)	0(0)	0,000**
Active	32(86,5)	61(89,7)		17(58,6)	76(100)	

Group 1: Distinguished, Levels I, II, and III. Group 2: Levels IV, V, VI, and VII.
*Pearson's Chi-squared test **Fischer's Exact Test

The bivariate analysis of the academic and professional characteristics of the Medical Technologists registered in RENACYT showed no statistically significant differences by sex in relation to master's degree (p=0.300), doctoral degree (p=0.817), university employment (p=0.267), second specialty (p=0.620), or active status (p=0.620). Likewise, when comparing by the researcher's RENACYT category, no significant differences were found in master's degree (p=0.610), doctoral degree (p=0.885), university employment (p=0.819), or second specialty (p=0.791). However, the activity status showed a statistically significant association with the grouped category of the RENACYT researcher (Fisher's exact test, p<0.001), with differences observed in the distribution of active and expired researchers between both classification groups (Table 3)

Discussion

This study identified 105 Medical Technologists registered as RENACYT researchers among the 23,200 qualified professionals in Peru, representing approximately 0.45% of the total. This participation should be interpreted within the national research context, where there are approximately 14,560 researchers for a Peruvian population of nearly 34 million inhabitants, equivalent to around 428 researchers per million inhabitants. Although this indicator allows for an assessment of national scientific capacity, it remains lower than that observed in countries with more consolidated scientific systems. According to international data, there are significant differences in the availability of researchers per million inhabitants, with higher values in higher-income countries due to greater levels of investment in research and development (R&D), scientific infrastructure, and human capital development.[11,17-19]

The proportion of Medical Technologists working as researchers is lower compared to other health professionals with a longer history of involvement in research. Among medical researchers in Peru, a study identified 723 professionals registered with RENACYT, representing 10.5% of all researchers and approximately 0.75% of registered physicians.[20] Similarly, in an analysis conducted using the former "Monge Medrano" classification, physicians represented 26.91% (190/706) of the researchers evaluated.[21] These differences demonstrate that integration into the scientific

system is not uniform across health professions.

Regarding academic qualifications, the Medical Technologists registered with RENACYT included professionals with postgraduate studies; 41.9% (44/105) held a master's degree and 39.0% (41/105) a doctoral degree. However, these proportions were lower compared to research groups in the medical and health sciences with more extensive scientific experience. Among researchers evaluated under the aforementioned classification, 80.3% held a master's degree, 71.2% a doctorate, and 84% were university professors.[21] Similarly, Mayta-Tristán et al. found that, of 1,848 individuals with doctoral degrees in Peru, only 262 (14.2%) belonged to the medical and health sciences, and approximately a quarter of them had research activity recognized through REGINA or indexed scientific publications.[22] Likewise, the Bicentennial Plan identified that a limited proportion of professionals with doctoral degrees in medical and health sciences engaged in research activities, demonstrating that advanced academic training needs to be complemented by research opportunities and scientific output.[23] These results show that attaining higher academic degrees is an important, but not sufficient, component for becoming a recognized researcher.

Regarding gender, the present study found greater male participation among Medical Technologists registered with RENACYT. This result coincides with that reported by researchers in the medical and health sciences, where 65.3% were male.[21] However, female participation in scientific research varies by region and discipline.[24] International data indicate that women represent approximately 31.4% of researchers worldwide, while in Latin America and the Caribbean this proportion reaches nearly 45%.[19] In the present study, although there was a higher proportion of male researchers, no statistically significant differences were found by gender in the academic and professional characteristics evaluated.

Regarding the professional area, Medical Technologists registered with RENACYT were primarily concentrated in Clinical Laboratory and Anatomical Pathology (71.3%), followed by Physical Therapy and Rehabilitation (18.1%) and Radiology (5.7%). Currently, there are no national studies describing the distribution of researchers specifically by area of Medical Technology, so these results constitute a first approximation for this profession. However, the greater presence of the Clinical Laboratory area may be related to its proximity to biomedical and diagnostic research. In Peru, medical sciences represent approximately 31.2% of national scientific output, constituting one of the areas with the highest research activity.[13] Likewise, a bibliometric analysis of scientific publications in health in Latin America showed that Brazil accounted for 58.55% of regional production, followed by Cuba (10.52%) and Colombia (8.30%), highlighting significant differences in scientific capacity between countries.[12]

The employment institution was another relevant aspect of the identified profile. In this study, 67 (63.7%) Medical Technologists working as researchers were employed at universities, while 19 (18.1%) worked at healthcare institutions and 17 (16.2%) at research institutes. This university predominance coincides with the role of universities as the primary spaces for research training, scientific production, and the development of academic groups. Bibliometric studies conducted at Peruvian universities using Scopus analyzed 2,927 publications between 2014 and 2023, finding that institutional policies, scientific collaboration, and research strategies influence scientific production and visibility, although differences in productivity and impact persist among institutions.[25] Similarly, among physician researchers in the United States, it was observed that 24% of those with academic affiliations participated in research, compared to lower participation in other groups, highlighting the importance of the university environment for developing scientific activity.[26] Regarding the RENACYT classification, Medical Technologists showed a greater concentration in lower categories, primarily at level VII

(41%), followed by levels III (12.4%), IV (11.4%), and VI (11.4%). In contrast, higher levels were less represented, such as Distinguished Researcher (5.7%) and Level I (1.9%). This distribution reflects a research population in the process of consolidation. Previous studies have shown that factors such as tenure, H-index, thesis supervision, and scientific productivity are related to higher research classification levels.[27] Therefore, the transition to higher categories requires the progressive accumulation of scientific output, academic leadership, and continuous participation in research.

