ISSN: 2938-6586

Clinical Innovations in Health Research-HJM

VOLUME 3 - NUMBER 1 / January-March 2026 www.clinicalinnovinhealthresearch-hjm.com

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ISSN: 2938-6586

Clinical Innovations in Health Research-HJM

VOLUME 3 - NUMBER 1 / January-March 2026 www.clinicalinnovinhealthresearch-hjm.com

An official scientific journal of the Hospital Juárez de México

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EDITORIAL

Diabetes remission beyond glycemic control: science, environment, and equity

Remisión de la diabetes más allá del control glucémico: ciencia, entorno y equidad

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Type 2 diabetes mellitus represents a rapidly expanding global health burden, driven by demographic changes, accelerated urbanization, and social determinants that extend beyond the clinical sphere[1]. For decades, type 2 diabetes was understood as an inevitably progressive metabolic disease, with management strategies focused primarily on delaying complications rather than altering its natural course. However, accumulating evidence and recent international consensus have proposed an operational definition of "remission," understood as sustained normalization of glycemia below diagnostic thresholds (glycated hemoglobin < 6.5%) for at least 3 months in the absence of glucose-lowering pharmacotherapy[2].

This emerging paradigm compels a reconsideration not only of clinical practice but also of the conceptual framework of the disease. Remission thus ceases to be an exclusively biochemical target and instead raises broader questions regarding therapeutic strategies, healthcare system design, behavioral determinants, and social contexts that shape both disease development and its potential reversibility.

The clinical evidence supporting diabetes remission has expanded substantially over the past decade. Randomized controlled trials such as DiRECT and DIADEM-I, together with data from metabolic surgery, report remission rates ranging from 30% to 80%, depending on the magnitude of weight loss, disease duration, and residual beta-cell function[3-6]. Nevertheless, interpretation of these findings requires methodological caution. Many studies are conducted under highly structured conditions, including intensive caloric restriction, continuous nutritional supervision, behavioral support, and close metabolic monitoring, settings that are difficult to replicate in routine clinical practice, particularly within overburdened public health systems. Moreover, study populations often exclude older adults, individuals with long-standing disease, multimorbidity, or pronounced social vulnerability, groups that constitute a substantial proportion of real-world patients.

Sustainability also raises critical concerns. Relapse is not an exception but an expected outcome when structural support weakens. Consequently, although the biomedical evidence is robust, its generalizability should not be assumed uncritically. Observed success rates reflect not only biological reversibility but also implementation contexts that are difficult to generalize.

Lifestyle modification remains the cornerstone of remission strategies. Substantial weight loss, sustained physical activity, and dietary changes are consistently associated with metabolic improvement. However, framing remission as a direct consequence of individual behavioral change oversimplifies a phenomenon that is deeply conditioned by structural determinants. The capacity to modify behavior is not an isolated decision but a possibility constrained by concrete material and

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Date of reception: 29-12-2025
Date of acceptance: 20-02-2026
DOI: 10.24875/CIHR.M26000018

Available online: 31-03-2026
Clin. Innov. Health Res-HJM. 2026;3(1):1-2
www.clinicalinnovinhealthresearch-hjm.com

social limits. Economic activity, labor demands, chronic stress exposure, food environments, urban infrastructure, and educational opportunities decisively influence the ability to initiate and sustain behavioral change. Expecting homogeneous change without addressing these factors reveals an overly individual-centered model that underestimates the complexity of social realities.

Food systems dominated by ultra-processed products and labor conditions that restrict time and energy for self-care create structurally adverse environments. Healthcare systems themselves may reinforce this asymmetry. Limited consultation time, insufficient multidisciplinary integration, and restricted access to preventive programs reduce the feasibility of intensive remission-oriented interventions. In this context, remission cannot be analyzed solely as a biomedical criterion but rather as a socially conditioned outcome. Structural inequalities shape both the likelihood of achieving remission and the sustainability of metabolic improvements. When material conditions facilitate healthy behaviors, remission is plausible; when they do not, responsibility is implicitly shifted onto the individual, reinforcing pre-existing inequities.

Clinical communication, therefore, requires balance. Presenting remission as broadly attainable without acknowledging its structural constraints may generate unrealistic expectations and implicit guilt. Failure to achieve remission should not be interpreted as a lack of commitment but as a predictable consequence of unequal material conditions. Therapeutic discussions demand transparency regarding benefits, risks, sustainability, and contextual limits. Balancing hope with realism requires recognizing that remission is not merely a metabolic correction, but a process embedded within social structures.

Viewed critically, remission emerges as a multidimensional construct shaped by biological reversibility, behavioral sustainability, healthcare system design, and social organization. Its feasibility depends as much on metabolic physiology as on political environments, food systems, labor conditions, and equitable access to preventive care. Promoting remission as a therapeutic goal requires more than clinical innovation; it demands alignment between medical practice and public policy, investment in preventive infrastructures, and explicit strategies to reduce inequalities.

Ultimately, diabetes remission cannot be understood solely as a metabolic outcome. It is a conditional and contextual process that reflects the extent to which science, healthcare systems, and public policies are aligned with the social realities of those living with the disease. More than a clinical marker, the possibility of remission thus becomes an indicator of coherence, or fracture, between scientific knowledge, collective responsibility, and social equity.

In the Mexican context, advancing toward an operational framework for diabetes remission requires adapting international consensus to criteria that are clinically and institutionally feasible, prioritizing individuals with a higher biological likelihood of remission, particularly those with shorter disease duration, through standardized protocols for early detection at the primary care level and structured pathways for intensive intervention with multidisciplinary follow-up. Systematic evaluation of these efforts necessitates integrating metabolic monitoring into registries capable of assessing sustainability and relapse, while explicitly incorporating equity indicators that account for material conditions, healthcare coverage, and social context, so that remission does not become a privilege but rather an evaluable possibility within real-world healthcare systems.

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Clinical Innovations
in Health Research-HJM

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ORIGINAL ARTICLE

Functional prognosis in patients with ischemic stroke undergoing reperfusion therapy in the intensive care unit and neurology ward

Pronóstico funcional en pacientes con infarto cerebral sometidos a terapia de reperfusión en la unidad de cuidados intensivos y servicio de neurología

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Abstract

Background: *Patients with acute stroke who receive reperfusion therapy should continue close monitoring of vital signs and neurological status in a stroke unit or intensive care unit (ICU). However, high patient demand and limited space sometimes lead to their admission to a general hospital ward.* **Objective:** *The objective of the study was to determine the functional prognosis in stroke patients undergoing reperfusion therapy in the ICU and neurology service.* **Method:** *This was a retrospective observational comparative cohort study that included patients over 18 years of age with acute cerebral infarction who underwent reperfusion therapy at the Juárez Hospital in Mexico City.* **Results:** *Thirty-three (41%) patients were admitted to the neurology ward for monitoring, and 48 (59%) were admitted to the ICU. Patients were classified according to the modified Rankin Scale as follows: good prognosis (mRS 0-2), poor prognosis (mRS 3-5), and death (mRS 6). Only 24% had a good prognosis (20 patients), 44% (35 patients) had a poor functional prognosis, and 36% (26 patients) experienced treatment failure.* **Conclusion:** *There are no significant differences in functional prognosis in patients with cerebral infarction undergoing reperfusion therapy in the ICU and the neurology ward.*

Keywords: *Ischemic stroke. Thrombolytic therapy. Thrombectomy. Intensive care units. Treatment outcome.*

Resumen

Antecedentes: *Los pacientes con infarto cerebral agudo que reciben terapia de reperfusión deben continuar con una monitorización estrecha de los signos vitales y estado neurológico en una unidad de ictus o unidad de cuidados intensivos (UCI). Sin embargo la alta demanda y la falta de espacio físico en ocasiones conducen a su ingreso a piso de hospitalización.* **Objetivo:** *El objetivo del estudio fue determinar el pronóstico funcional en infarto cerebral en pacientes que recibieron terapia de reperfusión en UCI y el piso de hospitalización.* **Método:** *Estudio de cohorte observacional retrospectivo que incluyó pacientes mayores de 18 años con infarto cerebral agudo que recibieron terapia de reperfusión en el Hospital Juarez de la Ciudad de México.* **Resultados:** *Treinta y tres (41%) de los pacientes fueron admitidos a piso de hospitalización de neurología para monitorización, y 48 (59%) fueron admitidos a UCI. Los pacientes fueron clasificados acorde a la escala modificada de Rankin como sigue: buen pronóstico (mRS 0-2), mal pronóstico (mRS 3-5) y muerte (mRS 6). Solo 24% tuvieron buen pronóstico (20 pacientes), 44% (35 pacientes) tuvieron un mal pronóstico y 36% (26 pacientes) muerte.*

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Date of reception: 21-09-2025
Date of acceptance: 14-11-2025
DOI: 10.24875/CIHR.25000021

Available online: 31-03-2026
Clin. Innov. Health Res-HJM. 2026;3(1):3-7
www.clinicalinnovinhealthresearch-hjm.com

Conclusión: *No encontramos diferencias significativas en el pronóstico funcional en pacientes con infarto cerebral agudo que recibieron terapia de reperfusión en UCI y en piso de hospitalización de Neurología.*

Palabras clave: *Ictus isquémico. Terapia trombolítica. Trombectomía. Unidades de cuidados intensivos. Resultado del tratamiento.*

Introduction

Stroke is a major cause of death worldwide, as well as a leading cause of disability in patients who did not previously suffer from it[1].

