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Presente

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Tengo el agrado de dirigirme a usted, para saludarle cordialmente y al mismo tiempo informarle que en el marco de cumplimiento del compromiso de mejora establecido en el DS N° 036-2023-SA, Ficha N° 41 "Fortalecimiento de acciones de fomento de la investigación en salud", el Hospital Regional de Loreto, adjunta al presente el informe anual de cumplimiento de compromiso de mejora de Investigación.

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Sin otro particular, me suscribo de usted no sin antes reiterarle las muestras de mi consideración y estima personal.

Atentamente,



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Multiple primary cutaneous melanoma in the amazon region of Peru

Melanoma cutáneo primario múltiple en la región amazónica de Perú

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Abstract

We report an 82-year-old male from Iquitos, Amazon region of Peru, with a three-month history of mild-to-moderate painful skin lesions on the right lower limb. The clinical examination revealed four tumors of the right shin, exhibiting exophytic growth, verrucose appearance, and ulceration. Two subcutaneous nodules were noted. Enlarged inguinal lymphadenopathy was observed. The histopathological examination revealed a diagnosis of melanoma. This case emphasizes the need for comprehensive and multidisciplinary surveillance in regions with limited melanoma data leading to a subdiagnosis of this malignancy. Also, it highlights the importance of primary prevention such as sun protection in tropical areas to prevent cutaneous melanoma, advocating for increasing awareness and preventive measures.

Keywords: Melanoma; Skin Neoplasms; Amazonian Ecosystem; Peru; Tropical Zone (source: MeSH NLM).

Resumen

Reportamos el caso de un hombre de 82 años residente de Iquitos, región amazónica del Perú, con una historia de tres meses de lesiones cutáneas dolorosas de leves a moderadas en la extremidad inferior derecha. El examen clínico reveló cuatro tumores en la tibia derecha, que exhibían crecimiento exofítico, apariencia verrugosa y ulceración. Se observaron dos nódulos subcutáneos. Se observó linfadenopatía inguinal agrandada. El examen histopatológico reveló un diagnóstico de melanoma. Este caso enfatiza la necesidad de una vigilancia integral y multidisciplinaria en regiones con datos limitados sobre melanoma que conducen a un subdiagnóstico de esta malignidad. Además, destaca la importancia de la prevención primaria como la protección solar en zonas tropicales para prevenir el melanoma cutáneo, abogando por aumentar la concienciación y las medidas preventivas.

Palabras clave: Melanoma; Neoplasias Cutáneas; Ecosistema Amazónico; Perú; Zona Tropical (fuente: DeCS BIREME).

INTRODUCTION

Melanoma is a deadly skin cancer originating from malignant melanocytes, predominantly present as primary cutaneous melanomas, constituting the most common subtype⁽¹⁾. The majority of cutaneous melanomas (CM) are sporadic and, to a lesser extent have dominant autosomal hereditary patterns⁽²⁾. Exposure to chronic ultraviolet light (UV) is the principal risk factor to CM⁽³⁾.

According to the 2020 GLOBOCAN report, CM ranks as the 13th most common type in Peru, with an incidence of 1.8 per 100 000, and a mortality rate of 1% per 100 000⁽⁴⁾. Notably, there is a lack of published epidemiological data on CM prevalence in Iquitos, a tropical city in northeastern Peru with warm and rainy weather, where the average temperature is 26 °C. At in 2016, one case of CM was reported at Hospital Regional de Loreto⁽⁵⁾. Historically, numerous cases of CM were attended at the Instituto Nacional de Enfermedades Neoplásicas (INEN) located in Lima (Peru)⁽⁶⁾. In Peruvian population, acral melanoma is the most prevalent subtype, a form typically associated with a poor prognosis⁽⁷⁾. A 2024 study from INEN identified nodular subtype representing the 12.8% of cases. Besides, the lower extremities were the most common primary site for melanoma⁽⁸⁾.

This case report enhances the existing knowledge by presenting a rare case of multiple nodular melanomas in a male patient from this amazon and tropical region of Peru. Institutional Research Ethics Committee of Hospital Regional de Loreto (N° 048/24) approved this study. The authors obtained informed consent from the patient.

CASE REPORT

An 82-year-old male patient, originally from a rural community in Maynas, Iquitos (Peru) was admitted to the Hospital Regional de Loreto and hospitalized by the Infectious Diseases Department. He presented with a three-month history of painful skin lesions on his right lower limb. The patient's medical history was not contributory. The patient reported that initial skin lesions originated as a small nodule on

his leg, and over subsequent weeks, three additional similar lesions emerged, all of which progressively increased in size. During this period, the patient noted swelling in his right leg and foot; however, he did not seek medical advice.