Early training in researchers is also a relevant aspect for expanding the scientific participation of this profession. Among Peruvian university students, a study reported that only 13 were recognized as RENACYT (National Registry of Science, Technology and Innovation) researchers, of whom 3 (23.1%) were in the health sciences, although some had publications indexed in databases such as Scopus and SciELO.[28] These results highlight the importance of strengthening a research culture from the early stages of professional training.

Finally, the results of this study should be understood within the Peruvian and Latin American scientific landscape, characterized by differences in investment, number of researchers, and knowledge generation capacity. Global investment in R&D increased from 1.71% of GDP in 2015 to 1.92% in 2023, but with marked differences between regions; Europe and North America reached approximately 2.55% of GDP, while other regions show considerably lower values.[19] In this context, strengthening the participation of Medical Technologists in research requires increasing opportunities for scientific training, mentorship programs, project funding, and collaboration between universities and health institutions.

This study has some limitations. First, the identification of research Medical Technologists was carried out using the official registries of RENACYT and CONCYTEC's CTI Vitae. Therefore, the results represent professionals officially recognized in this system, and the existence of Medical Technologists who conduct scientific research but are not registered in RENACYT cannot be ruled out. Furthermore, by using information from secondary registries, the availability and updating of some data depended on the information recorded by the researchers themselves on the consulted platforms. Finally, due to the cross-sectional design of the study, the results allow us to describe the academic, professional, and scientific characteristics of the registered Medical Technologists, as well as explore associations between variables; however, they do not allow us to establish causal relationships.

The Medical Technologists registered in RENACYT represent a small group within the Peruvian scientific system. Most belong to the area of clinical laboratory and anatomical pathology, work in universities, and are in entry-level categories, demonstrating a research trajectory still in development. These results highlight the need to strengthen research training, postgraduate studies, and scientific development opportunities for Medical Technologists.

Conclusion

This study provides the first nationwide characterization of the scientific profile of Medical Technologists registered in RENACYT. These professionals represent a small group within the Peruvian scientific system, predominantly working in clinical laboratory science and anatomical pathology, employed at universities, and concentrated in the registry's entry-level categories. The findings highlight the need to strengthen their research training, postgraduate education, and opportunities for scientific development.

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Research article

Age-Related Associations Between Red Blood Cell Indices and Hemoglobin A1c in Pediatric and Adult Patients: A Retrospective Study

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Objective: **Hemoglobin A1c (HbA1c) is the primary laboratory marker for assessing long-term glycemic status, but its interpretation may be influenced by erythrocyte physiology. This study evaluated the association between routinely reported red blood cell (RBC) indices and HbA1c in pediatric and adult diabetic and non-diabetic patients.**

Methods: **A retrospective observational study was conducted using electronic medical record and laboratory information system data from the University of Texas Medical Branch between 2010 and 2025. The pediatric cohort included 565 encounters, and the adult cohort included 14,790 encounters. Hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW) were evaluated using correlation, group comparison, and multivariable regression analyses.**

Results: **Significant associations between HbA1c and multiple RBC indices were identified in both pediatric and adult populations, although the pattern of associations differed by age. Pediatric patients demonstrated predominantly hemoglobin-related associations, whereas adult patients showed stronger relationships involving erythrocyte morphology. Adult diabetic patients also demonstrated significant differences in several RBC indices compared with matched non-diabetic controls. However, glycemic control was not independently associated with the overall presence of abnormal RBC indices after multivariable adjustment.**

Conclusion: **Routine CBC-derived RBC indices demonstrated age-related associations with HbA1c across pediatric and adult populations. Although these indices should not be considered independent markers of diabetes or glycemic control, they may provide additional laboratory context when interpreting HbA1c results.**

Keywords: Glycated Hemoglobin; Erythrocyte Indices; Diabetes Mellitus; Age Factors; Retrospective Studies.

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Introduction

Hemoglobin A1c (HbA1c) is the primary laboratory marker for assessing long-term glycemic status and plays a central role in the diagnosis and management of diabetes mellitus. Because HbA1c reflects the nonenzymatic glycation of hemoglobin throughout the lifespan of circulating erythrocytes, its interpretation depends not only on glucose exposure but also on red blood cell (RBC) physiology, lifespan, and turnover.[1–4]

Conditions that alter erythrocyte survival or morphology may therefore influence HbA1c independent of true glycemic status, potentially affecting clinical interpretation.[2–4] Growing evidence suggests that chronic hyperglycemia is associated with oxidative stress, membrane glycation, altered erythrocyte deformability, and inflammatory changes that may affect routinely reported CBC-derived RBC indices, including hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW).[5–9] Because these parameters are generated as part of routine complete blood count testing, they have attracted increasing interest as potential adjunctive markers that may provide additional context for HbA1c interpretation without requiring additional laboratory testing.[5,6]