In Mexico, the incidence of cerebrovascular disease is approximately 90 cases/100,000 inhabitants[2], and disability in patients in their seventh decade of life represents more than 60% of cases[3]. This means that after this event, the patient may be unable to return to work or may be dependent on others for activities they previously performed independently. Those who experience a stroke within the window period and who meet the criteria for reperfusion therapy, whether with alteplase, tenecteplase, mechanical thrombectomy, or combinations thereof, should, according to AHA recommendations, continue their follow-up in a stroke unit or, failing that, in an intensive care unit (ICU), with the aim of maintaining close monitoring. This hospital unit does not have a stroke unit, and access to ICU beds is sometimes limited due to high patient demand. Therefore, some patients are admitted to the neurology ward. Vital signs are monitored more closely in the ICU than on the ward. The main objective is to determine whether the close monitoring provided by the ICU versus the routine monitoring on the neurology ward has a similar impact on the functional prognosis, as measured by the modified Rankin Scale, in patients at hospital discharge[4].

Materials and methods

We conducted a retrospective observational cohort study at the Juárez Hospital in Mexico City, including patients with stroke who received reperfusion therapy from January 2022 to March 2025. Patients were assigned to the ICU or neurology ward according to bed availability or the attending physician's clinical judgment; they were not randomly assigned.

Participants

Patients over 18 years of age with cerebral infarction within the window period for receiving intravenous thrombolysis, thrombectomy, or a combination of both treatments were included. Patients with intracerebral hemorrhage (ICH), transient ischemic attack, incomplete medical records, or who were transferred to another hospital unit were excluded.

Variables

The objective was to determine the functional prognosis of patients at discharge in both groups (ICU vs. neurology ward). For this, the modified Rankin Scale was used, where a favorable outcome was defined as a score of 0-2, an unfavorable outcome as 3-5, and death as 6. We also considered other variables such as patient age, sex, NIHSS score, type of reperfusion therapy used, complications, and length of hospital stay.

Data collection

Data were collected from the patient's medical record and progress notes. Complications such as ICH were identified through the institutional imaging system.

Bias

To reduce selection bias, we included all patients who met the inclusion criteria during the aforementioned period using standardized data extraction and variable verification.

Study size

We included eighty-one patients during the aforementioned period; however, since this was a retrospective study, we did not calculate the sample size.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median with interquartile range, depending on the data distribution. The comparison of the ICU versus neurology groups was performed using Student's t-test or Mann-Whitney U test for continuous

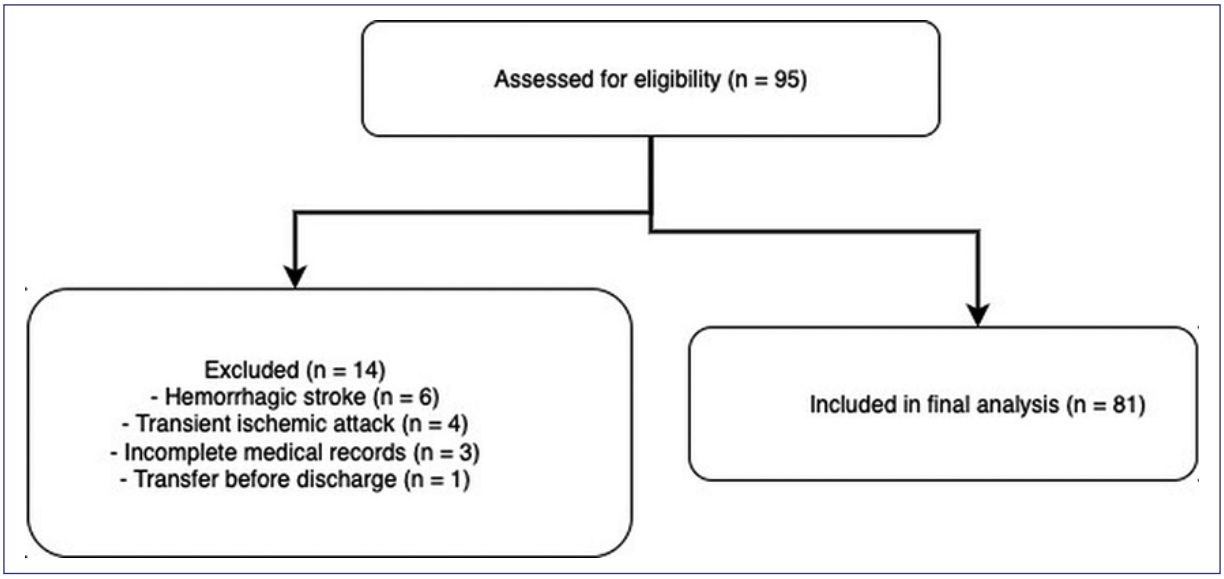

Figure 1. Flowchart of patient inclusion and exclusion.

variables and X^2 test or Fisher's exact test for categorical variables.

An exploratory multivariable logistic regression model, adjusted for age, NIHSS score, and type of reperfusion therapy used, was used to identify independent associations with a favorable outcome, defined as an mRs of 0-2. A $p < 0.05$ was considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences version 26.0.

Results

Eighty-one patients were included, with a mean age of 68 ± 14 years, of whom 58% were women. The majority of patients (89%) received intravenous thrombolysis, 10% received both therapies (thrombolysis and thrombectomy), and only 1% received thrombectomy alone.

The mean NIHSS score was 14 ± 6, indicating that the patients already had a moderate to severe neurological deficit upon admission. Symptomatic ICH was a complication in 31% of the patients, while infections and other complications were the least frequent. The mean length of hospital stay was 7.5 ± 5.6 days.

When comparing both groups, patients admitted to the ICU had higher initial NIHSS scores, although this difference was not statistically significant. ICH occurred in 32% versus 30% of patients, with mortality (modified Rankin Scale score of 6) occurring in 34% versus 31%.

At hospital discharge, 24% of patients had favorable outcomes (modified Rankin Scale score of 0-2), 44% had unfavorable outcomes (modified Rankin Scale score of 3-5), and 32% of patients died.

When adjusted for age, NIHSS score at admission, type of reperfusion therapy used, and hospital ward (ICU versus neurology ward), these factors were not independently associated with a favorable outcome as measured by the modified Rankin Scale.

These results are presented in table 1, which summarizes the patients' characteristics, while table 2 shows the outcomes and complications. Figure 1 illustrates the patient selection process.

Discussion

The study included 81 patients who received reperfusion therapy at this hospital and had two different hospital destinations: the neurology ward and the ICU. The study was conducted from January 2022 to March 2025 with the objective of determining the functional prognosis at hospital discharge in both groups.

Regarding the patients demographic characteristics, no significant differences were found between groups, which ensures homogeneity within the study population. At this hospital, there was a greater predominance of females around 60 years of age, and the most frequently identified comorbidity was systemic arterial hypertension.

Table 1. Baseline demographic and clinical characteristics by monitoring location (ICU vs. ward) with p values

Characteristic	ICU	Ward	p/test
Age, years	68.2 ± 14.2	68.1 ± 14.6	Mann-Whitney U, p = 0.766
Female, n (%)	31 (64.6%)	16 (48.5%)	X^2, p = 0.225
NIHSS at admission	15.6 ± 5.9; median 16.0 (11.8-20.0)	14.5 ± 6.8; median 15.0 (9.0-20.0)	Student's t-test, p = 0.478
Therapy: IV thrombolysis	43 (89.6%)	29 (87.9%)	-
Therapy: thrombectomy	0 (0.0%)	1 (3.0%)	-
Therapy: combined	5 (10.4%)	3 (9.1%)	X^2, p = 0.473
Length of stay, days	7.6 ± 5.6; median 6.0 (4.0-9.2)	7.4 ± 5.4; median 6.0 (4.0-9.0)	Mann–Whitney U, p = 0.890

ICU: intensive care unit.

