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DE SAN LUIS POTOSÍ

FACULTAD DE MEDICINA

Centro de Investigación en Ciencias de la Salud y Biomedicina (CICSaB)

Estudio del peNil de expresión de los lncRNA "s linc-PlNT, MEG3, BALR6 y£EB1-AS1 en pacientes con Leucemia Linfoblástica Aguda de precursores B

TESIS QUE PRESENTA

M. C. GABRIEL MATA I MORENO

PARA OBTENER EL GRADO DE
DOCTOR EN CIENCIAS BIONÉDICAS BÁSICAS

CO-DIRECTORES DE TESIS
DRA. ESTHER LAYSECA ESPINOSA
DR. EDGAR A. TURRUBIARTES MARTÍNEZ

SAN LUIS POTOSÍ, S.L.P.
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Tesis que presenta:
M. C. Gabriel Mata Moreno

PARA OBTENER EL GRADO DE **DOCTOR**
EN CIENCIAS BIONÉDICAS BÁSICAS

CO-DIRECTORES DE TESIS
Dra. Esther Layseca Espinosa
Dr. Edgar A. Turrubiartes Martínez

ASESORES DE TESIS
Dra. Perla del Carmen Niño Moreno
Dr. Roberto F. González Amaro

ASESOR EXTERNO
Dra. Carla Daniela Robles Espinoza

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Dra. Lina Raquel Riego Ruiz

SINODAL SUPLENTE
Dra. Adriana Elizabeth Monsiváis Urenda

SAN LUIS POTOSÍ, S.L.P.
Agosto 2026

RESUI' IEN

La leucemia linfoblástica aguda de precursores B (B-ALL) constituye la neoplasia maligna más frecuente en la población pediátrica y representa un importante problema de salud pública debido a su elevada incidencia y al riesgo de recaída asociado con la persistencia de enfermedad residual. En la actualidad, la evaluación de enfermedad mínima residual (EMR) mediante citometría de flujo multiparamétrica es considerada uno de los principales indicadores pronósticos para determinar la respuesta al tratamiento y estimar el riesgo de recurrencia. Sin embargo, las limitaciones relacionadas con la disponibilidad de infraestructura **especializada,** los **costos** operativos y la complejidad técnica de estas metodologías han impulsado la búsqueda de biomarcadores complementarios que permitan una caracterización más amplia de la biología tumoral.

En este contexto, los ARN largos no codificantes (long non-coding RNAs, lncRNAs) han surgido como moléculas de gran interés debido a su participación en la regulación de múltiples procesos celulares implicados en la oncogénesis, incluyendo la proliferación celular, la apoptosis, la reparación del ADN, la diferenciación celular y la resistencia al tratamiento. Diversos estudios han demostrado que la expresión aberrante de determinados lncRNAs puede **asociarse** con el desarrollo, progresión y pronóstico de múltiples tipos de cáncer, incluyendo neoplasias hematológicas.

El presente estudio explora el papel de cuatro lncRNAs con funciones previamente relacionadas con procesos clave de la leucemogénesis: MEG3, LINC-PINT, BALR6 y ZEB1-AS1. Para ello, se analizó su expresión en una cohorte de pacientes pediátricos mexicanos diagnosticados con B-ALL, comparando los niveles observados al momento del diagnóstico con aquellos detectados al finalizar la terapia de inducción a la remisión. Asimismo, se evaluó la relación entre la expresión de estos biomarcadores y el estado de enfermedad mínima residual determinado por citometría de flujo.

Los resultados muestran que los perfiles de expresión de algunos de estos lncRNAs difieren significativamente entre pacientes que alcanzan remisión y aquellos que presentan persistencia de enfermedad. En particular, se identificaron cambios relevantes en la expresión de MEG3, LINC-PINT y BALR6, sugiriendo que estas moléculas podrían reflejar procesos biológicos **asociados** con la sensibilidad o resistencia al tratamiento. Por el contrario, ZEB1-AS1 no mostró **asociaciones** significativas con la respuesta terapéutica en la cohorte estudiada.

Más allá de la identificación de posibles biomarcadores, este trabajo aporta evidencia acerca de la utilidad de los lncRNAs como herramientas para complementar la evaluación convencional de la EMR. Al reflejar mecanismos celulares relacionados con la supervivencia, proliferación y capacidad de adaptación de las células leucémicas, estos biomarcadores podrían contribuir a una mejor estratificación pronóstica y al desarrollo de estrategias de seguimiento más personalizadas.

En conjunto, esta investigación representa una de las primeras caracterizaciones longitudinales de la expresión de MEG3, LINC-PINT, BALR6 y ZEB1-AS1 en pacientes pediátricos mexicanos con B-ALL, y proporciona información relevante sobre el potencial de los lncRNAs como marcadores moleculares complementarios para la monitorización de la respuesta terapéutica en leucemia linfoblástica aguda.

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Article

Long Non-Coding RNA Expression in B-Cell Precursor Acute Lymphoblastic Leukemia: Analysis of LINC-PINT, MEG3, BALR6, and ZEB1-ASI

Gabriel Mata Moreno [1,2], Edgar A. Turrubiartes Martínez [1,3], Lourdes Cecilia Correa González [4], Eduardo Roberto Caballero Lugo [4], Óscar Pérez Ramírez [4], Perla Niño Moreno [5]* and Esther Layseca Espinosa [2,6]*

[1] Medical Genonaics Section, Research Center in Health Sciences and fiiomedicine, Universidad Autonoma de han Luis Potosí, han Luis Pcatc si 78210, Mexico; Gabriel.mataOuaslp.mx (G.M.M.); edgar.turrubiartesAuas1p.mx (E.A.T.M.)
Mcalecular and Translational Medicine Section, Pxesearch Center for Health Sciences and Biomedicine, Universidad Autéancrna de San Luis Pcatosí, San Luis Pr te si 78210, Mexiccn
[3] Henaatolcngy Laboratory, Faculty of Chemical Sciences, Universidad Autúnncama de San Luis Potosí, San Luis Potosi 78210, Mexico
Hcaspital Re$icnnal de Alta Especialidad "Dr. I acica Mcnrcanes Prietca", San Luis Pcatcasi 75290, Mexicca; cecilia.correaOuaslp.nix (L.C.C.G.); caballerolugo.hematopediaOgmail.com (E.R.C.L.); c scar.perezBuas1p.mx (Ó.P.R.)
[5] Faculty enf Chemical Sciences, Universic4ad Autónoma de San Luis Pcatosí, San Luis Potosi 78210, Mexico
Department cal Immunology, Faculty of Medicine, Universidad Autónoma de San Luis Potosí, San Luis Potosi 78210, Mexiccn
Correspondence: ncarmenpHuaslp.mx (P.N.M.); esther.laysecaOuas1p.mx (E.L.E.); Tel.: +52-4448261450 (ext. 8545) (P.N.M.); +52-4448261450 (ext. 8536) (E.L.E.)

Abstract

Background/Objectives: Long non-coding RNAs (lncRNAs) have been identified as potential biomarkers for cancer diagnosis and prognosis. In the present study, we proposed the analysis of four lncRNAs as a diagnostic support candidate for the follow-up of leukemia patients. The aim of this study was to characterize the expression of BALR6, LINC-PINT, MEG3, and ZEB1-AS1 in patients with B-cell acute lymphoblastic leukemia (B-ALL) at diagnosis and at the end of remission induction therapy. Methods: B-ALL diagnosis and MRD assessment were performed by flow cytometry, while lncRNA expression levels were quantified using TaqMan probe-based assays. Results: Fifteen pediatric patients with B-ALL were followed longitudinally. MRD evaluation identified seven refractory and eight remitted patients. Significant expression changes were observed for MEG3 in remitted patients and for BALR6 and LINC-PINT in refractory patients. No statistically significant differences were detected for ZEB1-AS1. Conclusions: Changes in MEG3, LINC-PINT, and BALR6 lncRNA expression are associated with treatment response and MRD status in pediatric B-ALL, supporting their potential role as complementary biomarkers to conventional MRD monitoring.

Keywords: lncRNA; leukemia; B-ALL; minimal residual disease

Academic Edith r: Kiminobu Sugaya

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1. Introduction

Cancer is considered the seventh leading cause of death from non-communicable diseases among children under 5 years of age and the second among those aged 5 to 14 years. Leukemia is the most frequent clinical presentation, with a recorded incidence of

3.2 new cases and 1.3 deaths per 100,000 population [1]. In Mexico, the incidence reaches 5.76 new cases and 5.18 deaths per 100,000 population. Acute lymphoblastic leukemia accounts for 85.35% of total cases, of which 52.69% correspond to precursor B-cell acute lymphoblastic leukemia (B-ALL) [2–4]

Successful treatment of acute lymphoblastic leukemia relies largely on two critical factors: early diagnosis and accurate monitoring of minimal residual disease (MRD) [5] MRD assessment has become a cornerstone of contemporary risk stratification, as numerous studies have consistently demonstrated its strong prognostic value for predicting relapse and guiding therapeutic decisions. However, in many low- and middle-income countries, access to MRD evaluation remains limited due to economic constraints and the restricted availability of specialized diagnostic assays [6] These disparities in diagnostic capacity contribute to differences in clinical outcomes. Indeed, while the 5-year survival rate for pediatric acute lymphoblastic leukemia exceeds 85°ñ in high-income countries, survival in Mexico remains approximately 60% [2–4,6]

Multiparametric flow cytometry is the gold standard for MRD diagnosis and evaluation. Antibody panels and analytical strategies have been refined and standardized in recent years to increase sensitivity and ensure reproducible, reliable results. Ideally, MRD assessment should be integrated into a comprehensive diagnostic approach that includes techniques such as fusion gene detection (via FISH or molecular biology) and karyotyping [7]

The main methodologies for MRD assessment—molecular techniques and flow cytometry—both exhibit high sensitivity and specificity [7]. However, molecular methods vary depending on the targeted genes and are limited by the low frequency of fusion gene alterations (approximately 42% of patients do not exhibit such changes) [8]. Meanwhile, flow cytometry is associated with elevated costs due to infrastructure and the technical expertise required for proper implementation. Therefore, there is a need to explore alternative approaches that offer MRD evaluation at a lower cost and greater accessibility. One promising option involves the use of long non-coding RNAs, which are being investigated as prognostic biomarkers in various types of cancer [9]

Long non-coding RNAs (lncRNAs) are RNA molecules longer than 200 nucleotides that lack protein-coding capacity but play critical regulatory roles in gene expression, including chromatin remodeling, transcriptional control, RNA processing, and translation. Dysregulated expression of lncRNAs has been strongly associated with the onset and progression of numerous malignancies [10] Several lncRNA expression signatures have been proposed as biomarkers for a variety of cancers, including both solid tumors and hematologic malignancies 1[10] . Some of these signatures have been validated, further supporting the role of lncRNAs as valuable tools for cancer diagnosis, monitoring, and prognosis.