Previous studies have reported associations between individual RBC indices and diabetes or HbA1c, particularly involving RDW, MCV, and MCH.[5,7–9] However, published findings remain inconsistent with respect to the magnitude and direction of these relationships, likely reflecting differences in study populations, diabetes subtype, disease duration, and underlying hematologic variability. In addition, many investigations have focused exclusively on either pediatric or adult populations or evaluated isolated RBC parameters rather than broader hematologic patterns, limiting direct comparison across age groups.[5,8,10] Because erythrocyte physiology differs throughout the lifespan, the relationship between HbA1c and RBC indices may also differ between pediatric and adult patients. Clarifying these age-related patterns may improve understanding of the biologic factors influencing HbA1c interpretation and provide additional insight into routinely available hematologic parameters encountered in clinical laboratory practice. The objective of this study was to evaluate the association between routinely reported RBC indices and HbA1c in pediatric and adult diabetic and non-diabetic patients using a large retrospective cohort from an academic health system. We further sought to determine whether these associations differed between age groups and to assess the potential interpretive value of CBC-derived RBC indices in the evaluation of HbA1c.

Materials and Methods

Study Design and Setting

A retrospective observational study was conducted using electronic medical record (Epic) and laboratory information system (LIS) data from the University of Texas Medical Branch (UTMB), an academic health system serving Southeast Texas. Clinical encounters between January 1, 2010, and December 31, 2025, were eligible for inclusion if a complete blood count (CBC) and hemoglobin A1c (HbA1c) were performed on the same day. The unit of analysis was the clinical encounter to preserve temporal alignment between hematologic and glycemic measurements. Pediatric (≤18 years) and adult (>18 years) cohorts were analyzed separately because of known physiologic differences in erythrocyte parameters.

Data Collection

Following Institutional Review Board (IRB) approval (26-0066.002), clinical and laboratory data were collected from the Epic electronic medical record and laboratory information system (LIS). Laboratory variables included complete blood count (CBC) parameters consisting of hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and hemoglobin A1c

(HbA1c). Demographic and clinical variables, including age, biological sex, body mass index (BMI), and diabetes status, were also collected. CBC and HbA1c results obtained during the same clinical encounter were paired to ensure temporal alignment between hematologic and glycemic parameters.

Study Population

Diabetic encounters were identified using ICD-10 codes for type 1 diabetes (E10.x), type 2 diabetes (E11.x), and other specified diabetes mellitus (E13.x). Encounters without diabetes-related ICD-10 codes served as non-diabetic controls. Adult diabetic and non-diabetic encounters were age- and sex-matched using a randomly selected sample, whereas all eligible pediatric encounters were included because of the smaller available cohort. Among pediatric diabetic encounters, 206 (72.0%) were classified as type 1 diabetes, whereas among adult diabetic encounters, 5,698 (77.0%) were classified as type 2 diabetes. Encounters associated with conditions known to affect erythrocyte physiology or HbA1c interpretation were excluded, including hemoglobinopathies, iron deficiency, vitamin B12 deficiency, folate deficiency, hemolytic anemia, bone marrow disorders, hematologic malignancies, chronic kidney disease, chronic liver disease, pregnancy or the postpartum period, blood transfusion within the preceding 3 months, active infection or inflammation, ICU encounters, and hemolyzed, incomplete, or otherwise invalid laboratory results.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 28 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as frequencies and percentages.

Among pediatric diabetic encounters, Spearman rank correlation was used to evaluate associations between HbA1c and individual RBC indices. Separate multivariable linear regression models were then performed to evaluate the association of each RBC index with HbA1c after adjustment for age, biological sex, and BMI. Regression analyses were performed using complete-case analysis; encounters with missing values for variables included in a given model were excluded from that analysis.

Differences between pediatric diabetic and non-diabetic groups were evaluated using independent-samples *t*-tests.

Adult diabetic encounters were stratified according to HbA1c <7% or ≥7%. Differences in the prevalence of abnormal RBC indices between glycemic control groups were assessed using x^2 tests, and multivariable logistic regression was performed to evaluate factors associated with the presence of at least one abnormal RBC index after adjustment for age, BMI, biological sex, and race. Abnormal RBC indices were classified using the institutional adult reference intervals in effect at the University of Texas Medical Branch during the study period. Hemoglobin and hematocrit abnormalities were determined using sex-specific reference intervals. An encounter was classified as having an abnormal RBC index if at least one evaluated RBC parameter fell below or above its corresponding reference interval. Adult reference intervals were as follows: hemoglobin, 14.0–17.5 g/dL (male) and 12.3–15.3 g/dL (female); hematocrit, 41.5–50.4% (male) and 35.9–44.6% (female); MCV, 80.0–96.1 fL; MCH, 27.5–33.2 pg; MCHC, 33.4–35.5 g/dL; and RDW, 11.6–14.6%.

Adult diabetic and non-diabetic groups were compared using independent-samples *t* tests for continuous variables and x^2 tests for categorical variables. Additional Spearman correlation analyses evaluated associations between HbA1c and RBC indices within each group. Statistical significance was defined as a two-sided $p < .05$.