Table 2. Complications and functional outcomes (including symptomatic intracerebral hemorrhage [ICH] and discharge mRS) by monitoring location with p values

Outcome	ICU	Ward	p/test
Symptomatic ICH, n (%)	16 (33.3)	9 (27.3)	X^2, p = 0.737
Mortality (mRS 6), n (%)	16 (33.3)	10 (30.3)	X^2, p = 0.964
mRS category, n (%)			X^2, p = 0.816
mRS 0-2, n (%)	10 (20.8)	10 (30.3)	
mRS 3-5, n (%)	22 (45.8)	13 (39.4)	
mRS 6, n (%)	16 (33.3)	10 (30.3)	

ICU: intensive care unit.

No statistically significant differences (p < 0.79) were found in prognosis between groups in any of the categories, which were good functional outcome (ranking 0-2 points, 30.3% vs. 21%), poor functional outcome (ranking 3-5 points, 39.4% vs. 46%), or death (ranking 6, 30.3% vs. 33%). These results are consistent with the established hypothesis, which could suggest that less stringent monitoring, such as that provided in the neurology ward, does not impact functional prognosis at hospital discharge.

Few studies similar to ours exist. The first study was conducted in 1998[5], including 802 patients randomly assigned to stroke units or hospital wards. Lower mortality was found in the latter group; however, functional outcomes were not compared.

In 2020, the OPTIMIST study[6] was published, where less invasive monitoring did not imply a greater risk of complications. The main limitations were the lack of randomization between groups. This was because, in our study, the lack of available beds was the main reason why a patient did not continue monitoring in the ICU, unlike the OPTIMIST study, where allocation was determined by the absence of critical care needs after thrombolysis. Furthermore, OPTIMIST provided follow-up for up to 90 days, whereas in our study, follow-up continued until hospital discharge, which varied depending on the severity of each patient's condition.

Some of the advantages are that we included a larger population (n = 81 vs. n = 35), with higher NIHSS scores (29 points vs. 10 points), and not only patients who received thrombolysis but also those who underwent mechanical thrombectomy or a combination of thrombolytic therapy.

Including higher NIHSS scores could explain why, despite being similar between groups in the hospital, functional outcomes were not as expected, with the vast majority having scores between 3 and 5 points at hospital discharge compared to scores between 0 and 3 points in the OPTIMIST study.

Another study similar to ours was conducted in Japan[7] with 6,977 patients distributed between stroke units and general hospital wards. This study had a larger population and also included patients who suffered ICH, unlike our study, which only included cerebral infarction. The results showed that stroke units reduced mortality compared to general wards, contradicting our review. However, there was no significant difference in functional prognosis at hospital discharge, which coincides with our results.

Conclusion

There are no significant differences in functional prognosis between stroke patients undergoing

reperfusion therapy in the ICU and the neurology ward. Therefore, we can conclude that they have similar outcomes at hospital discharge, which may contribute to a safer transfer of patients to the general ward.

These similar results between groups reflect the dedication and commitment of both nursing and medical staff in the follow-up of patients who underwent reperfusion therapy, regardless of their initial hospital admission.

However, despite these efforts, there is a high percentage of poor functional prognosis or death in both groups, which necessitates improvements in stroke code protocols at this institution for all services involved to achieve better outcomes.

Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors thank the staff of the Department of Neurology, Hospital Juárez de México, for their collaboration during patient care and data collection.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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ORIGINAL ARTICLE

Evolution from mild symptoms to severe COVID-19 in vaccinated and unvaccinated outpatients in Acapulco, Mexico: follow-up of a case series

Evolución de síntomas leves a COVID-19 grave en pacientes ambulatorios vacunados y no vacunados en Acapulco, México: seguimiento de una serie de casos

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Abstract

Background: *Although Coronavirus disease 2019 (COVID-19) vaccine effectiveness and age-related risk of severe disease are well established, real-world evidence from early vaccination phases remains relevant to understand how health systems operated during periods of rapid epidemiological transition.* **Objective:** *Assess the progression from mild to severe COVID-19 among vaccinated and unvaccinated outpatients during the Delta wave in a public health setting in Mexico.* **Method:** *A follow-up case series of 3,488 adult outpatients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection and mild disease at diagnosis, treated between May and August 2021, was conducted. Severe COVID-19 was defined as clinical deterioration requiring hospitalization and was confirmed through electronic medical records. Bivariate and Mantel-Haenszel multivariate analyses were performed to identify factors independently associated with severe outcomes.* **Results:** *Severe COVID-19 affected 3.2% of those initially presenting with mild symptoms. Some 12.6% of those with severe illness had received the vaccine. Vaccination protected against severe COVID-19 (adjusted odds ratio [ORa] = 0.05, confidence interval [CI] 95% 0.03-0.08). We found an association between severe COVID-19 and age 60 years or older (ORa = 9.3, CI 95% 5.9-14.6), and with one or more comorbidities (ORa = 6.2, CI 95% 4.0-9.5).* **Conclusion:** *During the Delta wave, vaccination substantially reduced the likelihood of severe COVID-19 among outpatients, while older age and comorbidities markedly increased risk. These findings provide contextual evidence of outpatient risk stratification and monitoring strategies implemented during an early phase of the pandemic.*

Keywords: *COVID-19. SARS-CoV-2. SARS-CoV-2 vaccine. Distance follow-up.*

Resumen

Antecedentes: *Si bien la efectividad de la vacuna contra la COVID-19 y el riesgo de enfermedad grave relacionado con la edad están bien establecidos, la evidencia práctica de las primeras fases de vacunación sigue siendo relevante para comprender el funcionamiento de los sistemas de salud durante períodos de rápida transición epidemiológica.* **Objetivo:** *Evaluar*

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Date of reception: 13-01-2026
Date of acceptance: 26-02-2026
DOI: 10.24875/CIHR.26000001

Available online: 31-03-2026
Clin. Innov. Health Res-HJM. 2026;3(1):8-15
www.clinicalinnovinhealthresearch-hjm.com

la progresión de COVID-19 leve a grave en pacientes ambulatorios vacunados y no vacunados durante la ola de la variante Delta en un servicio de salud pública en México. **Método:** *Se realizó una serie de casos de seguimiento de 3,488 pacientes ambulatorios adultos con infección por SARS-CoV-2 confirmada por laboratorio y enfermedad leve al diagnóstico, tratados entre mayo y agosto de 2021. La COVID-19 grave se definió como el deterioro clínico que requirió hospitalización y se confirmó mediante expedientes médicos electrónicos. Se realizaron análisis bivariados y multivariados de Mantel-Haenszel para identificar factores asociados de forma independiente con desenlaces graves.* **Resultados:** *La COVID-19 grave afectó al 3.2% de los pacientes que inicialmente presentaron síntomas leves. Alrededor del 12.6% de los pacientes con enfermedad grave habían recibido la vacuna. La vacunación protegió contra la COVID-19 grave (ORa = 0.05; IC 95%: 0.03-0.08). Se encontró asociación entre COVID-19 grave y edad de 60 años o más (ORa = 9.3; IC 95%: 5.9-14.6), así como con tener una o más comorbilidades (ORa = 6.2; IC 95%: 4.0-9.5).* **Conclusión:** *Durante la ola de la variante Delta, la vacunación redujo sustancialmente la probabilidad de COVID-19 grave en pacientes ambulatorios, mientras que la edad avanzada y las comorbilidades aumentaron notablemente el riesgo. Estos hallazgos proporcionan evidencia contextual de la estratificación del riesgo en pacientes ambulatorios y las estrategias de seguimiento implementadas durante una fase temprana de la pandemia.*

Palabras clave: *COVID-19. SARS-CoV-2. Vacuna contra el SARS-CoV-2. Seguimiento a distancia.*

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the seventh known coronavirus capable of causing human infection[1]. In some countries, up to five waves of infection have affected an estimated 225 million people worldwide[2,3]. In China, 40% of people with Coronavirus disease 2019 (COVID-19) presented with mild illness, 40% moderate, and 15% severe, progressing between 7 and 10 days to severe pulmonary disease[4]. Factors associated with severe COVID-19 are age, tobacco use, diabetes, high blood pressure, heart or pulmonary problems, obesity, and cancer. Nevertheless, anyone can have COVID-19 and develop severe illness[5].