In B-cell acute lymphoblastic leukemia (B-ALL), lncRNAs have been shown to be directly involved in the initiation and progression of neoplastic processes via cancer hallmarks proposed by Di Gesualdo (2014) [10–15] The lncRNAs evaluated in the present study were selected based on their reported involvement in biological processes associated with leukemogenesis. MEG3 functions as a tumor suppressor by promoting apoptosis and hematopoietic progenitor cell differentiation [16,17], thereby contributing to the regulation of cell survival and growth suppression. LINC-PINT participates in DNA damage repair and cell cycle control through modulation of the p53 signaling pathway and has been associated with apoptotic responses [18,19]. In contrast, BALR6 promotes leukemic cell proliferation and survival through activation of an SPI-driven transcriptional program [20], whereas ZEB1-AS1 contributes to leukemia maintenance by enhancing STAT3 signaling and other pathways related to cell proliferation and survival [21,22] Collectively, these lncRNAs are linked to hallmark processes such as sustained proliferative signaling, evasion

of growth suppressors, replicative immortality, and resistance to cell death, supporting their potential relevance as biomarkers of disease persistence and treatment response. Therefore, in the present study, we analyzed the relative expression of these lncRNAs and evaluated its association with MRD status as assessed by flow cytometry.

2. Materials and Methods

2.1. *Ethics 5tateiiient and Bone Marrow Aspiration Samples*

Samples were obtained under a protocol previously approved by the Research Ethics Committee from "Hospital Central Dr. Ignacio Morones Prieto" under registration CONBIOETICA-24-CEI-001-20160427. Bone marrow aspirate samples from patients with B-ALL were collected in EDTA tubes and kept at room temperature until processing (less than 24 h). Samples were collected at the time of diagnosis and at the end of remission treatment as part of routine laboratory tests.

2.2. *Sample* Die dcd *Flow CiJtoniet*ry *Acquisition*

Twenty-five microliters of the bone marrow aspirate sample were lysed with 925 JL of FACS™ Lysing Solution 1 x (BD Biosciences, San Jose, CA, USA; Cat. No. 349202) according to the manufacturer's specifications. The resultant pellet was resuspended in 1 mL of phosphate-buffered saline. Cellular counting was performed using a hemocytometer and trypan blue. A volume of the sample containing 150,000 cells was incubated for 30 min with CD45 (Beckman Coulter, Marseille, France; Cat. No. A74765), CD19 (Beckman Coulter, Marseille, France; Cat. No. IM1284U), CD10 (BD Biosciences, San Jose, CA, USA; Cat. No. 340923), CD34 (BD Biosciences, San Jose, CA, USA; Cat. No. 348791), CD56 (Beckman Coulter, Marseille, France; Cat. No. IM1430), CD38 (BioLegend, San Diego, CA, USA; Cat. No. 356616) and CD61 (BioLegend, San Diego, CA, USA; Cat. No. 349508). Erythrocyte lysis and fixation were performed using BD FACS Lysing Solution, after which the sample was resuspended in a final PBS volume of 150 ptL. Samples were acquired using a BD FACSCanto™ II flow cytometer (BD Biosciences, San Jose, CA, USA) until a minimum of 100,000 events were obtained. Analysis of the generated files was performed using Infinicyt software (version 2.0; Cytognos SL, Salamanca, Spain).

2.3. *Sample Preparation and* RNB *Extraction*

Bone marrow samples (600 qL) were processed for RNA extraction. Erythrocyte lysis was performed using Buffer EL (QIAGEN, Hilden, Germany; Cat. No. 79217); the resultant pellet was resuspended in 500 qL *ot* NucleoZol" (MACHEREY-NAGEL, Düren, Germany; Cat. No. 740404.200) and stored at —80 C until RNA extraction. Extraction was performed according to the NucleoZOL protocol, and RNA was resuspended in 30 JL of nuclease-free water. Quality and concentration were assessed by nano spectrophotometry using an Epoch™ Microplate Spectrophotometer (BioTek Instruments, Winooski, VT, USA; Agilent Technologies, Santa Clara, CA, USA).

2.4. *lncRNAs Evaluation*

cDNA was synthesized from purified RNA using RevertAid Reverse Transcriptase (Thermo Fisher Scientilic, Waltham, MA, USA; Cat. No. EP0441) with O1igo(dT) Primer (Thermo Fisher Scientific, Waltham, MA, USA; Cat. No. 50131) and RiboLock RNase Inhibitor (Thermo Fisher Scientific, Waltham, MA, USA; Cat. No. EO0382).

Quantitative PCR (qPCR) was performed using the following TaqMan™ Gene Expression Assays (20 x): Hs05031477_s1 (LINC-PINT), FAM™*-MGB probe (Thermo Fisher Scientific, Waltham, MA, USA; Cat. No. 4448484); Hs00292028_m1 (MEG3), FAM™-MGB probe (Thermo Fisher Scientific, Waltham, MA, USA; Cat. No. 4448484); Hs01398645_g1 (ZEBI-

AS1), FAM™*-MGB probe (Thermo Fisher Scientific, Waltham, MA, USA; Cat. No. 4426961); Hs00245445_m1, VIC™"-MGB probe, 20 x (Thermo Fisher Scientific, Waltham, MA, USA; Cat. No. 4448490); and a Custom TaqMan™* Gene Expression Assay (BALR6), FAM™"-MGB probe, 20 x (Thermo Fisher Scientific, Waltham, MA, USA; Custom Assay ID: APT2DV2). Reactions were carried out using TaqMan™ Universal PCR Master Mix (Advanced Master Mix Reagent) (Applied Biosystems, Foster City, CA, USA; Cat. No. 4444556) on a CFX96 Touch™* Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA, USA).

Data were analyzed using CFX Maestro™* Software v5.3.022.1030 (Bio-Rad Laboratories, Hercules, CA, USA). Relative lncRNA expression levels were calculated using the 2*^^Ct method, with ABU serving as the endogenous control gene.

2.5. MRD Evaluation

A second bone marrow aspirate sample was taken at the end of the induction therapy. The sample was processed as previously described with the following modifications: at least 1,200,000 cells were incubated with antibodies, and then 1,000,000 events were acquired in the cytometer. MRD was analyzed using the strategy shown in Figure I to distinguish neoplastic cells from hematogones. The cutoff was established at 0.01% of the total acquired events. Patients were considered MRD-positive when at least 100 cells exhibiting the leukemia-associated immunophenotype identified at diagnosis were detected, whereas patients with fewer than 100 such cells were considered MRD-negative.

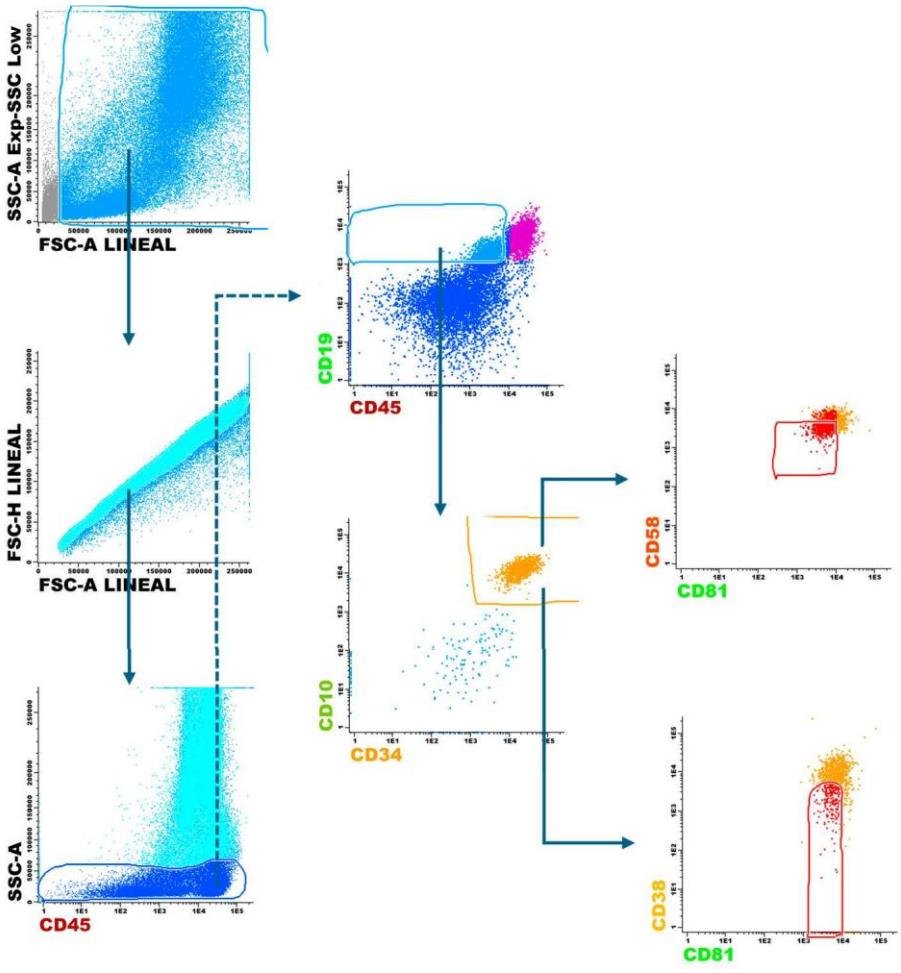

Figure 1. Gating strategy for MRD analysis. Cell populations were evaluated according to the initial leukemic immunophenotype (in this example by high CD10 and expression). B-cell precursor candidates

were identified as low side-scatter events with variable CD45 expression and positivity for CD19. The leukemic population was subsequently refined based on CD10 and CD34 co-expression. Expression patterns of CD3S, CD5S, and CD81 were then used to discriminate heinatogones (gold) front leukemic blasts (red) displaying a similar precursor B-cell phenotype, as previously described by Tsitsikov (2015) [23]. Blue arrows denote the sequential gating workflow employed during flow cytometric analysis, illustrating how each gated cell population was subsequently used to generate the next analytical plot.

2.6. *Statistical Analysis*

Paired comparisons of mean relative gene expression levels between diagnosis and MRD evaluation were performed using the Wilcoxon matched pairs signed-rank test (two-tailed). Comparisons of gene expression levels between remitted and refractory patients were performed at diagnosis and MRD evaluation using the Mann—Whitney U test (two-tailed), given the independent nature of the study groups. All statistical analyses were conducted using GraphPad Prism (version 10.4.1; GraphPad Software, San Diego, CA, USA). A p-value < 0.05 was considered statistically significant.

3. Results

3.I. *Cohort Char acteristics*

Complete follow-up data was obtained for 15 patients diagnosed with B-ALL, from the time of diagnosis through MRD evaluation at the end of remission induction therapy. The mean age of the patients was 9.4 (A4.5) years, and males accounted for 80*ñ of the cases. Clinical features of patients are summarized in Table 1; detailed sociodemographic data are included in Table S1.