Ethics

The study was approved by the University of Texas Medical Branch Institutional Review Board (IRB No. 26-0066.002), which granted a waiver of informed consent because of the retrospective design and minimal risk to

participants. All data were de-identified before analysis. The study was conducted in accordance with applicable institutional and federal requirements for human-subject research and the Health Insurance Portability and Accountability Act (HIPAA).

Results

Study Population

A total of 15,355 clinical encounters met the study eligibility criteria, including 565 pediatric encounters (286 diabetic and 279 non-diabetic) and 14,790 adult encounters (7,399 diabetic and 7,391 non-diabetic). All encounters included same-day complete blood count (CBC) and hemoglobin A1c (HbA1c) measurements following application of the predefined inclusion and exclusion criteria (Figure 1).

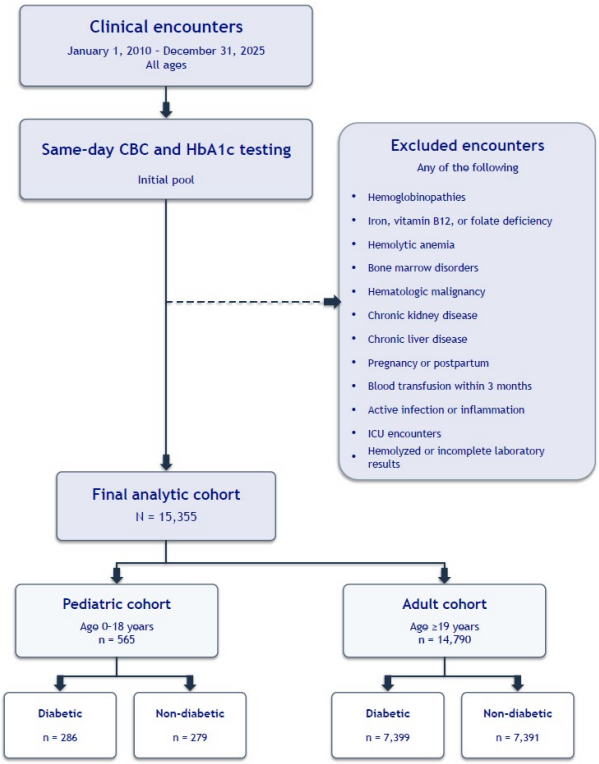


Figure 1. Study selection flow diagram.
Abbreviations: CBC, complete blood count; HbA1c, hemoglobin A1c; ICU, intensive care unit.

Baseline demographic and clinical characteristics are presented in Table 1. Pediatric diabetic and non-diabetic groups were matched on age and sex, with no significant differences in mean age, sex distribution, race, or body mass index (BMI). In contrast, while adult diabetic and non-diabetic groups were also matched on age and sex, diabetic adults had a significantly higher mean BMI and differed in racial distribution compared with non-diabetic adults ($p < .001$ for both). As expected, mean HbA1c was significantly higher in diabetic than non-diabetic patients in both pediatric and adult cohorts (Table 1).

Pediatric diabetes consisted predominantly of type 1 diabetes (206/286, 72.0%), whereas the adult diabetic cohort was primarily composed of patients with type 2 diabetes (5,698/7,399, 77.0%).

Compared with non-diabetic pediatric patients, diabetic pediatric patients demonstrated significantly higher Hgb, Hct, and MCHC values and significantly lower MCV, whereas MCH and RDW did not differ significantly (Table 2).

Among diabetic pediatric patients, HbA1c demonstrated the strongest positive correlation with Hgb ($\rho = 0.379$, $p < .001$), followed by Hct ($\rho = 0.295$, $p < .001$) and MCHC ($\rho = 0.267$, $p < .001$). MCH showed a weak positive correlation with HbA1c ($\rho = 0.138$, $p = .020$), whereas no significant correlations were observed for MCV or RDW (Table 2).

In multivariable linear regression adjusting for age, sex, and BMI, Hgb remained the strongest independently associated parameter with HbA1c (standardized $\beta = 0.375$, $p < .001$), followed by Hct ($\beta = 0.307$, $p < .001$) and MCHC ($\beta = 0.184$, $p = .002$). RDW demonstrated a small positive independent association with HbA1c ($\beta = 0.175$, $p = .003$), whereas MCV and MCH were not independently associated with HbA1c.

Compared with non-diabetic adults, diabetic patients demonstrated significantly lower Hgb, Hct, MCV, and MCH values and significantly higher RDW, whereas MCHC did not differ significantly between groups (Table 3).

Among diabetic adults, HbA1c demonstrated the strongest inverse correlation with MCV ($\rho = -0.250$, $p < .001$), followed by MCH ($\rho = -0.186$, $p < .001$). Weak positive correlations were observed for Hgb ($\rho = 0.121$, $p < .001$),

Table 1. Baseline Characteristics of the Study Population.