The Delta variant became globally predominant in 2021 due to its higher transmissibility compared with earlier lineages and was associated with increased risk of hospital admission and community spread in many countries[6-8]. Although different studies have consistently demonstrated strong vaccine effectiveness against severe COVID-19 caused by multiple variants[9-13], including Delta, real-world effectiveness estimates vary by setting, age group, and time since vaccination[6,7,14]. These findings highlight the importance of context-specific observational evidence to interpret vaccine performance and clinical progression in routine outpatient care.

Older age and underlying chronic conditions have been identified as major associated factors of severe COVID-19. Different studies indicate that older persons consistently experience higher risks of hospitalization and death compared with younger adults[8,15,16]. These age-related risk patterns are further modified by comorbidities such as cardiovascular disease, diabetes, and pulmonary disorders, underscoring the importance of age stratification and comorbidity adjustment in studies evaluating disease progression and outcomes[15,16].

In many health systems, structured outpatient monitoring strategies were implemented during periods of high transmission to detect early clinical deterioration among SARS-CoV-2–infected individuals and to optimize hospital resource utilization[17-19]. Although outpatient follow-up programs were widely adopted, the evidence base describing how clinical risk factors and follow-up processes interact under real-world conditions remains limited.

The present study does not aim to reassess the biological effectiveness of COVID-19 vaccines, which is well established, or to extrapolate risk estimates to the current epidemiological context. The study documents the evolution from mild symptoms to severe COVID-19 among vaccinated and unvaccinated outpatients during the Delta wave, under routine outpatient follow-up conditions in a public health care setting in Mexico. This historical-operational perspective provides insight into how vaccination status, age, and comorbidities interact within a real-world surveillance strategy distance follow-up during a critical phase of the pandemic.

Materials and methods

A follow-up series of cases was made from the database of the Epidemiological Surveillance National Platform for outpatients positive for COVID-19 at the Módulo de Atención Respiratoria del Seguro Social (Respiratory Care Module for Social Security) of the Unidad de Medicina Familiar No. 9 (UMF No. 9) in Acapulco, Mexico, from May 1 to August 31, 2021.

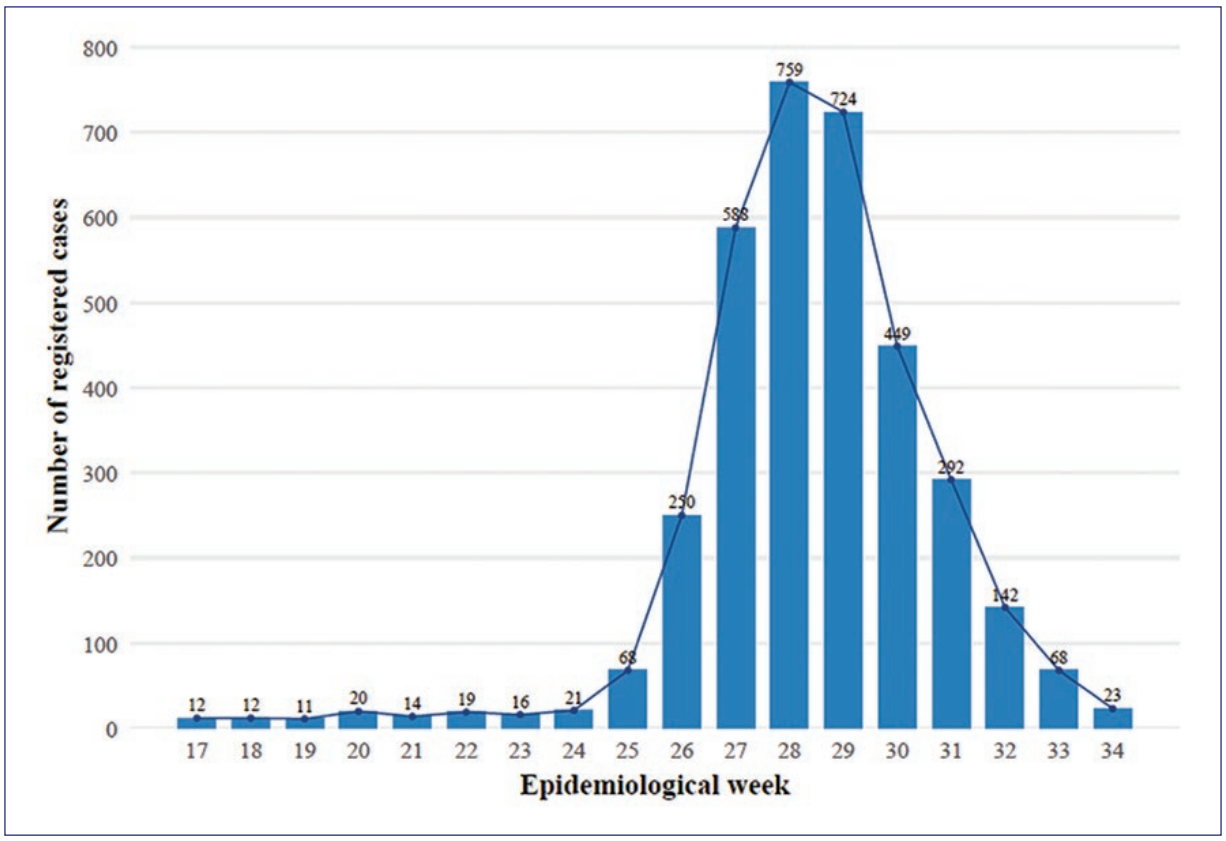

Figure 1. Confirmed cases of COVID-19 by week at IMSS Family Medicine Unit 9 in Acapulco, Mexico.

Selection criteria: outpatients of the UMF No. 9, attending the *Módulo de Atención Respiratoria* of the Seguro Social, with a positive quick antigen test for SARS-CoV-2, male or female, age ≥ 18 years old. Patients whose clinical files lacked key variables for the study and those who provided a phone number but did not answer the follow-up call were eliminated.

Questionnaire: a form designed by the researchers to collect information from epidemiological questionnaires for suspected cases of respiratory illness, used by all Mexican health institutions[20]. The template included two sections: sociodemographic (age, sex, and occupation) and clinical data. Age was initially analyzed in 5-year categories; exploratory analyses showed a marked increase in risk from 60 years onward, leading to the use of ≥ 60 years as the analytical cut-off. This covered the time between the symptoms, the week in which the diagnosis was confirmed for COVID-19, background for positive contact, comorbidities such as diabetes mellitus type 2, systemic high blood pressure, obesity, asthma, chronic obstructive pulmonary disease, pregnancy, and human immunodeficiency virus/acquired immunodeficiency syndrome. Information was also collected on vaccination status, vaccination schedule, follow-up days, and outcome at the end of remote follow-up.

A prescription kit containing a face mask and medications was distributed as part of institutional clinical practice during the study period. At the discretion of the treating physician, some patients received a pulse oximeter, with instructions to go to the hospital immediately if their oxygen saturation decreased by 3% or more from the initial baseline. The research team did not design, assign, or modify this kit, and it was not an intervention of the study.

IMSS staff made follow-up phone calls until the 10th day after diagnosis or until follow-up diagnosis of severe COVID-19.

The outcome was severe COVID-19, defined as clinical deterioration requiring hospital admission. Telephone follow-up was used solely as an early alert mechanism to identify worsening symptoms; all cases classified as severe were subsequently confirmed through electronic medical records documenting

Table 1. Sociodemographic and health characteristics of the study population at IMSS Family Medicine Unit No. 9 in Acapulco, Mexico (n = 3,488)

Variable	Category	Frequency	%
Age	18-29 years old	986	28.3
	30-39 years old	958	27.5
	40-49 years old	744	21.3
	50-59 years old	347	9.9
	60-69 years old	283	8.1
	70-79 years old	127	3.6
	80-89 years old	37	1.1
	90-95 years old	6	0.2
Sex	Man	1,697	48.7
	Woman	1,791	51.3
Occupation	Housewife	566	16.2
	Student	133	3.8
	Employee	2,436	69.8
	Health worker	163	4.7
	Pensioner	190	5.4
Contact history	Yes	218	6.2
	No	3,270	93.8
Comorbidity	Diabetes mellitus type 2	429	12.3
	High blood pressure	580	16.6
	Obesity	196	5.6
	Asthma	50	1.4
	Chronic obstructive pulmonary disease	7	0.2
	Pregnancy	33	0.9
	HIV/AIDS	16	0.5
	None	2,490	71.4
Prescriptions kit with a pulse oximeter	Yes	1,760	50.5
	No	1,728	49.5
Vaccine against COVID-19	Yes	1,156	33.1
	No	2,332	66.9

HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome.

hospitalization. No cases were classified as severe based exclusively on self-report or telephone information.