Table 1. Clinical features of B-ALL pediatric patients enrolled in this study.

Patient_ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Sex (F/M)	M	M	F	M	M	M	M	M	M	M	F	M	F	M	M
Age (years)	6	10	5	15	2	13	13	5	4	9	14	14	12	9	8
					ND	ND									
Leukocytes (K/µL)	3.86	2.30	6.49	5.98	4.49	2t .2i1	24.43	1.68	0.76	3.38	1.44	7.41	3.2g	ND	ND
MIiD (°o)	<0.01%	<0.01%	<0.01%	0.0114	<0.01%	0.439	0.04	<0.01%	0.028	0.017	<0.01%	<0.01%	0.0118	0.09	0.017

Abbreviations: ND—no data. EGIL—Eurcapean Grcaup for the Immunolcagical Characterization of Leukemias.

5.2. *MRD Evaluation at the End of Induction Therapy*

MRD assessment by flow cytometry identified seven patients with positive MRD, classified as refractory disease patients, and eight patients who achieved remission, classified as remitted disease patients. Details are shown in Table 1.

3.3. *lncRNA Expression* Pro fts *According to Treatment Response*

The relative expression of selected long non-coding RNAs (lncRNAs) was evaluated at diagnosis and at the end of induction therapy and then stratified according to treatment response (MRD+ vs. MRD—). Details are shown in Table 2.

Table 2. Relative lncRNA expression levels at diagnosis and at MRD evaluation.

	Refractory Disease (MRD-Positive)								nemitted Disease (MRD-Negative)							
	BALR6		LINC-PINT		MEG3		ZEB1-ASI		BALR6		LINC-PINT		MEG3		Z€B1-ASI	
	Dx	MRD	Dx	MRD	Dx	MRD	Dx	MRD	Dx	MRD	Dx	MRD	Dx	MRD	Dx	MRD
Meai	−1.19	2.67	1.07	−1.76	0.36	−1.71	1.99	0.17	0.21	*−0.J8*	−1.86	−2.83	1.W	−2.9W	1.W8	−0.30
SD	2.28	1.49	2.41	2.25	3.31	1.85	3.21	2.15	3.62	2.71	2.26	1.13	2.W2	1.8W	1.73	2.33
p—value	0.0469		0.0312		0.156ź		0.5751		0.5438		0.562a		0.0312		0.2158	

Abbreviations: Dx, diagncnsis; MRD, minimal residual disease at the end c f remissicon induction treatment. Bold values indicate statistically si ificant differences (p < 0.05).

3.3.1. Expression Levels of lncRNAs at Diagnosis and at the End of Induction Therapy

At diagnosis, a statistically significant difference in LINC-PINT expression was observed, with higher expression levels in patients with treatment-refractory disease compared to those who achieved remission. Furthermore, when evaluating the expression oi the molecules of interest at the end of induction therapy, a trend toward increased BALR6 expression was detected in patients with refractory disease relative to the remission group ($p = 0.0513$). Details are shown in Figure 2.

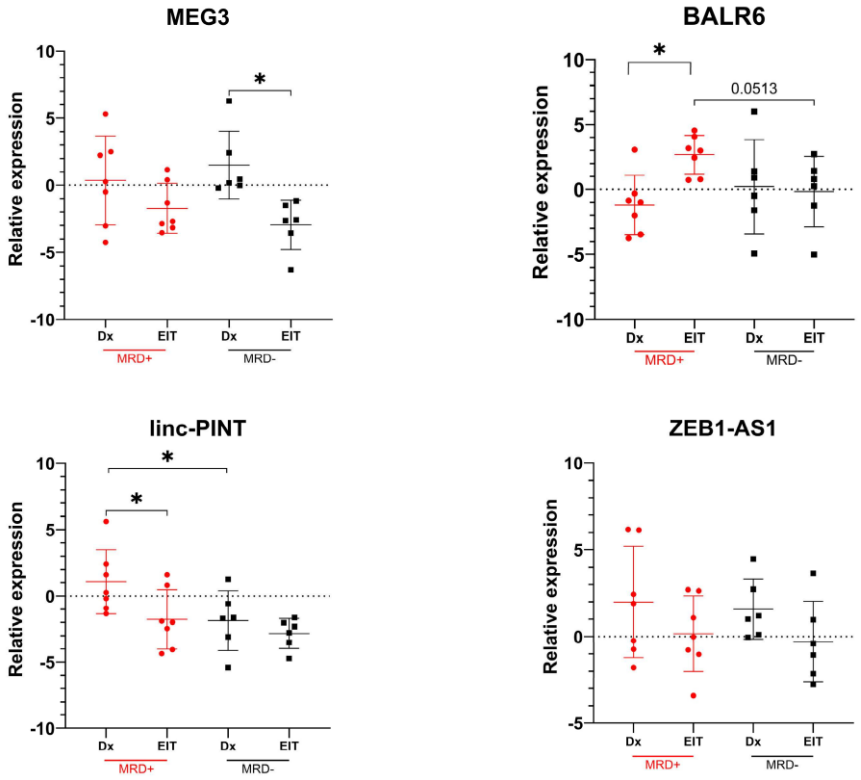

Figure 2. Relative lncRNA expression levels at diagnosis (Dx) and at the end of remission induction therapy (EIT). Patients with refractory disease (MRD-positive) are shown in red, whereas patients who achieved remission (MRD-negative) are shown in black. An asterisk (*) denotes a statistically significant difference ($p < 0.05$).

3.3.2. Differences in lncRNA Expression from Diagnosis to End of Induction Therapy

Regarding treatment-associated changes following induction therapy, a statistically significant increase in BALR6 expression was observed in patients with treatment-refractory disease. In contrast, MEG3 expression showed a statistically significant decrease in patients who achieved remission. Additionally, a significant reduction in LINC-PINT expression was detected in patients who did not achieve remission. No statistically significant differences were observed in ZEBI-AS1 expression when comparing baseline and end-of-treatment levels in either group. Details are shown in Figure 2.

4. Discussion

The natural history of leukemia includes the possibility that treatment-resistant clones may emerge during pharmacological therapy, leading to treatment failure or disease relapse after therapy completion. Such events may occur even several years after the conclusion of induction therapy aimed at achieving remission. To reduce this risk, strategies such as the assessment of MRD—primarily through flow cytometry and, in certain cases, through molecular methods—have been developed to evaluate the likelihood of relapse in individual patients (van Dongen, van der Velden et al., 2015) [7]. However, these methodologies

present an inherent limitation related to the resolution capacity of the available technologies; under no circumstances can it be guaranteed that a patient is entirely free of cells exhibiting neoplastic processes or characteristics (van Dongen, van der Velden et a1., 2015; Li, 2022) [8,24]

Consequently, there is a clear need to identify novel approaches capable of assessing patient status in a more comprehensive manner. These approaches should not rely solely on the expression of markers associated with active neoplastic processes but rather on indicators that reflect the intrinsic cellular capacity to initiate or sustain malignant transformation.

In the present study, we sought to characterize this capacity within bone marrow cells by evaluating five principal oncogenic hallmarks: sustained proliferative signaling, evasion of growth suppressors, activation of invasion and metastasis processes, enabling of replicative immortality, and resistance to cell death (Schmitt and Chang 2016) [25]. The long non-coding RNAs (lncRNAs) analyzed were selected based on existing evidence of their involvement in these processes, and their expression profiles were examined in relation to disease remission status (MRD-positive versus MRD-negative).

The significantly higher levels of MEG3 expression observed in patients who achieved remission suggest the ability of these cells to regulate apoptotic pathways through p53 signaling and other non-canonical mechanisms [26]. As previously reported by Gao (2021) [27] and Zhang and Qin (2024) [17], this regulatory capacity translates into a more favorable prognosis and an enhanced potential of hematopoietic precursor cells to undergo appropriate differentiation. Interestingly, despite the association between elevated MEG3 expression and remission, a reduction in MEG3 levels was observed following induction therapy. We propose that this finding may reflect changes in the cellular composition of the bone rriarrow during treatment response. As induction therapy reduces the leukemic burden and promotes marrow recovery, the overall MEG3 expression profile may shift due to the progressive replacement of leukemic cells by regenerating normal hematopoietic populations.

Although studies by Wang, Guo et a1. (2021) [19] and Lin, Chen et al. (2024) [28] have reported that elevated expression levels of LINC-PINT in solid tumors are associated with favorable clinical outcomes, our results reveal a markedly different scenario. The present study found that high LINC-PINT expression at the time of diagnosis was associated with a poorer response to induction therapy. This is likely to be due to the enhanced ability conferred by this lncRNA to repair DNA damage, as previously described by Wang, Guo et al. (2021) 1[19]. While these earlier studies focused on solid malignancies, Garitano-Trojaola, San José-Enériz et a1. (2018) [29] demonstrated that, under basal conditions, B-lineage cells (CDl9+) from healthy individuals exhibit low LINC-PINT expression, which is consistent with our observations in patients who achieved remission. Therefore, high levels of LINC-PINT expressions appear to enhance cellular DNA repair mechanisms, thereby mitigating the cytotoxic effects of administered therapies.

In agreement with the findings reported by Rodriguez-Malavé, Fernando et al. (2015) [30], our results demonstrate that high expression of the lncRNA BALR6 promotes the proliferation of leukemic clones, as evidenced by increased expression levels in MRD-positive patients at the end of induction therapy. These findings provide in vivo validation of previously reported experimental data. Additionally, patients who achieved remission following induction therapy exhibited low BALR6 expression levels at diagnosis and maintained comparable levels at treatment completion.

Regarding ZEB1-AS1, contrary to the observations reported by Wang, Du et al. (2017) [31], our data did not reveal statistically significant differences between patient groups or MRD stages. According to Hu, Cesano et a1. (1993) [32], leukemic B cells display limited responsiveness to IL-11, either alone or in combination with other cytokines, which may account for the absence of detectable effects.

While these findings suggest a potential association between lncRNA expression and treatment response, they should be interpreted in the context of the limited cohort size. Therefore, the observed trends require confirmation in larger studies before definitive conclusions regarding their clinical utility can be drawn.

It is important to highlight that the biological roles of lncRNAs may differ substantially between solid and hematological malignancies. For example, several studies have reported that elevated expression of lncRNAs such as MEG3 is associated with favorable clinical outcomes and tumor-suppressive functions in solid cancers 1[7] . But our findings suggest a more complex pattern in pediatric B-ALL, showing dynamic changes following induction therapy as described by Wang, Airong et a1. (2022) [33]. These discrepancies may reflect that differences exist between solid and hematologic malignancies. For these reasons, the functional role of lncRNAs cannot be generalized across malignancies and should be interpreted according to the biological context of each cancer type.