Pediatric Cohort			
Characteristic	**Diabetic (n = 286)**	**Non-Diabetic (n = 279)**	**p -Value**
Age, years	13.17 ± 4.00	13.24 ± 3.96	0.846
Male, n (%)	139 (48.6)	134 (48.0)	-
Female, n (%)	147 (51.4)	145 (52.0)	
White, n (%)	202 (70.6)	220 (78.9)	
Black, n (%)	75 (26.2)	53 (19.0)	0.078
Other race, n (%)†	9 (3.2)	6 (2.2)	
BMI, kg/m²	27.40 ± 10.54	27.68 ± 7.44	0.725
HbA1c, %	9.26 ± 2.40	5.42 ± 0.43	**<.001**
Adult Cohort			
Characteristic	**Diabetic (n = 7,399)**	**Non-Diabetic (n = 7,391)**	**p -Value**
Age, years	58.48 ± 14.59	58.55 ± 14.55	0.785
Male, n (%)	3,757 (50.8)	3,746 (50.7)	-
Female, n (%)	3,642 (49.2)	3,645 (49.3)	
White, n (%)	5,891 (79.6)	6,092 (82.4)	
Black, n (%)	1,192 (16.1)	883 (11.9)	<.001
Other race, n (%)†	316 (4.3)	416 (5.6)	
BMI, kg/m²	33.89 ± 8.45	31.06 ± 7.67	<.001
HbA1c, %	8.43 ± 2.17	5.52 ± 0.39	<.001

Abbreviations: *BMI, body mass index; HbA1c, hemoglobin A1c.*

†Other race includes Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander (adults only), multiracial/unknown, and other infrequently represented racial categories.

Table 2. Comparison of Red Blood Cell Indices Between Pediatric Diabetic and Non-Diabetic Patients and Their Association with HbA1c.

RBC Index	**Diabetic (n = 286) Mean ± SD**	**Non-Diabetic (n = 279) Mean ± SD**	**p -Value†**	**Spearman's ρ‡**	**p -Value**
Hemoglobin (g/dL)	14.30 ± 1.80	13.57 ± 1.46	<.001	0.379	<.001
Hematocrit (%)	42.37 ± 5.05	41.01 ± 3.86	<.001	0.295	<.001
Mean corpuscular volume (fL)	83.29 ± 5.03	84.43 ± 5.48	0.010	−0.020	0.732
Mean corpuscular hemoglobin (pg)	28.07 ± 2.20	27.94 ± 2.19	0.472	0.138	0.020
Mean corpuscular hemoglobin concentration (g/dL)	33.70 ± 1.60	33.07 ± 1.23	<.001	0.267	<.001
Red cell distribution width (%)	13.06 ± 1.16	13.03 ± 1.15	0.768	0.060	0.309

Abbreviations: *HbA1c, hemoglobin A1c. SD, standard deviation.*

† p-values comparing diabetic and non-diabetic pediatric patients were calculated using the independent-samples t-test.

‡ Spearman rank correlation coefficients represent the association between HbA1c and RBC indices among pediatric diabetic patients.

Table 3. Comparison of Red Blood Cell Indices Between Adult Diabetic and Non-Diabetic Patients and Their Association with HbA1c.

RBC Index	Diabetic (n = 7,399) Mean ± SD	Non-Diabetic (n = 7,391) Mean ± SD	p-Value†	Spearman's ρ (Diabetic)‡	p-Value	Spearman's ρ (Non-Diabetic) ‡	p-Value
Hemoglobin (g/dL)	13.59 ± 1.92	13.66 ± 1.86	0.026	0.121	<.001	−0.052	<.001
Hematocrit (%)	41.09 ± 5.32	41.26 ± 5.18	0.039	0.105	<.001	−0.017	0.148
Mean corpuscular volume (fL)	88.58 ± 5.73	90.22 ± 5.49	<.001	−0.250	<.001	−0.178	<.001
Mean corpuscular hemoglobin (pg)	29.30 ± 2.33	29.86 ± 2.26	<.001	−0.186	<.001	−0.213	<.001
Mean corpuscular hemoglobin concentration (g/dL)	33.06 ± 1.40	33.08 ± 1.28	0.343	0.106	<.001	−0.112	<.001
Red cell distribution width (%)	13.51 ± 1.51	13.45 ± 1.50	<.001	−0.115	<.001	0.229	<.001

Abbreviations: *HbA1c, hemoglobin A1c; SD, standard deviation.*

† p-values comparing diabetic and non-diabetic adult patients were calculated using the independent-samples t-test.

‡ Spearman's rank correlation coefficients (ρ) represent the association between HbA1c and each RBC index within diabetic and non-diabetic adult cohorts separately.

Hct (ρ = 0.105, p < .001), and MCHC (ρ = 0.106, p < .001), whereas RDW demonstrated a weak inverse correlation with HbA1c (ρ = −0.115, p < .001). Among non-diabetic adults, HbA1c demonstrated weak inverse correlations with MCV (ρ = −0.178, p < .001), MCH (ρ = −0.213, p < .001), and MCHC (ρ = −0.112, p < .001), whereas RDW demonstrated a weak positive correlation (ρ = 0.229, p < .001). No significant correlation was observed between HbA1c and Hct (ρ = −0.017, p = .148), while the inverse correlation with Hgb was statistically significant but very weak (ρ = −0.052, p < .001). These findings suggest that the relationships between HbA1c and RBC indices differ according to diabetic status (Table 3).