R statistical programming language was used to calculate 98% power to detect a two-fold vaccine effect protecting against severe COVID-19 in a series of 3,344 cases, a confidence level of 95%, with prevalence among unvaccinated of 44.3%[21].

CIETmap 2.1 was used for univariate analysis to get descriptive results and simple frequencies. Association

Table 2. Sociodemographic characteristics in hospitalized patients with severe COVID-19 (n = 111)

Variable	Category	Frequency	%
Age	20-39 years old	31	27.9
	40-59 years old	25	22.5
	60-79 years old	44	39.6
	80-93 years old	11	9.9
Sex	Man	57	51.4
	Woman	54	48.6
Occupation	Housewife	37	33.3
	Student	1	0.9
	Employee	45	40.5
	Health worker	2	1.8
	Pensioner	26	23.4
Contact history	Yes	3	2.7
	No	108	97.3
	Diabetes mellitus type 2	43	38.7
	High blood pressure	52	48.8
Comorbidity	Obesity	20	18
	Pregnancy	5	4.5
	Asthma	1	0.9
	HIV/AIDS	1	0.9
	None	30	27
Prescriptions kit with a pulse oximeter	Yes	92	82.9
	No	19	17.1
Vaccine against COVID-19	Yes	14	12.6
	No	97	87.4
Result of severe COVID-19	Improvement	64	57.7
	Death	47	42.3

HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome.

of factors was estimated by a bivariate analysis with the Mantel-Haenszel procedure unvaccinated and vaccinated, with complete immunization, and with an incomplete immunization. Confidence intervals of (95%) were calculated with the Miettinen procedure. Multivariate analysis included variables with a significant association in the bivariate analysis. Weakest association was eliminated one by one from the saturated model until all associations were significant at the 5% level in the final model. Zelen's test was used to identify possible effect modifiers.

The study was carried out by the research standards and procedures of the Mexican Social Security Institute. The study was approved by the Local Health Research Committee 1101 on January 10, 2022, with registration R-2021-1101-045, and by the Research Ethics Committee 11018 on February 03, 2023.

Table 3. Bivariate analysis of factors associated with severe COVID-19 in beneficiaries of IMSS Family Medicine Unit No. 9, Acapulco, Mexico

Variable	Category	Severe COVID-19		ORna[a]	95% CI[b]
		Yes	No		
Age	≥ 60 years	55	398	7.35	5.25-10.28
	18-59 years	56	2,979		
Sex	Male	57	1,640	1.12	0.77-1.63
	Female	54	1,737		
Occupation	Unpaid	38	661	2.14	1.44-3.17
	Paid	73	2,716		
Epidemiological contact	Yes	108	3,162	2.45	0.80-7.49
	No	3	215		
Comorbidity	≥ 1 comorbidity	81	917	7.24	5.01-10.48
	None	30	2,460		
Prescriptions kit with a pulse oximeter	No	19	1,709	0.2	0.13-0.32
	Yes	92	1,668		
COVID-19 vaccination	≥ 1 dose	14	1,142	0.28	0.17-0.48
	Unvaccinated	97	2,235		

[a]Unadjusted odds ratio.
[b]Miettinen 95% confidence interval.
COVID-19: coronavirus disease 2019.

Results

A total of 3,891 electronic medical records of patients with confirmed SARS-CoV-2 infection were reviewed. Of these, 403 cases were excluded: 251 due to missing key information, 145 because severe COVID-19 was present at baseline, three for being under 18 years of age, two for confirmed reinfection, and two duplicates. The final database comprised 3,488 adult outpatients with mild COVID-19 at diagnosis.

Participants ranged in age from 18 to 95 years, with a mean age of 40.1 years (standard deviation [SD] 15.0). Sociodemographic and baseline clinical characteristics in detail are presented in table 1.

Temporal distribution and follow-up

Nearly half of the patients (48%; 1,675/3,488) sought medical care within 2 days of symptom onset, with a mean of 2.9 days (SD 2.1). Confirmed COVID-19 cases increased from epidemiological week 25, peaked at week 28, and declined thereafter (Fig. 1).

The mean duration of outpatient follow-up was 9.8 days (SD 1.0), during which patients were monitored for clinical deterioration.

Incidence of severe COVID-19

Severe COVID-19 occurred in 111 patients, representing 3.2% of the study cases. All severe cases required hospitalization and were confirmed through electronic medical records. Among hospitalized patients, 47 died, corresponding to a case fatality rate of 42.3%.

The incidence density of severe COVID-19 was 3.2 cases/1,000 person-days of observation. Among unvaccinated individuals, the incidence was 4.2/1,000 person-days, compared with 1.2/1,000 person-days among vaccinated individuals, yielding a crude risk ratio of 3.5.

Characteristics of patients with severe COVID-19

Among patients who developed severe COVID-19, 50.4% (56/111) were aged 20-59 years. Men accounted

Table 4. The final model of multivariate analysis of factors associated with severe COVID-19 in beneficiaries of IMSS Family Medicine Unit No. 9, Acapulco, Mexico

Variable	ORna[a]	ORa[b]	95% CI[c]	χ^2 MH[d]	Zelen's test (p)
Age ≥ 60 years	7.35	9.3	5.91-14.63	92.95	0.83
≥ 1 comorbidity	8.58	6.17	4.01-9.51	68.11	0.78
≥ 1 dose of COVID-19 vaccine	0.28	0.05	0.03-0.08	103.22	0.99

[a]Unadjusted odds ratio.
[b]Adjusted odds ratio.
[c]Miettinen 95% confidence interval.
[d]Mantel-Haenszel's χ^2 for two or more strata.
CI: confidence interval; COVID-19: coronavirus disease 2019.

for 51.4% (57/111) of severe cases. At least one comorbidity was present in 73.0% of hospitalized patients, most commonly hypertension and Type 2 diabetes mellitus. Detailed characteristics of hospitalized patients are shown in table 2.

Bivariate and multivariate analysis

In bivariate analyses, age ≥ 60 years, having at least one comorbidity, unpaid occupation status, lack of COVID-19 vaccination, and receipt of a prescription kit were significantly associated with severe COVID-19 (Table 3).

Variables associated with severe COVID-19 in bivariate analysis were included in a multivariate model. After adjustment, three variables retained an independent association with the outcome: age ≥ 60 years, presence of at least one comorbidity, and receipt of at least one dose of COVID-19 vaccine (Table 4).

Discussion

Study found an association between vaccination and not developing severe COVID-19, while age ≥ 60 years and having at least one comorbidity were associated with severe forms of the illness. During the follow-up, 3% of the patients had severe COVID-19. Of these, 58% improved, and 42% died. This study documented the progression from mild symptoms to severe COVID-19 among outpatients during the Delta wave, within a structured outpatient follow-up strategy in a public health setting.

The observed association between vaccination and a reduced likelihood of severe disease aligns with previous reports[11,13,22,23], reinforcing the protective role of vaccination even in outpatient populations monitored remotely. Similarly, age ≥ 60 years and the presence of comorbidities were associated factors to severe COVID-19[24-28], consistent with international evidence.

The association found in the bivariate analysis between receiving a kit and severe cases of the disease can be explained by the fact that, given the shortage of pulse oximeter, treating physicians probably gave them to patients who showed signs of greater severity. These practices reflected the operational realities of the health system during the pandemic[18,19]. One study showed an association of the kit with not being hospitalized or dying[29]. The pulse oximeter is a diagnostic tool that can assist in the identification of patients who are at risk of developing atypical pneumonia, as well as those who already have the condition. A progressive decrease in oxygen levels is an indicator, so there is no need to wait until levels drop very low.

This study has limitations inherent to its observational design and historical context. The findings should not be extrapolated to later variants or current epidemiological conditions. Nevertheless, the results offer valuable insights into outpatient surveillance, risk stratification, and health system preparedness during periods of rapid epidemiological transition.

Conclusion

This study documents the progression from mild to severe COVID-19 among outpatients during the Delta wave in a public health setting in Mexico, capturing real-world conditions during an early phase of epidemiological transition. Although vaccination effectiveness and age-related risk are now well established, the findings illustrate how these factors operated within routine outpatient follow-up and health system practices. While not generalizable to later variants or current contexts, the results provide a historical-operational perspective relevant to outpatient surveillance and future epidemic preparedness.

Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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BRIEF COMMUNICATION

Proof-of-concept evidence for lncRNA NRIR downregulation in antiphospholipid syndrome and its obstetric subtype

Evidencia de prueba de concepto de la disminución de la expresión del lncRNA NRIR en el síndrome antifosfolípido y su subtipo obstétrico

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Abstract

Background/Objetive: *Long non-coding RNAs (lncRNAs) regulate immune signaling pathways, including interferon (IFN)-mediated responses implicated in antiphospholipid syndrome (APS). The IFN-inducible lncRNA NRIR (AC017076.5) exhibits context-dependent regulatory functions and has been associated with modulation of STAT1/STAT2 activation in human monocytes. Its expression profile in APS remains unexplored.* **Method:** *In this cross-sectional exploratory study, NRIR expression was quantified by reverse transcription–quantitative PCR in CD14-enriched peripheral blood monocytes from APS patients and age- and sex-matched healthy controls. Relative expression was calculated using the $2^{-\Delta\Delta Ct}$ method with GAPDH as endogenous control. Subgroup analyses compared obstetric APS (OAPS) and non-obstetric APS (NOAPS). Complementary in silico protein–protein interaction and pathway enrichment analyses contextualized NRIR within IFN-related networks.* **Results:** *NRIR expression was significantly reduced in APS compared with controls. OAPS patients exhibited less pronounced downregulation than NOAPS, showing an intermediate expression pattern. Network analysis identified a STAT1-centered IFN-enriched module related to antiviral and type I IFN signaling, with NRIR positioned peripherally. Functional inferences remain hypothesis-generating due to sample size and absence of direct IFN measurements.* **Conclusion:** *NRIR is downregulated in peripheral monocytes from APS patients, with phenotype-dependent differences. Further mechanistic and IFN-integrated studies are required.*

Keywords: *Antiphospholipid syndrome. Obstetric APS. NRIR. lncRNA AC017076.5. Interferon response. Monocytes.*

Resumen

Antecedentes/Objetivo: *Los ARN largos no codificantes (lncRNAs) regulan vías de señalización inmunológica, incluidas las respuestas mediadas por interferón (IFN) implicadas en el síndrome antifosfolípido (SAF). El lncRNA inducible por IFN NRIR (AC017076.5) presenta funciones regulatorias dependientes del contexto y se ha asociado con la modulación de la activación de STAT1/STAT2 en monocitos humanos. Su perfil de expresión en el SAF no ha sido previamente caracterizado.* **Métodos:** *En este estudio transversal exploratorio, la expresión de NRIR se cuantificó mediante PCR cuantitativa con trans-*

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Date of reception: 04-11-2025
Date of acceptance: 13-02-2026
DOI: 10.24875/CIHR.25000023

Available online: 31-03-2026
Clin. innov. health res-HJM. 2026;3(1):16-22
www.clinicalinnovinhealthresearch-hjm.com

criptasa reversa en monocitos de sangre periférica enriquecidos para CD14 de pacientes con SAF y controles sanos pareados por edad y sexo. La expresión relativa se calculó utilizando el método $2^{-\Delta\Delta Ct}$ con GAPDH como control endógeno. Se realizaron análisis por subgrupos comparando SAF obstétrico (SAFO) y SAF no obstétrico (SAFNO). Además, se efectuaron análisis in silico de interacción proteína–proteína y enriquecimiento de vías para contextualizar NRIR dentro de redes relacionadas con IFN. **Resultados:** *La expresión de NRIR fue significativamente menor en SAF en comparación con controles. Los pacientes con SAFO mostraron una disminución menos pronunciada que SAFNO, con un patrón intermedio de expresión. El análisis de redes identificó un módulo centrado en STAT1 enriquecido en señalización antiviral e IFN tipo I, con NRIR en posición periférica. Las inferencias funcionales son exploratorias.* **Conclusión:** *NRIR se encuentra disminuido en monocitos periféricos de pacientes con SAF, con diferencias según fenotipo clínico. Se requieren estudios mecanísticos adicionales integrando actividad de IFN.*

Palabras clave: *Síndrome antifosfolípido. SAF obstétrico. NRIR. lncRNA AC017076.5. Respuesta al interferón. Monocitos.*

Introduction

Long non-coding RNAs have emerged as essential regulators of innate and adaptive immune pathways through chromatin remodeling, transcriptional modulation, and post-transcriptional mechanisms[1-3]. Among these, the Negative Regulator of Interferon Response (NRIR, also known as lnc-CMPK2) represents a type-I interferon (IFN)-inducible transcript located immediately downstream of CMPK2 in a head-to-tail configuration. NRIR is spliced, polyadenylated, and predominantly nuclear, where it scaffolds transcriptional complexes and modulates the expression of IFN-stimulated genes (ISGs)[4]. Importantly, the functional role of NRIR is cell-type dependent. In hepatocytes, NRIR has been shown to act as part of a negative-feedback loop that restrains ISG transcription following IFN stimulation. In contrast, in monocytes and myeloid cells, NRIR supports STAT1/STAT2-dependent signaling and facilitates the expression of IFN-responsive chemokines such as CXCL10 and CXCL11[5]. This context-specific behavior indicates that NRIR cannot be interpreted as a uniformly inhibitory regulator of IFN responses, but rather as a transcriptional modulator whose directionality depends on cellular identity and molecular context.

Consistent with this complexity, altered NRIR expression has been reported across a broad range of immune-mediated and inflammatory conditions, including viral infections (e.g., hepatitis C virus, SARS-CoV-2, Hantaan virus), bacterial infections (*Mycobacterium tuberculosis*), and autoimmune diseases such as systemic lupus erythematosus and systemic sclerosis, all of which are characterized by varying degrees of IFN pathway activation[6-8]. Collectively, these studies position NRIR as a context-sensitive component of IFN-responsive transcriptional programs, rather than as a unidirectional regulator of inflammation.

Antiphospholipid syndrome (APS) is an autoimmune thrombo-inflammatory disorder characterized by thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies[9]. Accumulating transcriptomic and proteomic evidence suggests that a subset of APS patients exhibits heightened type I IFN pathway activity, particularly within monocytes and endothelial cells, indicating partial overlap with other IFN-driven autoimmune diseases[10]. Despite this, the contribution of lncRNAs to transcriptional heterogeneity in APS remains poorly characterized.

Given the established IFN responsiveness of NRIR and its cell-type–specific regulatory behavior in monocytes, we postulated that NRIR expression might be altered in APS compared with healthy individuals. Furthermore, we explored whether NRIR expression differs between obstetric and non-obstetric APS (NOAPS) phenotypes, recognizing that such comparisons are exploratory and may be influenced by clinical and therapeutic heterogeneity. To address these questions, we conducted an exploratory, proof-of-concept analysis of NRIR expression in monocyte-enriched peripheral blood mononuclear cells (PBMCs) from APS patients and healthy controls. This short communication reports our findings and discusses their implications in the context of transcriptional heterogeneity in APS, without inferring direct mechanistic involvement of the IFN axis.

Methods

Study population

Peripheral blood samples were obtained from 25 patients fulfilling established international classification criteria for APS and from 13 healthy donors. Among APS cases, 10 patients presented with obstetric manifestations and 15 with thrombotic or mixed clinical features. Demographic and clinical variables were recorded

at the time of blood sampling. All participants provided written informed consent under protocol PT-16-039, approved by the local ethics committee, in accordance with the Declaration of Helsinki.

PBMC isolation and monocyte enrichment

Five milliliters of peripheral blood collected in EDTA tubes were processed within 2 h of collection. PBMCs were isolated by density-gradient centrifugation using Histopaque-1077 (Sigma-Aldrich). Monocytes were enriched by depletion of $CD14^-$ cells using negative magnetic selection (Miltenyi Biotec), yielding a $CD14^+$-enriched cell fraction. Quantitative assessment of monocyte purity was not performed; therefore, residual contamination by non-monocytic cells cannot be fully excluded. Enriched cell fractions were lysed in TriPure reagent and stored at –74 °C until RNA extraction.

Table 1. Baseline clinical characteristics of the APS cohort

Characteristic	APS patients (n = 25)
Age (years), median (IQR)	40.0 (35.5-50.5)
Body mass index (kg/m²), median (IQR)	25.98 (25.06-29.12)
Sex, n (%)	
Female	20 (80.0)
Male	5 (20.0)
APS classification, n (%)	
Primary APS	20 (80.0)
Secondary APS	5 (20.0)
Obstetric manifestations, n (%)	10 (40)
Hydroxychloroquine (HCQ), n (%)	
No	14 (56.0)
Yes	11 (44.0)
Vitamin K antagonists, n (%)	
No	2 (8.0)
Yes	23 (92.0)

IQR: interquartile range; APS: antiphospholipid syndrome.