In context, a limited number of lncRNA-validated panels with diagnostic and prognostic relevance have already been reported for various malignancies, including gallbladder carcinoma (Mishra, Srivastava et al., 2024) [34], esophageal squamous cell carcinoma (Tong, Wang et al., 2015) [35], lung squamous cell carcinoma (Hu, Jie et a1., 2016; Satpathy, Krug et al., 2021) [36,37], hepatocellular carcinoma (Li, Shi et al., 2019; Zeng, Guo et al., 2019) [38,39], breast cancer (Li, Wang et al., 2018; Shaath, Elango et al., 2021) [40,41], colorectal cancer (Matouk, Abbasi et a1., 2009) [42], clear cell renal cell carcinoma (Wu, Wang et al., 2016; Zeng, Lu et a1., 2019) [43,44], head and neck squamous cell carcinoma (Xing, Zhang et al., 2019; Wang, Bian et a1., 2021) [45,46], and acute myeloid leukemia (Wang, Tian et al., 2018; Chen, Wang et a1., 2019) [47,48], among others.

5. Conclusions

Overall, this study represents, to the best of our knowledge, the first evaluation of MEG3, LINC-PINT, BALR6, and ZEBI-AS1 expression in a Mexican pediatric B-ALL cohort and the first assessment of their expression dynamics between diagnosis and MRD evaluation. Our findings demonstrate that cellular processes associated with leukemic persistence can be indirectly monitored through the evaluation of these molecules by providing a more comprehensive view of the residual cellular population persisting after induction therapy, contributing to improved risk stratification and the development *ot* more personalized disease-monitoring and therapeutic decision-making strategies. Nevertheless, larger naulticenter studies are required to validate these findings and establish the clinical utility of lncRNA-based biomarkers in routine leukemia monitoring.

Supplementary Materials: The following supporting information can be downloaded at: http : // ww .mdpi.crrsa /a rticle / â tJ.33 4tJ/1ited 607a 042/s1, Table S1: Sociodemographic and clinical data.

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Abbreviations

The following abbreviations are used in this manuscript:

B-ALL	B-cell acute lymphoblastic leukemia
lncRNA	Long non-coding RNA
MRD	Minimal residual disease
CD	Cluster of Differentiation

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viruses

Article

Global Extension and Predominance of Human Mełapneumovirus A2 Genotype with PartGal Gene Duplication

Juan Carlos Muñoz-Escalante *, Gabriel Mata-Moreno [2], Gerardo Rivera-Alfaro [1] and Daniel E. Noyola '•*

Microbiology Department, Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Pc tc sí 75210, Mexicca; earls s.esca1anteHuas1p.mx (J.C.M.-E.); a23S87lßalunuic s.uas1p.mx (G.R.-A.) Sectic n L f Molecular anc4 Translaticnnal Medicine, Centres de Investigacićan de Ciencias de la Salud y Biomedicina, Universidad Autónoina de San Luis Potosí, San Luis Potosí 78210, Mexico; alSS504ßalumnos.uas1p.mx
Correspondence: dnoyo1aØuaslp.mx; Tel.: +52-(444)-S2G-2344 (ext. 6656)

Abstract: Human metapneuniovirus (HMPV) is an important respiratory pathogen and is divided in two main groups (A and B). HMPV strains with partial duplications (111-nt and 150-nt duplication) of the G gene leave been reported in recent years. Since the initial reports, viruses with these characteristics have been reported in several countries. We analyzed all complete HMPV G gene ectodomain sequences available at GenBank to determine if viruses with 111-nt or 1ß0-nt duplication have become the leading HMPV strains worldwide, and to describe their temporal and geographic distribution. We identified 1462 sequences that fulfilled study criteria (764 HMPV A and 698 HMPV B) reported from 37 countries. The most frequent HMPV A genotype was A2b2 (rt = 366), and the most frequent B genotype was B2 (a = 374). A total of ß4 sequences contained the Ill-nt duplication, and 90 sequences contained the 180-nt duplication. Since 2016, viruses with a partial duplication comprise the most frequent HMPV A sequences globally and have displaced other HMPV A viruses in Asia, Europe, and South America; no sequences of viruses with partial duplication have been reported in North America or Africa so far. Continued surveillance of HMPV is required to identify the emergence and spread of epidemiologically relevant variants.

Keywords: human metapneumovirus; epidemiology; acute respiratory infections; genotype; molecular epidemiology; pneumovirus

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1. Introduction

Human metapneumovirus (HMPV) is an important causative agent of upper and lower respiratory infections in children and adults. This virus was first reported in 2001, although viral circulation can be traced back to the 1950s [I]. About half of children are infected by HMPV by two years of age, and by the age of five most children have already been infected by this virus. Infections caused by this pathogen are usually mild to moderate in healthy individuals; however, numerous reports have shown severe and even fatal pneumonia can occur, predominantly in elderly individuals and immunocompromised patients [2]

HMPV is an enveloped, negative-sense, single-stranded RNA virus that is classified, together with respiratory syncytial virus (RSV), in the Pneumoviridae family. The viral genome contains eight genes (N, P, M, F, M2, SH, G, and L), which encode a total of nine proteins, including three surface glycoproteins: F (fusion), SH (small hydrophobic), and G (attachment) [2]

HMPV strains are divided in four major genotypes: Al, A2, B1, and B2. The G protein gene is the most variable of all viral genes and mutations occur predominantly in the region encoding for the extracellular domain of the protein [3]. Diversity of HMPV has

Population-based Influenza and Respiratory Syncytial Virus Hospitalizations and In-hospital Mortality Rates Among Mexican Children Less Than Five Years of Age

Gabriel Mata-Moreno, MSc,[Sofía Bernal-Silva, MD, PhD,*[Christian A. García-Sepúlveda, MD, PhD,J Ana María González-Ortíz, MD,§ Uciel R. Ochoa-Pérez, MD, MSc,* Aldo Uzziel Medina-Serpa, MD, MPH,"f Luis Fernando Pérez-González, MD,ll and Daniel E. Noyola MD,* PhD*{

Background: Population-based information regarding the impact of respiratory syncytial virus (RSV) and influenza on hospital admissions and mortality is scant for many countries.

Methods: Prospective testing of RSV and influenza virus was undertaken in patients <5 years old admitted to hospital with acute respiratory infection (ARI) between July, 2014 and June, 2015, and mortality rates for children living in 3 municipalities in the state of San Luis Potosi were calculated.

Results: During the 12-month study period, 790 children living in these municipalities were admitted with ARI. RSV was detected in 245 (31%) and influenza in 47 (5.9%). History of preterm birth was recorded for 112 children on admission. For children <5 years old, ARI-, RSV- and influenza-associated admission rates were 23.2, 7.2 and 1.4 (per 1000 populatican), respectively. The corresponding admission rates per 1000 infants <1 year old were 78, 25.2 and 4.4. Preterm infant admission rates were 2 times higher than those of term infants. Six children died; RSV was detected in 4 (66.6%) of the deceased, while no deaths were associated with influenza. ARI and RSV in-hospital mortality rates for children <5 years were 0.18 and 0.12 per 1000 population. ARI and RSV mortality rates in preterm infants were 7 and 14 times higher than in term infants, respectively.

Conclusions: RSV was associated with both high admission and in-hospital mortality rates in children <5 years old. Specific interventions, such as active or passive immunization, to prevent RSV infections are required to reduce ARI-asscaciated infant mcartality.

Key Words: influenza, respiratory syncytial virus, acute respiratory infections, hospitalization, mortality, incidence, population-based studies

(Pediatr In[ect Dis J1024;XX:00-00)

cute respiratory infections (ARIs) are a major cause of morbidity And mortality in children <5 years old.' The World Health Organization estimates that pneumonia accounted for 14% of all deaths of children <5 years old in the world during 2019.' Respiratory viruses comprise the most common causes ofARl in children. Before the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) pandemic, respiratory syncytial virus (RSV) and influenza represented 2 leading causes ofsevereARI.[2] However, studies that report population-based rates for hospital admissions and mortality are not available for most countries and, therefore, reported rates for several of these countries are largely based on global data estimates.' While such estimates are useful, primary studies focused on assessing the contribution of individual pathogens in specific populations are required to guide preventive and therapeutic interventions by public health officials. In this study, we prospectively analyzed hospital records irom San Luis Potosi, Mexico to estimate population-based hospitalization and in-hospital mortality rates associated with RSV and influenza before the SARS-CoV-2 pandemic. This represents, to the best of our knowledge, the first study addressing population-based hospitalization rates for respiratory viral pathogens in Mexico, the 10th most populated country in the world.

SUBjECTS AND METHODS

This study was carried out in San Luis Potosí, Mexico. Children <5 years old admitted because of ARI between July 2014 and June 2015 to Hospital Central "Dr. Ignacio Morones Prieto," Hospital del Niño y la Mujer "Dr. Alberto Lopez Hermosa" and Hospital General de Soledad de Graciano Sánchez were eligible for participation. These hospitals are located in the metropolitan area of San Luis Potosí city (which includes both San Luis Potosí and Soledad de Graciano Sánchez municipalities), are part of the Mexican Ministry of Health hospital consortium and provide health care to patients not eligible for other social security institutions such as the Instituto Mexicano del Seguro Social (IMSS), Instituto de Seguridad y Servicios Sociales para los Trabajadores al Servicio del Estado (ISSSTE) and Hospital Militar de la Secretaría de la Defensa Nacional (SEDENA).

As patients from other regions of the state (even geographically remote areas) are referred to these hospitals, only residents of the municipalities of San Luis Potosí, Soledad de Graciano Sánchez and Mexquitic de Carmona were included in the present analysis to estimate population-based hospitalization rates. Iníants of these municipalities were selected to reduce the confounding effect relating to the inverse correlation that has been shown to exist between access (distance or transportation time) to medical care facilities and health care utilization.' Patients with nosocomial ARI (those admitted for other illnesses and presenting with respiratory symptoms >48 hours aíler admission, or patients presenting to the hospital with ARI who had been hospitalized during the preceding 2 weeks) were excluded from the study.

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*From the Microbiology Department, Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México; {Centro de Investigación en Ciencias de la Salud y Biomedieina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México; {Viral and Human Genomics Laboratory, Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México; §Hospital del Niño y la Mujer "Dr. Alberto Lúpez Hermosa", San Luis Potosí, México; JHospital General de Soledad de Graciano Sánchez, San Luis Potosí, México; and ||Pediatrics Division, Hospital Central "Dr. Ignacio Morones Prieto", San Luis Potosí, Mexico.

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Address for eorrespondence: Daniel E. Noyola, MD, PhD, Centro de Investigación en Ciencias de la Salud y Biomedieina, Universidad Autónoma de San Luis Potosí. Av. Sierra Leona 550, Colonia Lomas de San Luis. San Luis Potosí, S.L.P., México 78210. E-mail: dnoyola@uaslp.mx.