Among adult diabetic patients, the prevalence of at least one abnormal RBC index did not differ significantly between those with controlled and uncontrolled glycemia (51.1% versus 50.6%, respectively; p = .650). Patients with uncontrolled glycemia had a higher prevalence of abnormal Hct than those with controlled glycemia (29.2% versus 27.1%, p = .040). In contrast, abnormal MCHC (22.5% versus 18.8%, p < .001) and RDW (20.7% versus 14.8%, p < .001) were more prevalent among patients with controlled glycemia. No significant differences were observed for abnormal Hgb, MCH, or MCV.

In multivariable logistic regression adjusting for age, BMI, sex, and race, glycemic control was not independently associated with the presence of at least one abnormal RBC index (OR 1.07, 95% CI 0.97–1.18, p = .161). Increasing age, higher BMI, male sex, and Black

race remained independently associated with abnormal RBC indices.

Discussion

Principal Findings

Significant associations were identified between HbA1c and multiple routinely reported RBC indices across both pediatric and adult populations. However, the pattern of these associations differed by age. Pediatric patients demonstrated predominantly hemoglobin-related associations, with Hgb, Hct, and MCHC showing the strongest relationships with HbA1c, whereas adult patients demonstrated stronger associations involving erythrocyte morphology, particularly MCV, MCH, and RDW. These findings extend previous evidence that erythrocyte characteristics influence HbA1c interpretation and support the concept that the relationship between HbA1c and erythrocyte physiology varies across different stages of life. [1–4]

Although many of the observed differences were statistically significant, most were modest in magnitude and remained within their respective reference intervals. Accordingly, these RBC indices should not be interpreted as independent diagnostic markers of diabetes or glycemic control. Rather, they may serve as complementary laboratory parameters that provide additional context when interpreting HbA1c, particularly when HbA1c appears discordant with the clinical presentation or other measures of glycemia.[1–3,6] Furthermore, these findings reinforce the importance of integrating routinely available hematologic parameters into the broader interpretation of laboratory results rather than evaluating HbA1c in isolation. [6]

Pediatric Findings

The pediatric cohort demonstrated a distinct pattern in which HbA1c was most strongly associated with hemoglobin-related parameters. Hgb, Hct, and MCHC were significantly higher in diabetic than non-diabetic patients and remained independently associated with HbA1c after adjustment for age, sex, and BMI. In contrast, MCV and RDW were not independently associated with HbA1c. This pattern differs from that observed in many adult studies, in which alterations in erythrocyte morphology, particularly MCV and RDW, have shown stronger associations with glycemic status.[5,8,14]

One plausible explanation is the predominance of type 1 diabetes within the pediatric cohort. Children with newly diagnosed or poorly controlled type 1 diabetes frequently present with marked hyperglycemia accompanied by osmotic diuresis, resulting in relative intravascular volume depletion before treatment. This physiologic response may contribute to the higher Hgb and Hct values observed in our study. However, hydration status, timing relative to diabetes diagnosis, and disease duration were not available in this retrospective dataset, so this proposed mechanism could not be directly evaluated. Tihić-Kapidžić et al. likewise reported significant differences in hematologic indices between children with type 1 diabetes and healthy controls, supporting the concept that diabetes-related hematologic alterations are detectable early in the disease course.[10] In addition, Herance et al. demonstrated that type 1 diabetes is associated with metabolic and lipidomic alterations in erythrocytes, providing further evidence that hyperglycemia may influence erythrocyte physiology beyond glucose metabolism alone.[12]

Interestingly, MCV and RDW were not independently associated with HbA1c after adjustment, suggesting that structural alterations in erythrocytes may be less pronounced during pediatric diabetes than in adulthood. This may reflect shorter disease duration and reduced cumulative exposure to chronic hyperglycemia compared with adult populations. Similar observations have been reported by Salami et al., who demonstrated associations between RBC-related parameters and declining ß-cell function in children at risk for type 1 diabetes, suggesting that hematologic alterations occur early but may differ from those observed in established adult

diabetes.[13] Collectively, these findings suggest that the hematologic response to diabetes evolves over time and emphasize the importance of considering patient age when interpreting relationships between HbA1c and routine RBC indices.

Adult Findings

In contrast to the pediatric cohort, adult patients demonstrated a pattern characterized predominantly by alterations in erythrocyte morphology. Diabetic adults had significantly lower MCV and MCH values and higher RDW compared with non-diabetic adults, with MCV demonstrating the strongest inverse association with HbA1c. These findings are consistent with those reported by Alamri et al., who observed significantly lower MCV and MCH among adults with diabetes, and by Asmamaw et al., who demonstrated significant associations between multiple RBC indices and long-term glycemic control.[5,8] More recently, Meshesha et al. further reported that several RBC indices were associated with glycemic control and diabetes-related complications, supportting the growing evidence that chronic hyperglycemia is accompanied by measurable alterations in erythrocyte morphology.[13]

Several biologic mechanisms may explain these findings. Chronic hyperglycemia promotes nonenzymatic glycation of erythrocyte membrane proteins, increases oxidative stress, and contributes to chronic low-grade inflammation, all of which impair membrane stability, reduce erythrocyte deformability, and alter erythrocyte survival.[3,9,14,15] Alterations in erythrocyte lifespan may further influence both RBC indices and HbA1c interpretation, as demonstrated by Cohen et al. and Xu et al., who highlighted the importance of erythrocyte turnover in determining HbA1c values independent of glucose concentration.[2,4] The persistence of the observed associations following multivariable adjustment in the present study further supports the relationship between chronic glycemic exposure and erythrocyte morphology.