On admission, the patient exhibited normal vital signs, and his overall nutritional and hydration status appeared satisfactory. Dermatological examination revealed four skin tumors displaying an exophytic growth pattern, measuring approximately 4x5x4 cm each. These lesions were situated on the external anterolateral aspect of the right shin, and characterized by a verrucose-like appearance, sessile morphology, brown-to-black discoloration, and some with pink spots (Figure 1). Besides, two notable subcutaneous nodules, measuring 1.5 cm and 1.4 cm respectively, exhibited an infiltrative appearance (Figure 2). On sole examination of the affected lower limb, the patient exhibited a brown-to-black macule near his heel suggesting acral melanoma, unfortunately it was not biopsied (Figure 3). There was enlarged lymphadenopathy in the right inguinal area which was not painful. No other clinically relevant physical findings were observed.



Figure 1. Verrucose-like appearance of nodular melanoma.

The hematologic and biochemical laboratory investigations were within normal limits except for mild anemia, hypereosinophilia, and hypoalbuminemia. All serology tests were negative. Due to the tropical epidemiological context of our institution, subcutaneous fungus infection and cutaneous tuberculosis were suspected. However, melanoma prevailed as a relevant differential diagnosis, therefore a skin biopsy was requested.

On histopathological examination of the skin biopsy, it showed epithelial melanocytes proliferation with a nodular pattern, the presence of melanin pigment nests, associated with a superficial ulcerated bed (Grade IV), and an infiltrated profound border. No specific melanoma or other oncological biomarkers were assessed due to limited laboratory resources. The biopsy confirmed the diagnosis of ulcerated nodular melanoma, Breslow index of 5mm (Figure 4A and 4B). The patient was transferred to the Oncology Department for further medical evaluation.

DISCUSSION

Cutaneous melanoma is a malignant tumor arising from the uncontrolled activity of melanocytes. Extracutaneous manifestations are less frequent. Traditionally, CM is subdivided into 4 categories: lentiginous, acral, superficial spreading, and nodular⁽¹⁾. A Peruvian cohort study found that 72.1% of melanomas occurred on the lower extremities, with many lesions being pigmented and ulcerated⁽⁸⁾, similar to our patient. In our setting, CM may be underdiagnosed due to factors like limited healthcare access. For our patient, the vertical growth pattern of nodular melanoma was key to the clinical presentation

Our patient skin lesions resembled a patient in the clinical presentation of vascular-like lesions, displayed in a multiple nodular pattern, and an onset presentation. Furthermore, the cutaneous compromise showed a unilateral distribution as seen in our patient⁽⁹⁾. Notably, nodular CM may present as a giant mass in the back with lung and brain metastases as seen in an elderly patient⁽¹⁰⁾. Another more aggressive presentation of multiple



Figure 2. Subcutaneous nodular lesions.

nodular melanoma may encompass dermal and subcutaneous tissue along the entire right side of the body⁽¹¹⁾.

However, the clinical presentation can vary based on factors such as geographic origin, as seen in the Indian Subcontinent, where a patient presented with

multiple nodules with a bosselated surface on the lower limb⁽¹²⁾. Remarkably, nodular melanoma has been documented as a congenital mass in a newborn⁽¹³⁾. To our knowledge, this clinical presentation of nodular melanoma has not been previously reported in the Peruvian tropics. Reports from Lima provide valuable in-

sights into melanoma cases. One study described an exophytic lesion on the right sole, revealing a giant acral melanoma, along with multiple nodular lesions on the right lower limb, closely resembling our patient's presentation⁽¹⁴⁾. Additionally, another study reported an acral nodular type affecting the first toe⁽¹⁵⁾.

In tropical regions, diagnosing skin lesions like those in our patient can be challenging, as infections may mimic neoplasia or vice versa. For instance, a case of multiple nodular-ulcerative lesions initially misdiagnosed as sporotrichosis, leading to ineffective antifungal treatment, was later revealed to be melanoma⁽¹⁶⁾. Subcutaneous fungus infections, including distinct forms of localized lobomycosis⁽¹⁷⁾, confluent nodular lesions of chromoblastomycosis⁽¹⁸⁾, and verrucose plaque or nodules of phaeohyphomycosis⁽¹⁹⁾ should be considered for differential diagnosis. We must also consider protozoan parasite infections, especially the verrucose presentation of leishmaniasis⁽²⁰⁾, due to their high prevalence in our region.

Various infectious diseases present with verrucose or nodular lesions and distinguishing them from the neoplastic condition is crucial for appropriate treatment. The physicians should be able to differentiate the basic morphology of lesions and use proper diagnostic tests such as histopathology examination, imaging studies, and tumor markers.

In Iquitos, Loreto, heightened awareness of melanoma risk factors is crucial due to the region's proximity to the equator and high UV exposure. Residents should prioritize sun protection by consistently applying sunscreen, wearing protective clothing, and undergoing regular dermatological checkups. Tailoring educational efforts to the local context emphasizes the importance of effective preventive measures, promoting a community-wide commitment to skin health.