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viruses

Aríicle

Respiratory Syncytial Virus and Other Respiratory Viruses in Hospitalized Infants During the 2023—2024 Winter Season in Mexico

José J. Leija-Martínez[1], Sandra Cadena-Mota [2], Ana María González-Ortiz [3], Juan Carlos Muñoz-Escalante [1], Gabriel Mata-Moreno [4], Pedro Gerardo Hernández-Sánchez ', María Vega-Morúa ' and Daniel E. Noyola "[2]' *

[1] Infectious Diseases Laboratory, Centro de Investigación en Ciencias de la Salud y £liomedicina, Universidad Autéancama de San Luis Pcntcnsí, San Luis Potcasi 78210, Mexicra; jesus.leijaOuas1p.mx (J.J.L.-M.); carlcas.esca1anteOuas1p.nix (J.C.M.-E.)
Microbiology Department, Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Pr te si 78210, Mexico ; sandra.cadenaAuas1p.mx
[3] Hospital del Niño y la Mujer "Dr. Alberto López Hermosa", San Luis Potosi 78364, Mexico; ana$on7ldyahoo.cont.nix (A.M.G.-O.)
Histcaccnnapatibility Labcaratory, Centran de Investigacicon en Ciencias de la Salud y Bicomedicina, Universidad Autéanoma de San Luis Pcntcasí, San Luis Pr tosi 75210, Mexicra; gabriel.mataOuas1p.mx
Cc rrespcradence: dncayco1aAuas1p.mx

Abstract: Respiratory syncytial virus (RSV) is the leading cause of lower respiratory trac-t infec-tions in young c•hi1dren. During the COVID-19 pandemic, a significant change in the epidemiology of RSV and other viruses occurred worldwide, leading to a reduction in the circulation of these infectious agents. After the pandemic, the resurgence of seasonal respiratory viruses occurred, but some features of these infections contrast to those registered prior to the pandemic. In the present work, we studied 390 children <5 years old admitted to the hospital to determine the contribution of RSV, SARS-CoV-2, human metapneumovirus (hMPV), and influenza viruses to acute respiratory infections during the 2023—2024 winter season in Mexico. RSV was the most frequently detected virus (n = 160, 41%u), followed by SARS-CoV-2 (n = 69, 17.7%), hMPV (n = 6S, 17.4%), and influenza A or B (n = 40, 10.26%u). Fourteen patients required admission to the intensive care unit, including six (42.5%) with RSV infection. Four children died (1%). At least one of the four viruses was detected in all deceased patients: SARS-CoV-2 in one; SARS-CoV-2 and hMPV in two; and RSV, influenza A, and SARS-CoV-2 in one. The high impact *ot* RSV and other respiratory viruses indicates the need to implement specific preventive programs to reduce the morbidity and mortality associated with them.

Keywords: respiratory syncytial virus; severe acute respiratory syndrome coronavirus type 2; human metapneumovirus; influenza; acute respiratory infections; hospitalization; mortality; Mexico

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1. Introduction

Acute respiratory infections are one of the leading causes of morbidity and mortality worldwide, particularly in children [1]. While the etiology of these infections is wide, respiratory viruses are the leading cause of lower respiratory tract infections (LRTIs) in infants. Respiratory syncytial virus (RSV) is the most commonly recognized cause of LRTIs worldwide [2]. In 2019, there were an estimated 33.0 million RSV-related LRTIs, 3.6 million RSV-related LRTI hospital admissions, and 26,300 RSV-related LRTI in-hospital deaths [2]. In addition, human metapneumovirus (hMPV), influenza, and other viruses also contribute significantly to LRTI-associated hospitalizations in children [3,4]. Moreover, the SARS-CoV-2 pandemic has underscored the contribution of emerging viruses as causes of hospitalizations and deaths.

The role of respiratory viruses as leading causes of hospital admissions in children has been established for a long time. For example, a systematic review reported that the

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RESEARCH ARTICLE

Classification of hepatitis A virus in clades based on VP1/2A region allows higher geographic and temporal resolution than conventional genotyping: a global sequences analysis

Juan Carlos Muñoz-Escalante[a,b], Alan Axel Castro-Reséndiz[c], Mayra Colunga-Saucedo[d], Pedro Gerardo Hernández-Sánchez[b], Gabriel Mata-Moreno[a], Pedro Torres-González[a,b] and Daniel E. Noyola[a,b]

[a]Microbiology Department, Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México; [b]Infectious Diseases Laboratory, Centro de Investigación en Ciencias de la Salud y Biomedicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico; [c]Bioinformatics Research Unit, Centro de Investigación en Ciencias de la Salud y Biomedicina, Universidad Autónoma de han Luis Potosí, San Luis Potosí, Mexico; [d]Hi5tOcompatibility Laboratory, Centro de Investigación en Ciencias de la Salud y Biomedicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico

ABSTRACT

Infections caused by the Hepatitis A virus (HAV) occur worldwide. Molecular epidemiology is crucial to understanding the transmission dynamics; however, the current genotype assignment fails to provide useful epidemiologic information. We classified HAV sequences available in GenBank based on 460 bp of the VP1/2A region in clades. Additionally, we associated the site of isolation of the strains with the country's HAV endemicity. We analyzed 1369 sequences available in GenBank up to December 2023 which fulfilled inclusion criteria for our study. The collection date ranged from 1957 to 2023, and genotypes IA (*n* — 986) and IB (*n* — 290) comprised the majority of sequences. Sequences were assigned to 70 different clades; sequences from most clades (n = 36) were detected in one country or a few countries within a single continent, while sequences of only 9 clades were detected in more than two continents. Countries with lower HAV endemicity showed higher diversity of clades compared with countries with higher HAV endemicity. In addition, multinational HAV outbreaks were associated with specific clades. In conclusion, characterization of HAV strains below the genotype level should be helpful to analyze transmission patterns within and between countries.

KEYWORDS

Hepatitis A; viral hepatitis; hepatitis A virus; genotyping; molecular epidemiology

Introduction

Hepatitis A is a widespread viral hepatitis caused by the hepatitis A virus (HAV). It is transmitted by person-to-person contact through the fecal-oral route and by contaminated food and water [1]. HAV virus is endemic to many world regions, mainly developing countries with poor sanitation and low immunization rates [2] Most HAV infections occur during childhood in these areas, mainly as asymptomatic or self-limited diseases that confer lifelong immunity. Molecular epidemiology studies are rarely conducted in these regions since they present continuous sporadic cases, and contagion sources are seldom identified. Additionally, many HAV strains may be circulating simultaneously in these settings, limiting the usefulness of molecular epidemiology in controlling virus transmission [3]

Based on the prevalence of antibodies at different ages, countries have been classified as having high levels of endemicity (those in which >90% of the population has evidence of infection by age 10 years), intermediate (countries in which 50% of the population is positive by age 15 years, with <90% by age 10), low (countries with 150% of the population with infection by age 30 years, with <50% by age 15), and very low (<50% of the population infected by age 30 years) [4]. However, recent epidemiological shifts indicate that many countries are transitioning from high to intermediate or low HAV endemicity, resulting in a change in the age of infection, moving from childhood to early adulthood, when individuals are more likely to be symptomatic and can lead to severe outcomes, including hepatic failure [5–9]

In these settings, outbreaks of hepatitis A are more frequent, and molecular epidemiology studies are recommended to contain the spread of the disease and to identify a common source of contagion [6,10] . Moreover, large outbreaks of hepatitis A have been described among men who have sex with men and are caused by specific HAV strains [11—3].

The global implementation of molecular epidemiological tools is essential to studying HAV transmission dynamics effectively. While six HAV genotypes have been assigned (only genotypes I, II, and III, each with two sub-genotype5, affect humans), insights derived solely from genotyping are limited [14]. For instance,

CONTACT Daniel E. Noyola dnoyola@uaslp.mx Centro de Investigación en Ciencias de la Salud y Biomedicina, Universidad Autónoma de San Luis Potosí, Av. Sierra Leona 550, Colonia Lomas de San Luis, San Luis Potosí, 78210, México

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viruses

MDP

Article

Wastewater-Based Surveillance of Respiratory Viruses in the SARS-CoV-2 Post-Pandemic Period in Mexico

Oscar Uriel Ulloa-Medina *•[2], Pedro Gerardo Hernández-Sánchez [1], Gabriel Mata-Moreno [1], Luis Rubén Jaime-Rocha *•[3], Sara del Carmen Alatorre-Camacho *•[3], Ignacio Lara-Hernández [1], Mauricio Comas-García [1,3], Juan Carlos Muñoz-Escalante [1], Ana María González-Ortiz [4], Pedro Torres-González *•[2] and Daniel E. Noyola *•[2]•*

Centrca de Investigaciúan en Ciencias de la Salud y Bicnmedicina, Universidad Autóncama de San Luis Pratrasí, Av. Sierra Lejana 550, Llamas de San Luis, San Luis Pr te sí 78210, SLP, Mexico; odeoscar9Bgmai1.com (O.U.U.-M.); pedro.hernandezAuas1p.mx (P.G.H.-S.); gabriel.mataAuaslp.nix (G.M.-M.); car1c s.escalanteAuaslp.mx (J.C.M.-E.); pedrcatcnrres$canzalezA$naail.com (P.T.-G.)

Facultad de Medicina, Universidad Autónoma de San Luis Potosí, Av. Venustiano Carranza 2405, Lomas Icas Filtro s, San Luis Pr te sí 75210, SLP, Mexicca

[3] Facultad de Ciencias, Universidac4 Autéanoma c4e San Luis Potosí, Av. Parc{ue Chapultepec 1570, Privadas del Pedregal, San Luis Pote sí 78295, SLP, Mexico

Hcaspital de la Niñez y la Mujer "Dr. Albertca Lénpez Hermcasa", Blvd. Antcanica Rcncha Cc rdero 2510, San Juan de Guadalupe, San Luis Potosí 75364, SLP, Mexico; anagon7lüyahoo.cont.mx

Cc rrespondence: dncayco1aAuas1p.mx

Abstract

In recent years, wastewater (WW)-based epidemiology has been increasingly used for siirveillance of SARS-CoV-2 and has emerged as a potential tool for monitoring other respiratory viruses. Most evidence on the use of WW for detecting multiple respiratory viruses comes from developed countries. In this study, we assessed the feasibility of multi-respiratory virus sewage surveillance in a middle-income country and explored signals that may be potentially used as early warning signs for Public Health authorities. We examined the presence of SARS-CoV-2, irifluenza virus, respiratory syncytial virus (RSV), and human metapneumovirus (hMPV) in 238 WW samples collected from three treatment plants in San Luis Potosí, Mexico, over one year. The weekly detection of each virus was compared with the weekly number of hospital admissions for respiratory infections caused by that virus in pediatric patients. SARS-CoV-2, influenza, hMPV, and RSV were detected in 152 (63.9%), 108 (45.4%), 95 (39.9%), and 24 (10.1%) samples, respectively. There was no significant correlation between viral detection in WW and the number of hospitalizations during that week. However, analyses of WW viral detection with hospitalizations in subsequent weeks showed an increasing correlation reaching a maximum correlation for a lag of 12 weeks for SARS-CoV-2 (r, = 0.63, p = 0.001), 9 weeks for irifluenza (ra 0.62, p = 0.0001), 2 weeks for RSV (rs = 0.30, p = 0.05), and 3 weeks for hMPV (r, = 0.39, p = 0.009). In addition, we identified time-periods of SARS-CoV-2, influenza, and RSV widespread circulation (several consecutive weeks in which viruses were detected in the three treatment plants); most hospitalizations caused by these viruses occurred after widespread circulation was detected in WW, suggesting this may be used as an early alert for public health systems. Overall, our results show that WW-based surveillance of multiple respiratory viruses is feasible and has potential applications as an early warning system in middle-income countries.