An additional finding of interest was the differing relationship between RDW and HbA1c according to diabetic status. Although RDW was significantly higher in diabetic than non-diabetic adults overall, HbA1c demonstrated a weak inverse correlation with RDW within the diabetic cohort, whereas a positive correlation was observed among non-diabetic adults. This finding differs from several previous studies reporting positive associations between RDW and glycemic measures.[7,9] One possible explanation is the rigorous exclusion criteria applied in the present study. By excluding patients with iron deficiency, chronic kidney disease, active inflammation, malignancy, hemoglobinopathies, and other conditions known to independently influence RDW, the present analysis may have reduced important sources of confounding that contributed to the positive associations reported previously. Nevertheless, the underlying mechanisms remain uncertain and warrant prospective investigation incorporating biomarkers of iron metabolism, inflammation, reticulocyte production, and erythrocyte lifespan.

Age-Related Differences in RBC–HbA1c Associations

A major finding of this study was the identification of distinct age-related patterns in the relationship between HbA1c and routinely reported RBC indices. In pediatric patients, HbA1c was most strongly associated with hemoglobin-related parameters, whereas in adults, the strongest associations involved erythrocyte morphology, particularly MCV, MCH, and RDW. Previous studies have largely evaluated pediatric or adult populations independently, making direct comparisons across age groups difficult.[5,8,10,11,13] By evaluating both cohorts using the same study design, laboratory parameters, and analytical approach, the present study provides a more comprehensive assessment of how the relationship between HbA1c and RBC indices differs across the lifespan.

Several factors may contribute to these age-related differences. The predominance of type 1 diabetes in the pediatric cohort and type 2 diabetes in the adult cohort likely

reflects differences in disease pathophysiology, duration of hyperglycemia, and cumulative metabolic exposure. Adults generally experience longer exposure to chronic hyperglycemia, oxidative stress, and inflammation, all of which contribute to progressive erythrocyte membrane damage and altered cell survival.[3,4,14,15] In contrast, pediatric patients may exhibit earlier physiologic responses to hyperglycemia before substantial structural remodeling of erythrocytes has occurred. These age-related differences may explain why hemoglobin-related parameters predominated in the pediatric cohort, whereas morphology-related indices were more strongly associated with HbA1c in adults.

Our findings also provide a possible explanation for the variability reported across previous studies evaluating RBC indices in diabetes. Differences in patient age, diabetes type, disease duration, study populations, and exclusion criteria may contribute to the inconsistent associations reported between HbA1c and individual RBC indices. By examining both pediatric and adult cohorts within a single analytical framework while applying rigorous exclusion criteria to minimize hematologic confounders, the present study demonstrates that the relationship between HbA1c and erythrocyte indices is not uniform but varies according to patient characteristics and disease context. These findings underscore the importance of considering age when interpreting the interaction between erythrocyte physiology and HbA1c.

Clinical Significance

The findings of this study should be interpreted within the context of routine clinical laboratory practice. Although several RBC indices differed significantly between diabetic and non-diabetic patients and demonstrated significant associations with HbA1c, most of these differences were modest in magnitude and remained within established reference intervals. Consequently, these parameters should not be considered independent diagnostic markers of diabetes or replacements for HbA1c. Rather, they should be viewed as complementary laboratory findings that may provide additional context during interpretation of HbA1c results.[1,3,6]

These findings are particularly relevant when HbA1c appears discordant with the clinical presentation or other measures of glycemia. Current laboratory guidelines emphasize that HbA1c reflects not only glycemic exposure but also erythrocyte biology, including factors affecting erythrocyte lifespan and turnover.[1–4] Routine CBC parameters are inexpensive, widely available, and already incorporated into standard clinical practice. While they should not be used in isolation to guide diabetes diagnosis or management, awareness of age-related hematologic patterns may assist laboratorians and clinicians in recognizing situations in which erythrocyte physiology could influence HbA1c interpretation.

Strengths and Limitations

This study has several strengths. It included a large cohort of more than 15,000 pediatric and adult clinical encounters evaluated over a 16-year period using standardized laboratory measurements performed within a single health system. The inclusion of both pediatric and adult populations allowed direct comparison of age-related patterns using a common analytical framework, an approach that has been infrequently reported in the literature. In addition, rigorous exclusion criteria were applied to minimize the influence of conditions known to affect RBC indices or HbA1c interpretation, thereby reducing potential confounding and strengthening the validity of the observed associations.

Several limitations should also be acknowledged. First, the retrospective observational design permits identification of associations but does not establish causality. Second, analyses were performed at the encounter level rather than the patient level; therefore, repeated encounters from the same individual may not have been fully accounted for. Third, important variables that may influence erythrocyte physiology, including

disease duration, diabetes treatment, iron status, reticulocyte count, and direct measures of erythrocyte lifespan, were unavailable. Although extensive exclusion criteria were implemented to reduce confounding, residual confounding from unmeasured factors remains possible. Finally, many of the observed associations, while statistically significant, were modest in magnitude, and most RBC indices remained within their respective reference intervals. Consequently, these findings should be interpreted as complementary to existing approaches for HbA1c interpretation rather than as evidence supporting the independent clinical use of RBC indices.