In conclusion, the CM poses challenges in the tropics due to diagnostic complexities. In our patient, nodular melanoma exhibited a unique presentation crucial for diagnosis. Comparisons with other cases reveal varied clinical presentations worldwide. In tropical regions,



Figure 3. A brown-to-black macule near the right heel.

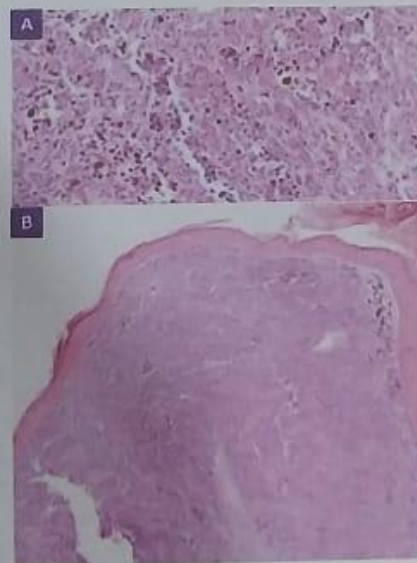


Figure 4. A. High resolution image showing polymorphic tumor cells, increased mitotic activity, perinuclear halo and intracytoplasmic brown pigment (40X, H&E). B. High resolution image depicting nodular collection of melanocytes (20X, H&E).

distinguishing between neoplasia and infections poses a challenge, requiring proper diagnostic. In Iquitos, awareness of melanoma risk factors highlights the need for prevention strategies. Residents should prioritize sun protection and regular dermatological checkups due to the high UV exposure. We recommend continued, high-quality data collection on cancer diagnoses, especially melanoma, to inform public health decisions effectively.

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Uso de antimicrobianos en la unidad de cuidados intensivos de un hospital público de Loreto

Use of antimicrobials in the intensive care unit of a Loreto public hospital

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Resumen

Introducción. El uso inapropiado de antimicrobianos en las unidades de cuidados intensivos (UCI) contribuye a la resistencia bacteriana. **Objetivo.** El propósito del presente estudio fue medir el uso y tipo de antimicrobianos en los pacientes hospitalizados en la Unidad de Cuidados Intensivos del Hospital Regional de Loreto (HRL). **Métodos.** Estudio de tipo descriptivo. Revisamos 120 historias clínicas en pacientes de UCI-HRL desde enero a junio 2023. **Resultados.** La mayoría de los pacientes usaron antimicrobianos (74,2%), indicados por shock séptico (42,7%), de 1 a 3 antimicrobianos (93,2%), con terapia de 1 a 3 días (45%). Del total de antimicrobianos usados, la mayor proporción fueron bactericidas 89 (90,4%), de la familia de cefalosporinas (33,1%) y carbapenémicos (23,5%); los fármacos más empleados fueron ceftriaxona (26,5%) y meropenem (21,1%) por vía intravenosa (90,4%). **Conclusión.** La mayor proporción de pacientes hospitalizados usan antimicrobianos de la familia de cefalosporinas y carbapenémicos.

Palabras clave: Antibióticos, Antiinfecciosos, Bactericidas, Unidad de Cuidados Intensivos (Fuente: DeCS BIREME).

Abstract

Introduction. Inappropriate use of antimicrobials in the Intensive Care Unit (ICU) contributes to bacterial resistance. **Objective.** The purpose of the present study was to measure the use and type of antimicrobials in patients hospitalized in the Intensive Care Unit of the Loreto Regional Hospital (HRL). **Methods.** Descriptive study. We reviewed 120 medical records in ICU-HRL patients from January to June 2023. **Results.** Most patients used antimicrobials (74.2%), indicated for septic shock (42.7%), 1 to 3 antimicrobials (93.2%), with therapy of 1 to 3 days (45%). Of the total number of antimicrobials used, the greatest proportion were bactericides 89 (90.4%), from the cephalosporin family (33.1%) and carbapenemics (23.5%), the most commonly used drugs were ceftriaxone (26.5%) and meropenem (21.1%) by the intravenous route (90.4%). **Conclusion.** The highest proportion of hospitalized patients use antimicrobials of the cephalosporin and carbapenemics family.

Keywords: Antibiotics, Anti-Infective Agents; Anti-Bacterial Agents; Intensive Care Units. (Fuente: MeSH NCBI)

INTRODUCCIÓN

En las unidades de cuidados intensivos (UCI) se reportan agentes bacterianos resistentes, en este servicio se encuentran los pacientes con alteraciones de las barreras físicas por el uso de catéteres periféricos o venosos centrales, tubos endotraqueales, entre otros; esta condición aumenta el riesgo de transmisión y colonización bacteriana, dificultando el tratamiento de los hospitalizados^(1,2). Por esa razón, la prescripción precoz de un antimicrobiano basado en el contexto epidemiológico local de resistencia microbiana⁽³⁾, es fundamental para el tratamiento adecuado de las infecciones graves en las UCI, especialmente, en casos de sepsis y neumonía asociada a ventilación mecánica⁽⁴⁾.