RNA extraction and reverse transcription

Total RNA was extracted according to the manufacturer's instructions. RNA purity was assessed spectrophotometrically (A260/280 ≥ 1.8), and RNA integrity was evaluated by agarose gel electrophoresis. Blood RNA stabilization systems were not used; however, all samples were processed within 2 h of collection to minimize pre-analytical variability. Two hundred fifty nanograms of total RNA were reverse transcribed using the QuantiNova Reverse Transcription Kit (Qiagen) following the supplier's protocol.

Quantitative polymerase chain reaction (qPCR)

qPCR was performed using RT² SYBR Green Master Mix (Qiagen) on a CFX96 Real-Time PCR System (Bio-Rad). Cycling conditions consisted of an initial denaturation at 95 °C for 10 min, followed by 40 cycles of 95°C for 15 s and 60 °C for 60 s. Specific amplification was verified by melt-curve analysis, and non-template controls were consistently negative. The long non-coding RNA NRIR (lncRNA AC017076.5) was quantified relative to the reference gene *GAPDH*. All reactions were performed in technical duplicates. Relative expression values were derived for downstream analysis.

Systems-level network analysis (Supplementary data)

To contextualize NRIR within IFN-associated signaling architecture, a STRING-derived protein-protein interaction network was constructed using canonical IFN-responsive genes. Network topology metrics and Gene Ontology enrichment were computed using igraph and clusterProfiler packages in R. Detailed methodology and outputs are provided in the Supplementary data.

Statistical analysis

Two pre-specified comparisons were conducted: (1) APS patients versus healthy controls, and (2) obstetric APS (OAPS) versus NOAPS. Values were summarized as median and interquartile range (IQR) and compared using exact Mann-Whitney U tests. All analyses were exploratory and hypothesis-generating. Statistical analyses and data visualization were performed using SPSS version 24 (IBM) and GraphPad Prism version 8. A two-tailed $p < 0.05$ was considered statistically significant. Analyses were not adjusted for treatment exposure or other clinical covariates.

Results

The study cohort comprised 25 patients diagnosed with APS. Baseline demographic and clinical characteristics are summarized in table 1. The median age at the time of sampling was 40.0 years (interquartile range [IQR], 35.5-50.5), and the median body mass index was 25.98 kg/m² (IQR, 25.06-29.12). The cohort was predominantly female, with 20 women (80.0%) and 5 men (20.0%).

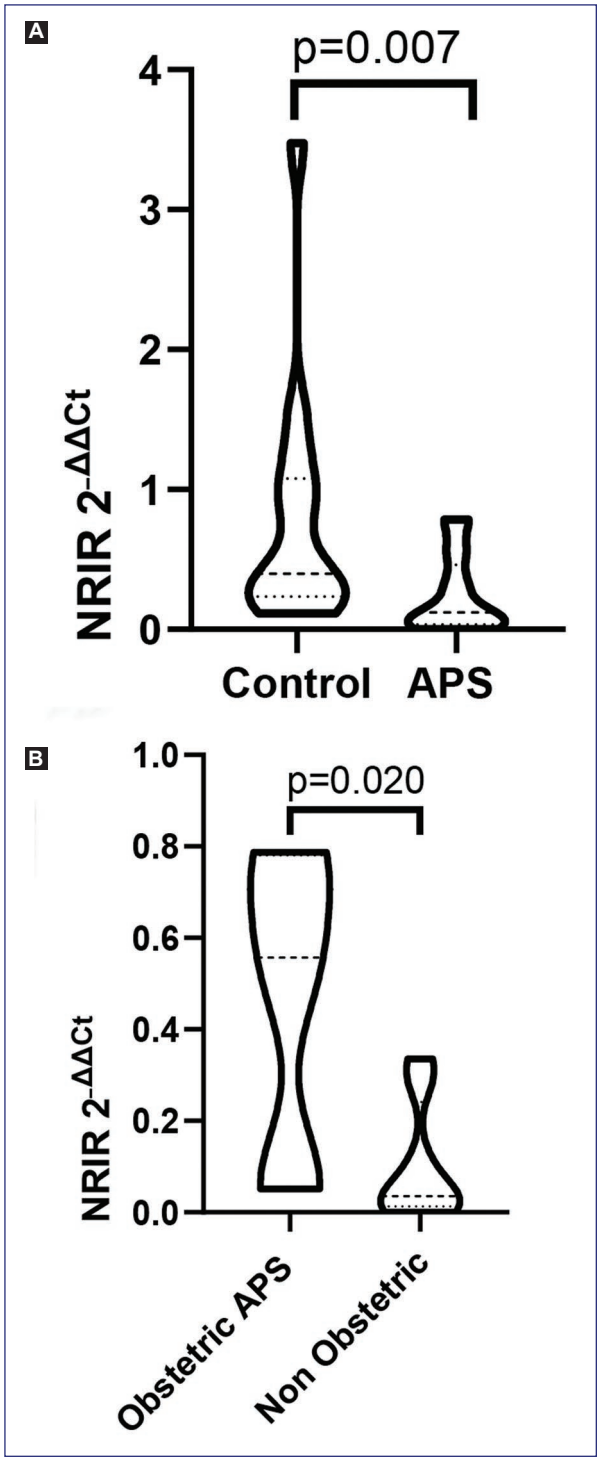

Figure 1. A and **B:** comparison of lncRNA NRIR between interests' groups.

Most patients were classified as having primary APS (n = 20, 80.0%), whereas 5 patients (20.0%) had secondary APS. Obstetric manifestations were present in 10 patients (40.0% of the cohort). Regarding ongoing treatments at the time of blood collection, 11 patients (44.0%) were receiving hydroxychloroquine, whereas 14 patients (56.0%) were not. Vitamin K antagonists were used by the majority of patients (n = 23, 92.0%), whereas 2 patients (8.0%) were not receiving this therapy.

NRIR expression was quantified in monocyte-enriched peripheral blood samples from all study participants. Analysis of ΔCt values demonstrated significantly lower NRIR expression in APS patients compared with healthy controls (p = 0.007), indicating downregulation of this lncRNA in the APS cohort (Fig. 1A).

Within the APS group, patients with obstetric manifestations exhibited less pronounced NRIR downregulation compared with those with NOAPS phenotypes (p = 0.020; Fig. 1B). Individual data points are shown in the corresponding figures to illustrate within-group variability.

To provide systems-level context, we constructed a STRING-derived IFN-responsive network (Supplementary data and Fig. 2). The module demonstrated high interconnectivity (density = 0.71), with STAT1 emerging as the dominant structural hub. Incorporation of NRIR-associated RNA-binding proteins positioned NRIR peripherally within the network (degree = 2). Functional enrichment analysis confirmed strong overrepresentation of type I IFN and antiviral pathways (Supplementary data), supporting the interpretation that NRIR operates within an established IFN module rather than constituting a primary signaling driver.

Discussion

In this exploratory study, we report that NRIR expression is reduced in monocyte-enriched peripheral blood cells from patients with APS compared with healthy controls. This observation aligns with prior evidence of transcriptional dysregulation affecting IFN-responsive pathways in subsets of APS patients, particularly within myeloid compartments. However, the present findings should be interpreted cautiously, as NRIR expression alone does not provide direct information on IFN pathway activity[11,12].