Conclusion

In conclusion, significant associations were observed between HbA1c and multiple routinely reported RBC indices in both pediatric and adult patients, although the pattern of these associations differed according to age. Pediatric diabetes was characterized predominantly by associations with hemoglobin-related parameters, whereas adult diabetes demonstrated stronger relationships involving erythrocyte morphology, particularly MCV, MCH, and RDW. These findings suggest that the interaction between glycemic control and erythrocyte physiology is age dependent and should be considered when interpreting HbA1c in clinical practice.

Although the observed differences were generally modest and do not support the independent clinical use of RBC indices for diagnosing or monitoring diabetes, routinely available CBC parameters may provide valuable complementary information when HbA1c appears discordant with the clinical presentation or other measures of glycemia. Future prospective studies incorporating longitudinal follow-up and direct measures of erythrocyte lifespan are warranted to further clarify the mechanisms underlying these age-related differences and their potential implications for HbA1c interpretation.

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Data Availability Statement

The data that support the findings of this study are not publicly available because they contain protected health information. Data may be made available from the corresponding author upon reasonable request and with approval from the University of Texas Medical Branch.

Conflict of Interest

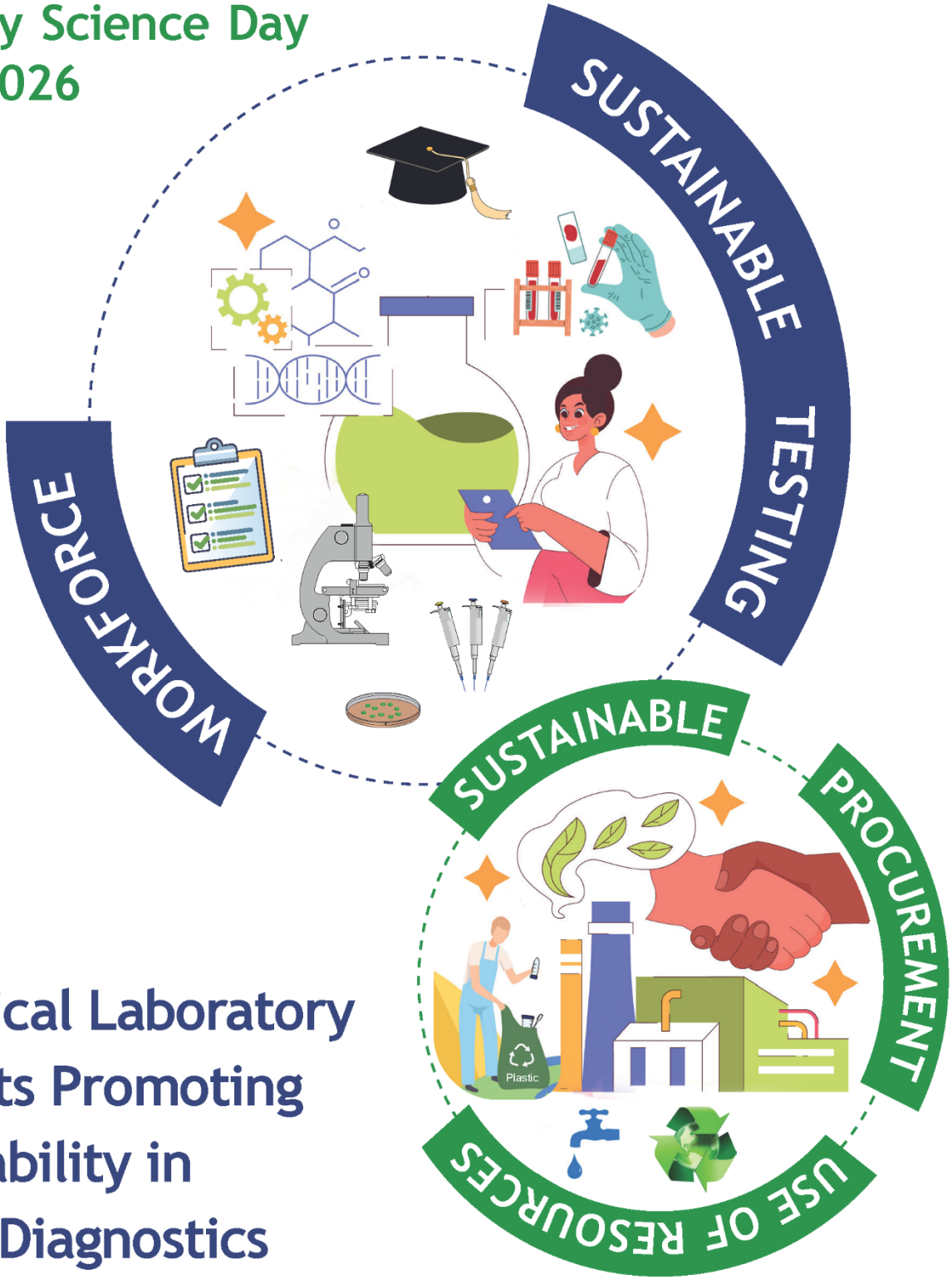
The authors declare that they have no conflicts of interest.

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