Keywords: wastewater; wastewater-based epidemiology; SARS-CoV-2; influenza; respiratory syncytial virus; human metapneumovirus; COVID-19; infectious diseases; surveillance; environmental surveillance

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CENTRO DE INVESTIGACIÓN CIENCIAS DE LA SALUD Y BIOMEDICINA

FACULTAD DE MEDICINA

Estudio del perfil de expresión de los lncRNA´s linc-PINT, MEG3, BALR6 y ZEB1-AS1 en pacientes con Leucemia Linfoblástica Aguda de precursores B

MSc Gabriel Mata Moreno

Agosto 2026

1

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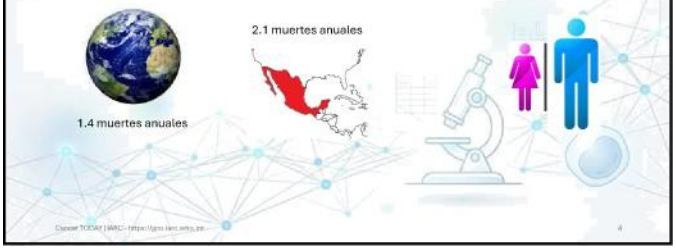
2

Incidencia (casos/100,000 habitantes)

3

Mortalidad (muertes/100,000 habitantes)



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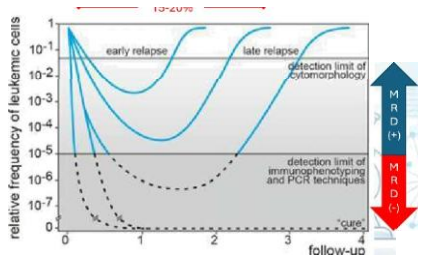
Historia natural de la enfermedad

5

Respuesta al tratamiento



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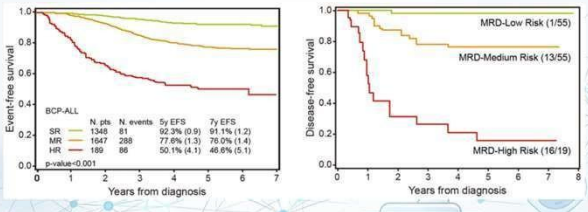
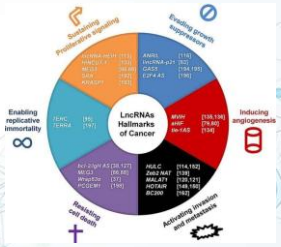
Importancia de MRD en LLA



7

RNA “s largos no codificantes

- A partir del 70% del genoma humano no codificante para proteínas
- Secuencias >20Ont sin aparente potencial codificante de proteínas
- Específicos de tejido y célula



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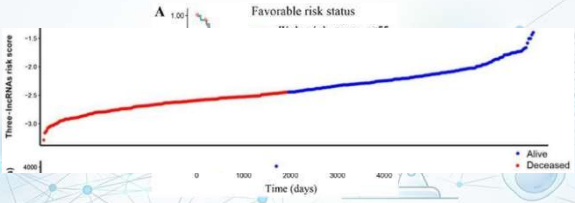
Firma de 3 lncRNA's para la predicción pronóstica de pacientes con LMA

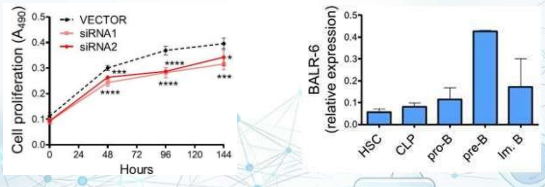


9

lncRNA's candidatos para el estudio

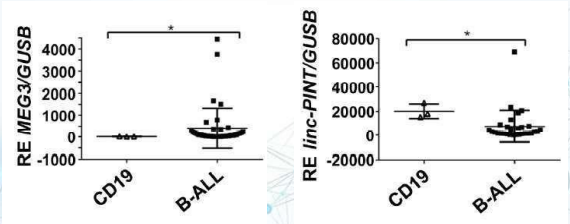
10

BALR-6 promueve la proliferación celular en líneas celulares de LLA



11

Expresión de MEG3 y lincPINT en células leucémicas



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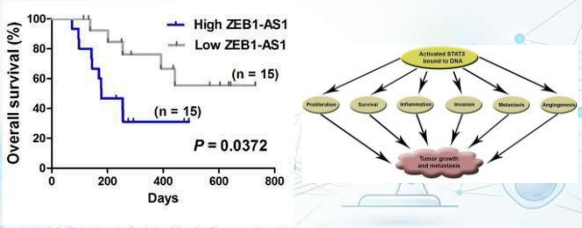
ZEB1-AS1 contribuye al mantenimiento de la LLA



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Justificación

GM1

- La LLA-B es una patología con una importante incidencia en pacientes pediátricos
- Su alta heterogeneidad, complica el seguimiento y monitorización de los pacientes.
- Es necesario contar con blancos diagnósticos que permitan realizar la monitorización de una manera más confiable y sencilla

Proponemos estudiar un perfil de cuatro lncRNA “s como complemento de la evaluación de MRD.

14

Hipótesis

Los pacientes con Leucemia Linfoblástica Aguda de precursores B enfermedad mínima residual positiva exhibirán una expresión relativa de lncRNA's distinta a los pacientes que logran la remisión de la enfermedad

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Objetivo general

Estudiar la expresión relativa de los lncRNA's linc-PINT, l lEG3, BARLR6 y ZEB1-AS1 en pacientes con Leucemia Linfoblástica Aguda de precursores B

16

Objetivos específicos

- Realizar la inmunofenotipificación de Leucemia Linfoblástica Aguda de precursores B y la detección de Enfermedad Mínima Residual mediante citometría de flujo
- Determinar la expresión de los RNA's Largos No Codificantes linc PINT, MEG3, BALR6 y ZEB1-AS1
- Analizar la concordancia entre el perfil de lncRNA's y la detección de Enfermedad Nlínima Residual por citometría de flujo en pacientes con Leucemia Linfoblástica Aguda de precursores B

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Metodología

18

Diapositiva 14

GM1 Acotar a puntos

GABRIEL MATA MORENO, 2026-07-10T01:22:22.941

Diseño del estudio

- Estudio de cohorte prospectiva exploratoria
- En colaboración con los servicios de Oncología-Hematología del Hospital Regional de Alta Especialidad "Dr. Ignacio Morones Prieto"
- Aprobado por Comité de Ética y Comité de Investigación bajo registro 23-19.

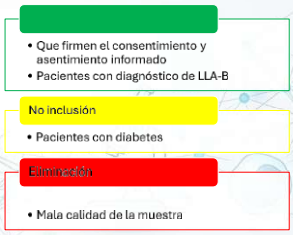

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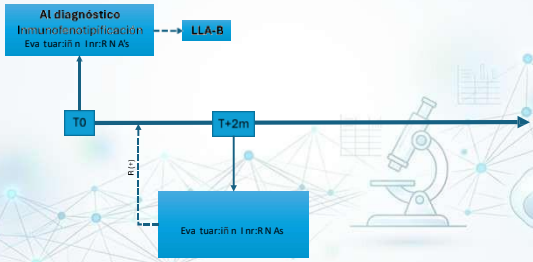
Diagrama general



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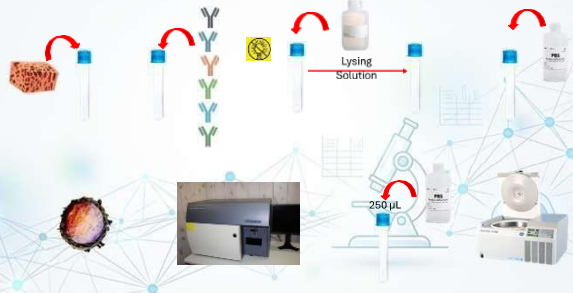
Análisis mediante CF



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Panel de anticuerpos

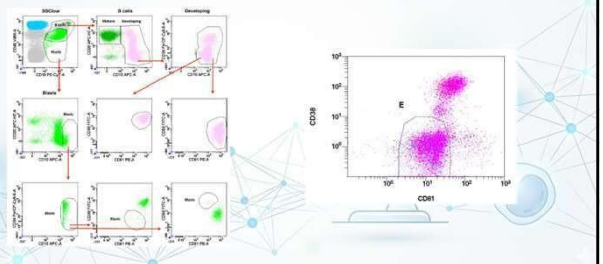
InmunofenotipificaciÓn

MRD

Intracelular		

22

Discriminación de células EMR+ con respeto a hematogonias



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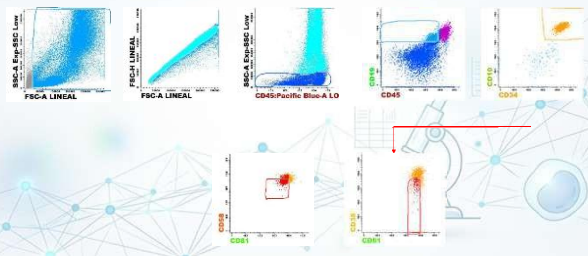
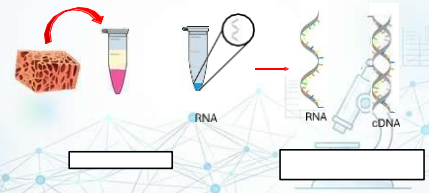
Estrategia de análisis para evaluación de MRD



24

Extracción de ácidos nucleicos



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Evaluación de lncRNA's mediante qPCR

Sonda Hs05031477 s1 para a detección de linc-PFNT
Sonda Hs00292028_m1 para la detección de MEG3
Sonda Hs01398645_g1 para la detección de ZEB1-AS1

- Sonda Custom TaqMan™ Gene Expression Assay para la evaluación de BALR6
- Sonda Hs00245445_m1 para la detección de ABU

- Housekeeping ABU
- TaqMan™ Universal PCR Master

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Análisis estadístico

- Estadística descriptiva para caracterizar la población de estudio. Variables continuas reponadas como medidas de tendencia central y dispersión.
- Variables categóricas descritas como frecuencias y porcentajes.
- **Prueba de rangos con signo de Wilcoxon para muestras pareadas (dos colas):** comparación de los niveles de expresión génica entre el diagnóstico y la evaluación de MRD
- **Prueba U de Mann-Whitney (dos colas):** comparación de los niveles de expresión genica entre pacientes en remisión y pacientes refractarios, tanto al diagnóstico como a la evaluación de MRD
- Nivel de significancia estadística: $p < 0.05$.
- GraphPad Prism versión 10.4.1