NRIR is frequently described as a "Negative Regulator of Interferon Response", yet its functional behavior is strongly dependent on cellular context. While NRIR attenuates ISG transcription in hepatocytes, studies in monocytes and related myeloid cells indicate that NRIR can instead support STAT1/STAT2-dependent transcriptional programs, including the expression of chemokines such as CXCL10 and CXCL11. Consequently, reduced NRIR expression in APS monocytes cannot be

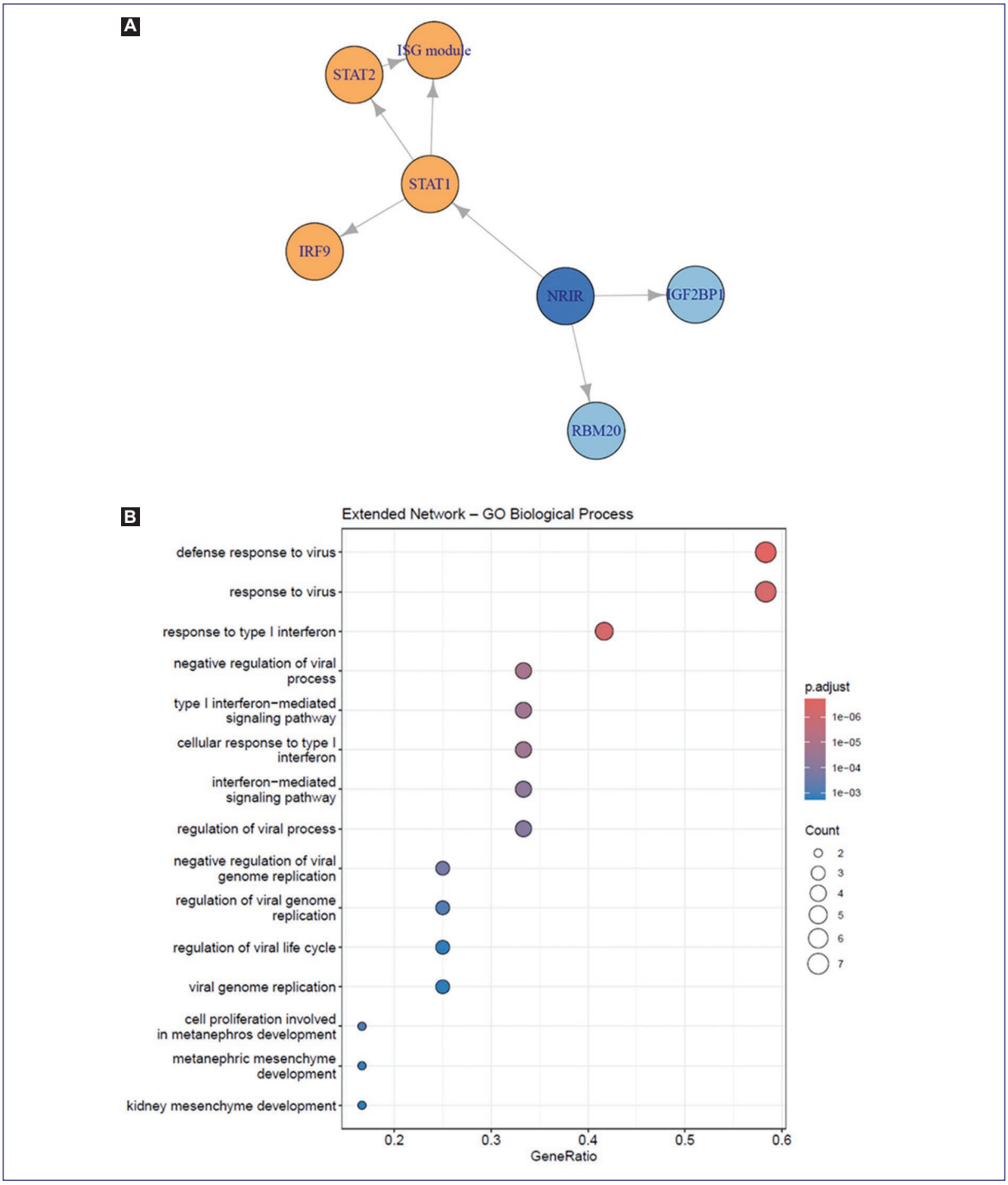

Figure 2. Integrated NRIR-Interferon Interaction Network and Functional Enrichment Analysis. **A:** conceptual integrated network depicting NRIR-centered interactions. NRIR (blue) is connected to RNA-binding proteins (IGF2BP1 and RBM20; light blue) identified through ENCORI CLIP-seq data and positioned in relation to the STRING-derived interferon (IFN) signaling module (orange), where STAT1 emerges as the principal hub linking STAT2, IRF9, and IFN-stimulated genes (ISG module). Edge connections within the IFN cluster represent experimentally supported protein-protein interactions from STRING (score ≥ 0.4). **B:** Gene Ontology (GO) biological process enrichment analysis of the extended network genes. Dot plot displays the top enriched terms ranked by adjusted p-value (Benjamini-Hochberg correction). Dot size corresponds to gene count per term, and color intensity reflects statistical significance (p.adjust). Enrichment is strongly dominated by type I IFN signaling, antiviral defense, and regulation of viral genome replication, supporting the positioning of NRIR within an IFN-associated regulatory landscape.

straightforwardly interpreted as either enhanced or diminished IFN signaling. Rather, it represents a transcriptional alteration whose functional consequences remain unresolved in the absence of direct measurements of ISGs, STAT activation, or composite IFN scores[13,14]. The biological significance of NRIR downregulation in APS, therefore remains open to interpretation. One possibility is that reduced NRIR expression reflects an adaptive or compensatory transcriptional response within monocytes exposed to chronic inflammatory cues. Alternatively, it may represent a broader disruption of IFN-responsive regulatory networks without a simple directional effect on pathway output. Importantly, these interpretations remain hypothetical and cannot be distinguished based on the present data, underscoring the need for functional and pathway-level validation in future studies.

Within the APS cohort, we observed less pronounced NRIR downregulation in OAPS compared with non-obstetric phenotypes. This finding should be considered exploratory, given the limited sample size of the obstetric subgroup and the absence of stratification by treatment exposure or disease activity. Differences in standard-of-care therapies between obstetric and NOAPS, such as anticoagulation strategies or hydroxychloroquine use, may contribute to the observed expression patterns and cannot be excluded as confounding factors. Moreover, because all samples were derived from peripheral blood, no inferences can be made regarding immune regulation at the maternal-fetal interface or placental compartments. As such, the observed subgroup differences are best interpreted as indicative of potential transcriptional heterogeneity rather than as evidence of phenotype-specific immune adaptation[15,16].

Altered NRIR expression has been described across a range of IFN-associated conditions, including systemic lupus erythematosus, systemic sclerosis, and multiple viral infections, where its direction and magnitude of regulation vary substantially by disease context and cell type. The present findings extend these observations to APS and further reinforce the concept that NRIR functions as a context-sensitive component of IFN-responsive transcriptional programs, rather than as a uniform regulator with predictable effects across immune settings[7,17,18].

A supplementary systems-level network analysis further supports a restrained interpretation of our findings. The IFN-responsive genes analyzed form a densely interconnected module centered on STAT1, consistent with canonical type I IFN signaling architecture. NRIR did not exhibit hub-like topological properties within this framework, suggesting that its role in APS may reflect context-dependent modulation rather than structural control of IFN signaling. These observations reinforce the exploratory nature of our study and underscore the need for functional validation.

Limitations

This study has several limitations. The cross-sectional design and modest sample size, particularly within the OAPS subgroup, limit statistical power and preclude multivariable adjustment. Although baseline characteristics are provided, potential confounding by treatment exposure cannot be excluded, and subgroup findings should be considered exploratory.

NRIR quantification was performed using standardized reverse transcription-quantitative polymerase chain reaction methodology, and raw Ct values are provided for transparency; however, normalization relied on a single reference gene (*GAPDH*), which may introduce residual bias despite stable Ct distribution across groups. Peripheral blood was collected in EDTA tubes and processed within 2 h; although RNA quality metrics were acceptable, RNA-stabilizing collection systems could further reduce pre-analytical variability. Monocyte enrichment was achieved by CD14-negative magnetic selection, but formal purity quantification was not performed, leaving open the possibility of minor lymphocyte contamination.

Importantly, ISGs, STAT phosphorylation, and composite IFN scores were not measured. Therefore, the relationship between NRIR expression and *in vivo* IFN activity in APS remains inferential. The supplementary network analysis provides systems-level context but does not substitute for functional validation. Larger, mechanistically integrated studies are required to clarify the biological and clinical relevance of NRIR dysregulation in APS.

Conclusion

NRIR (AC017076.5) expression is reduced in monocyte-enriched peripheral blood cells from patients with APS compared with healthy controls. Within the APS cohort, obstetric cases exhibited less pronounced NRIR downregulation than non-obstetric phenotypes, a finding that should be interpreted as exploratory given clinical and therapeutic heterogeneity. Although these observations do not establish a functional role for NRIR in IFN signaling or disease pathogenesis, they identify NRIR as a candidate long non-coding RNA associated with transcriptional variability in APS. Future studies

integrating NRIR profiling with IFN pathway measurements, treatment stratification, and longitudinal sampling will be required to clarify its biological and clinical relevance.

Funding

The authors declare that this work was partially supported by CECIHTI under the grant CBF-2025-I-3139 (Ciencia Básica y de Frontera 2025).

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

Supplementary data

Supplementary data are available at DOI: 10.24875/CIHR.25000023. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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