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Resultados

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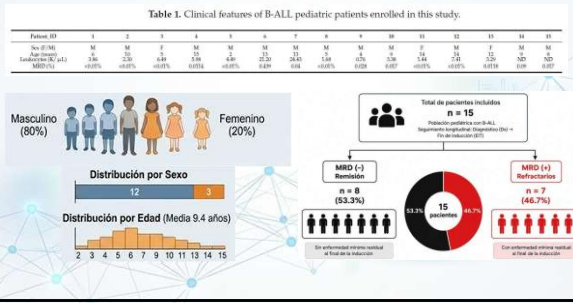
Grupo de estudio



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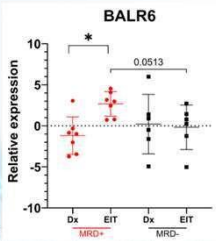
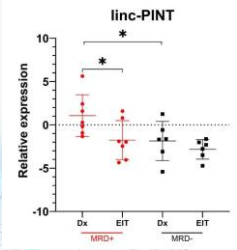
Niveles de expresión de lncRNA's al diagnóstico y al momento de la evaluación de MRD: BALR6



- En pacientes f•1RD+ se observa un aumento en la expresión BALR6 con respecto a los niveles al momento del diagnóstico
- Al EIT se observa una tendencia a una mayor expresión de BALR6 en pacientes MRD+ Vs. MRD-

30

Niveles de expresión de lncRNA's al diagnóstico y al momento de la evaluación de MRD: LINC-PINT



- Mayor expresión de linc-PINT al diagnóstico de los pacientes MRD+ con respecto a N\RD-
- Pacientes MRD+, presentan una disminución de linc-PINT en EIT con respecto al diagnóstico

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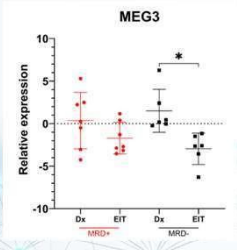
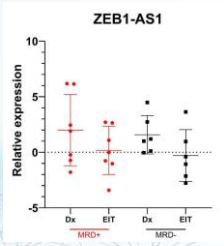
Niveles de expresión de lncRNA's al diagnóstico y al momento de la evaluación de MRD: MEG3



Disminución de los niveles de expresión al EIT con respecto al diagnóstico, en pacientes MRD-

32

Niveles de expresión de lncRNA's al diagnóstico y al momento de la evaluación de MRD: ZEB1-AS1



- No se observaron diferencias estadísticamente significativas entre los niveles de expresión entre los grupos de pacientes
- No se observaron diferencias estadísticamente significativas entre los niveles de expresión al diagnóstico con respecto a EIT

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Discusión

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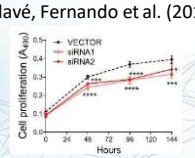
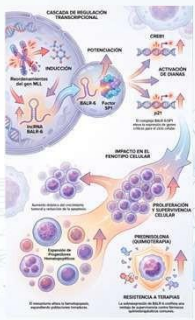
BALR6

- Alta expresión en procesos neoplásicos activos (MRD+)
- Validación in vivo de los hallazgos de Rodríguez-Malavé, Fernando et al. (2015).





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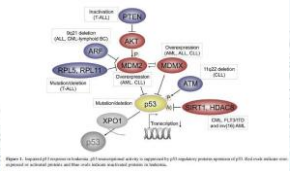
LINC-PINT

- A diferencia de lo previamente reportado por Garitano-Trojaola A. (2018), una alta expresión de linc-PINT se asocia con un mal pronóstico
- Altos niveles de un determinado biomarcador (p53) no siempre coinciden con un mejor pronóstico



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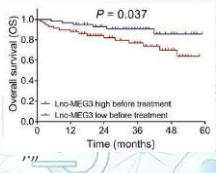
MEG3 (I)

Los altos niveles de expresión al inicio del tratamiento pueden ser indicativos de la capacidad de la célula para iniciar los procesos de apoptosis y/o diferenciación. Esto, en el marco de funciones no canónicas de regulación de ciclo celular.



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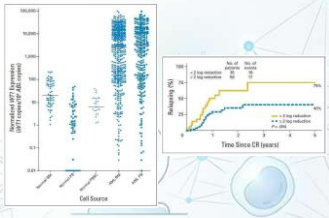
MEG3 (II)

Consideramos que la disminución de la expresión una vez finalizado el tratamiento de inducción a la remisión responde al cambio en la médula ósea de las poblaciones celulares predominantes, algo normal dado que una vez erradicada la población neoplásica, debe generarse la reconstitución de la médula ósea.



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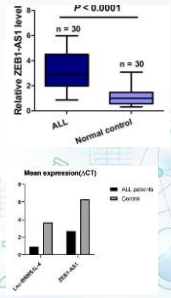
ZEB1-AS1

A diferencia de lo previamente reportado por Wang, Du (2017), nuevos estudios demuestran que de manera basal, las células de linaje B expresan bajos niveles de ZEB1-AS1, y las células de leucemia niveles considerablemente más reducidos.

Este bajo nivel de expresión podría limitar la actividad de ZEB1-AS1 y, en consecuencia, reducir sus efectos sobre las vías moleculares que regula.



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Resultados preliminares del análisis exploratorio de sensibilidad/especificidad

- **LINC-PINT** muestra la mejor capacidad para identificar pacientes con persistencia de enfermedad residual.
- NEG3 muestra una tendencia para identificar pacientes que remiten la enfermedad.
- BALR6 y ZEB1-ASI presentan capacidades discriminatorias cercanas al azar.

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Limitaciones del estudio

- Tamaño muestral reducido
- Ausencia de sujetos sanos para evaluar niveles basales de expresión
- Necesaria la inclusión de una Éohorte independiente
- Se trabajó con muestras de aspirado total

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Conclusión

El presente estudio demostró que existen diferencias entre los niveles de expresión de los lncRNAs MEG3, BALR6 y LINC-PINT entre pacientes con LLA-B en remisión de la enfermedad con respecto a pacientes EMR positiva.

Debido al tamaño limitado de la cohorte, estos hallazgos deben considerarse exploratorios y requieren validación en poblaciones independientes incluyendo un mayor número de individuos.

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Perspectivas

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Validación

Identification and Validation of Novel Long Non-coding RNA Biomarkers for Early Diagnosis of Oral Squamous Cell Carcinoma

- Multiplataforma
- Multicéntrico

The Clinical Utility of lncRNAs and Their Application as Molecular Biomarkers in Breast Cancer

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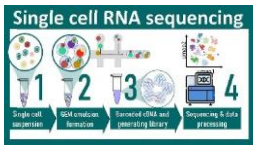
Sorting celular

- Caracterización específica de blastos leucémicos
- Se elimina el efecto de la reconstitución hematopoyética
- Análisis de una población homogénea



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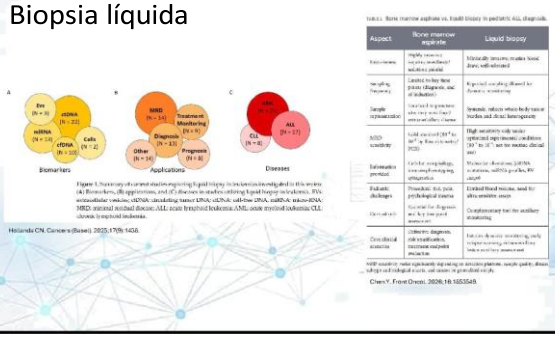
Biopsia líquida



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Productos generados

47

Capacitaciones

48

Artículo

Mata Moreno, G.; Turrubiartes Martínez, E.A.; González, L.C.C.; Lugo, E.R.C.; Pérez Ramírez, Ó.; Moreno, P.N.; Layseca Espinosa, E. Long Non-Coding RNA Expression in B-Cell Precursor Acute Lymphoblastic Leukemia: Analysis of LINC-PINT, MEG3, BALR6, and ZEB1-AS1. *Life* **2026**, *16*, 1042.

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Adicionales

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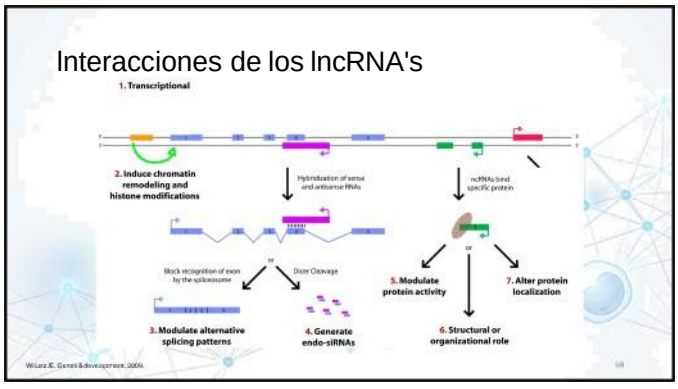

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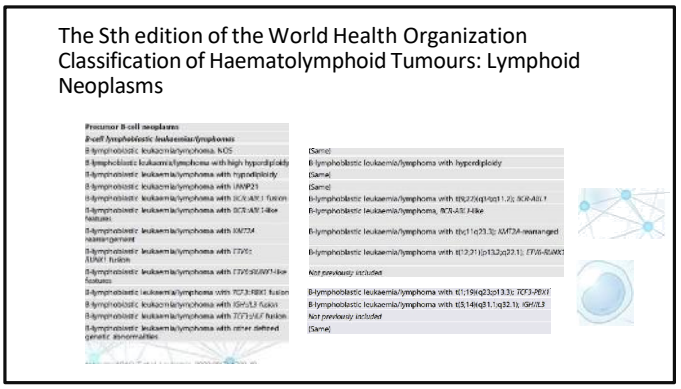

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Principales aberraciones cromosómicas en LLA

Aberración cromosómica/genes implicados	Infantes		Adultos	
	Frecuencia	Pronóstico	Frecuencia	Pronóstico
Hiperdiploidía	23-30%	Favorable	7-8%	Favorable
t(12;21)(p13;q22)/ETV6-RUNX1 (TEL-AML1)	22-26%	Favorable	0-4%	ND
t(9;22)(q34;q11.2)/BCR-ABL1	1-3%	Adverso	11-29%	Adverso
t(4;11)(q21;q23)/MLL-AFF1(AF4)	1-2% 55% en infantes	Adverso	4-9%	Adverso
Otras (6 distintas 0.7-15%)	41.7%	Variable	41%	Variable
Cariotipo normal	31-42%	Favorable	15-34%	Intermedio

Mrózek K. Hematology/Oncology Clinics. 2009.

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Referencias

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Referencias

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Características sociodemográficas

	Male	Male	Female	Male	Male	Male	Male	Male	Male	Male	Female	Male	Female	Male	Male
	ND	ND	I	ND	ND	ND	ND	C	ND	C	ND	ND	C	ND	ND
	ND	ND	T2DM	ND	T2MD	T2DM	ND	DM M	SK T2DM PC	DM GC	DM	ND	DM HR EC	ND	ND
Relevant clinical data	ND	ND	TLS SH CE	ND	ND	ND	BT AS WK PLL DY WL	PT RBCT	HY Aberrant CD13	ND	ND	OI	CNSi, nausea vomiting hyporexia	CAP	CNSi PA LAP

AS: Asthenia; **BT:** Blood transfusions; **C:** Complete; **CAP:** Community-acquired pneumonia; **CE:** Cranial exostosis; **CNSI:** CNS infiltration; **CW:** Construction worker; **DL:** Day laborer; **DY:** Dyspnea; **ED:** Eutocic delivery; **GC:** Gastric cancer; **HM:** Homemaker; **HR:** Hypertension; **HY:** Hepatomegaly; **I:** Incomplete; **LAP:** Lymphadenopathy; **M:** Miscarriages; **MD:** Mellitus diabetes; **OI:** Ocular infiltration; **PA:** Platelet aggregation; **PC:** Pancreatic cancer; **PLL:** Pallor; **PT:** Platelet transfusion; **RCT:** Red blood cell transfusion; **SE:** Self-employed trader; **SH:** Subdural hematoma; **SK:** Smoking; **ST:** Septic tank; **T2MD:** Type 2 mellitus diabetes; **TLS:** Tumor lysis syndrome; **U:** Unfinished/unpaved; **WK:** Weakness; **WL:** Weight loss.

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Características sociodemográficas

Patient_ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Floor material	U	ND	Finished cement	ND	U	U	U	U	Finished cement	ND	U	Finished cement	ND	Finished cement	Finished cement
Cooking fuel	Firewood	ND	Gas	ND	ND	Firewood	ND	Gas	Gas/fire wood	Gas	Firewood	Gas	ND	Gas	Gas/fire wood
Sanitation facilities	St	ND	C	ND	C	St	ND	St	St	C	St	C	St	C	St
Electricity access	Yes	ND	Yes	ND	Yes	Yes	ND	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Animal exposure	Poultry	ND	ND	ND	Poultry and swine	ND	ND	Poultry	ND		ND	ND	Cattle	ND	ND
Father age (years)	ND	ND	39	ND	ND	34	33	49	30	43	48	28	39	25	33
Father occupation	Dl	ND	USA	ND	ND	Cw	ND	Dl	Migrant USA	Se	Dl	Dl	Farmer	Dl	Manual laborer
Mother age (years)	30	ND	37	ND	39	32	33	42	30	44	38	28	40	24	24

AS: Asthenia; **BT:** Blood transfusions; **C:** Complete; **CAP:** Community-acquired pneumonia; **CE:** Cranial exostosis; **CNSI:** CNS infiltration; **CW:** Construction worker; **DL:** Day laborer; **DY:** Dyspnea; **ED:** Eutocic delivery; **GC:** Gastric cancer; **HM:** Homemaker; **HR:** Hypertension; **HY:** Hepatomegaly; **I:** Incomplete; **LAP:** Lymphadenopathy; **M:** Miscarriages; **MD:** Mellitus diabetes; **OI:** Ocular infiltration; **PA:** Platelet aggregation; **PC:** Pancreatic cancer; **PLL:** Pallor; **PT:** Platelet transfusion; **RCT:** Red blood cell transfusion; **SE:** Self-employed trader; **SH:** Subdural hematoma; **SK:** Smoking; **ST:** Septic tank; **T2MD:** Type 2 mellitus diabetes; **TLS:** Tumor lysis syndrome; **U:** Unfinished/unpaved; **WK:** Weakness; **WL:** Weight loss.

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Tratamiento(I)

Medicamento	Categoría	Clase farmacológica	Fracción	Porcentaje
Vincristina (oncovin)	Quimioterapia	Alcaloide de la vinca (inhibidor de microtubulos)	13/15	86,67
Daunorrubicina	Quimioterapia	Antraciclina (inhibidor de topoisomerasa II)	12/15	80
Prednisona	Quimioterapia	Glucocorticoide antileucemico	12/15	80
Leunase	Quimioterapia	Asparaginasa (enzima antineoplasica)	9/15	60
Metotrexato	Quimioterapia	Antimetabolito antifolato	9/15	60
Dexametasona	Quimioterapia	Glucocorticoide antileucemico	8/15	53,33
L - asparaginasa	Quimioterapia	Asparaginasa (enzima antineoplasica)	5/15	33,33
Mercaptopurina	Quimioterapia	Analogo de purina	5/15	33,33
Etoposido	Quimioterapia	Inhibidor de topoisomerasa II	4/15	26,67
Citarabina	Quimioterapia	Analogo de pirimidina	4/15	26,67
Metilprednisolona	Quimioterapia	Glucocorticoide antileucémico	1/15	6,67
Ciclofosfamida	**Quimioterapia**	Agente alquilante	1/15	6,67
Ac. Folico	**Rescate/Soporte**	Suplementacion con folatos	6/15	40
Filgrastim	**Rescate/Soporte**	Factor estimulante de colonias granulociticas (G-CSF)	3/15	20
Cardioxane	Soporte	Cardioprotector (dexrazoxano)	8/15	53,33
MESNA	Soporte	Uroprotector	1/15	6,67

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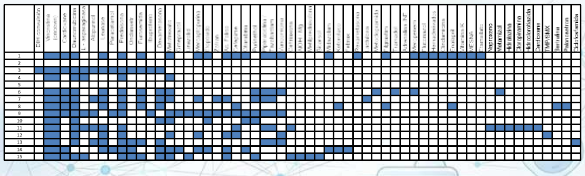
Tratamiento (II)



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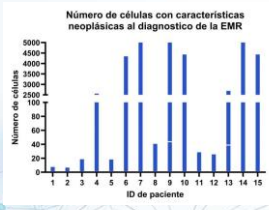
Sensibilidad de la metodología de evaluación de MRD mediante citometría de flujo



Se logró el establecimiento de una metodología de 7 colores

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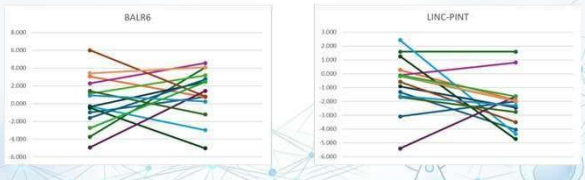
Seguimiento longitudinal de la expresión de lncRNA's



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Seguimiento longitudinal de la expresión de lncRNA's (II)

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Sensibilidad/Especificidad de los lncRNA vs. MRD (I) (Análisis exploratorio)

lncRNA	EVENTO DE INTERÉS: MRD POSITIVA (persistencia de enfermedad residual)			
	LINC-PINT	BALR6	MEG3	ZEB1-AS1
Dirección de asociación con MRD+	↑ Expresión elevada ↑ (asociada a mayor riesgo)	↑ Expresión elevada ↑ (tendencia positiva)	↓ Expresión disminuida ↓ (asociada a mayor riesgo)	↑ Expresión elevada ↑ (tendencia en casos extremos)
Sensibilidad	100.0%	85.7%	28.6%	28.6%
Especificidad	50.0%	37.5%	75.0%	100.0%
AUC	0.732	0.518	0.357	0.482
Interpretación global	MEJOR DESEMPEÑO para identificar MRD+	Desempeño intermedio cercano al azar	Desempeño pobre (asociación inversa)	Muy específico pero poco sensible

CLAVE
- Desempeño favorable (bueno)
- Desempeño intermedio / exploratorio
- Desempeño pobre (limitado)

SÍMBOLOS DE DIRECCIÓN
- ↑ Expresión elevada asociada al desenlace de interés
- ↓ Expresión disminuida asociada al desenlace de interés

CONCLUSIÓN GENERAL
- ↑ LINC-PINT: La expresión elevada de LINC-PINT al diagnóstico se asocia con mayor probabilidad de MRD positiva (alto riesgo).
- ↓ MEG3: La expresión elevada de MEG3 al diagnóstico se asocia con mayor probabilidad de alcanzar MRD negativa (mejor respuesta).

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Sensibilidad/Especificidad de los lncRNA vs. MRD (II) (Análisis exploratorio)

lncRNA	EVENTO DE INTERÉS: MRD NEGATIVA (respuesta favorable)			
	LINC-PINT	BALR6	MEG3	ZEB1-AS1
Dirección de asociación con MRD−	↓ Expresión disminuida ↓ (asociada a mayor probabilidad de MRD−)	↓ Expresión disminuida ↓ (tendencia positiva)	↑ Expresión elevada ↑ (asociada a mayor probabilidad de MRD−)	↓ Expresión disminuida ↓ (tendencia positiva)
Sensibilidad	50.0%	37.5%	75.0%	100.0%
Especificidad	100.0%	85.7%	28.6%	28.6%
AUC	0.268	0.482	0.643	0.518
Interpretación global	Asociación opuesta (bajo desempeño)	Desempeño intermedio cercano al azar	MEJOR DESEMPEÑO para identificar MRD−	Sensibilidad alta pero especificidad baja

CLAVE
- Desempeño favorable (bueno)
- Desempeño intermedio / exploratorio
- Desempeño pobre (limitado)

SÍMBOLOS DE DIRECCIÓN
- ↑ Expresión elevada asociada al desenlace de interés
- ↓ Expresión disminuida asociada al desenlace de interés

CONCLUSIÓN GENERAL
- ↑ LINC-PINT: La expresión elevada de LINC-PINT al diagnóstico se asocia con mayor probabilidad de MRD positiva (alto riesgo).
- ↓ MEG3: La expresión elevada de MEG3 al diagnóstico se asocia con mayor probabilidad de alcanzar MRD negativa (mejor respuesta).

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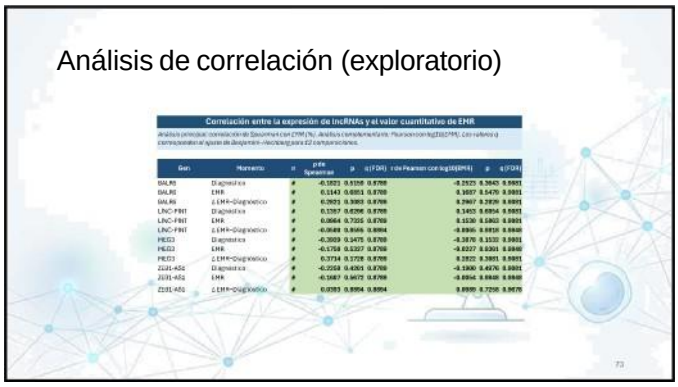
Análisis de correlación (exploratorio)



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