En el Perú, según los datos de diversos estudios en las UCI, la media de edad de los pacientes que usan antimicrobianos son los mayores de 40 años y, en su mayoría, mujeres. Más del 95% de los hospitalizados presentan dispositivos invasivos durante sus hospitalizaciones⁽⁵⁾. Las bacterias más frecuentes son enterobacterias portadoras de *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella sp.*, *Enterobacter cloacae* y *Proteus mirabilis*⁽⁶⁾.

Los diagnósticos más frecuentes son neumonía, infección de la piel y partes blandas e infección urinaria baja. Así mismo, los antimicrobianos más utilizados son ceftriaxona, meropenem y vancomicina^(7,8). En respuesta a la situación, la Organización Mundial de la Salud (OMS) recomienda Instaurar Programas de Optimización de Antimicrobianos (PROA), que son estrategias basadas en evidencia científica sobre el uso correcto de antibióticos para reducir los costos de hospitales y reducir/estabilizar los niveles de resistencia bacteriana⁽¹⁾. Dentro de estas estrategias, se incluyen la racionalización de la duración de tratamientos-profilaxis y la desintensificación-rotación^(2,7). Según estudios, estas acciones no aumentan la mortalidad ni la duración de la estadía en UCI, pero reducen la incidencia de resistencia y sobreinfección⁽⁶⁾.

Por lo expuesto, el objetivo del presente estudio es medir el uso y tipo de antimicrobianos en los pacientes hospitalizados en la UCI del Hospital Regional de Loreto durante el primer semestre del 2023.

MÉTODOS

Diseño de estudio

Realizamos un estudio descriptivo. Los datos procedieron de historias clínicas de pacientes hospitalizados en la Unidad de Cuidados Intensivos del Hospital Regional de Loreto (UCI-HRL) de enero a junio del 2023, en la ciudad de Iquitos, Perú.

Población y muestra

La población de estudio estuvo conformada por las historias clínicas de 120 pacientes hospitalizados en la UCI Medicina del Hospital Regional de Loreto entre el 1º de enero 2023 y el 30 de junio 2023. La UCI Medicina del HRL cuenta con 7 camas de hospitalización y el tiempo promedio de estancia hospitalaria mínimo es de 3 días y el máximo de 3 semanas. Para la muestra de estudio incluimos 89 historias clínicas con registro de pacientes de ambos sexos que usaron antimicrobianos en la UCI Medicina. Se incluyó solo a UCI Medicina debido a que es la única UCI que realiza hemocultivos. Excluimos a las historias clínicas de pacientes hospitalizados en otros servicios como UCI Cirugía, UCI pediatría, salas de hospitalización y de consultorios externos, además de aquellos que no usaron antimicrobianos y a los que no tenían historias clínicas legibles.

Variables de estudio y procedimientos

Consideramos las variables edad (categorizada en 18 a 29 años, 30 a 59 años y 60 años a más), sexo, estancia hospitalaria (1 a 3, 4 a 6 días y 7 días a más), estado nutricional (IMC <18,5, 18,5 a 24,9, 25 a 29,9 y >30), comorbilidad, diagnóstico principal, intervención quirúrgica, cateterismo, intubación, cultivo microbiológico, tipo de indicación, duración de terapia antimicrobiana (1 a 3, 4 a 7 y más de 7 días), uso de antimicrobiano, tipo de antimicrobiano, familia de antimicrobiano, agente antimicrobiano y vía de administración. La información fue obtenida de las historias clínicas físicas (área de admisión) posterior a la aprobación del estudio y autorización del área de registros médicos del HRL.

Análisis estadístico

Diseñamos una base de datos en el programa *Microsoft Excel*® (versión para

Windows 10) para recopilar la información. El análisis fue realizado en el programa estadístico *IBM SPSS Statistics* versión 27.0 en español, para *Windows 11* en español. Se describieron las variables cualitativas mediante frecuencias absolutas y relativas, y las medias de variables cuantitativas mediante previa evaluación del supuesto de normalidad, con la prueba de Kolmogorov-Smirnov.

Aspectos éticos

El estudio fue aprobado por el Comité de Ética en investigación del HRL (Oficio N° 034-CIEI-2023). Se respetó la confidencialidad de los datos usando códigos numéricos. No se consideró necesaria la solicitud del consentimiento informado en el estudio porque se recolectó la información desde las historias clínicas.

RESULTADOS

En el periodo de estudio se evaluaron 120 pacientes hospitalizados en la UCI Medicina-HRL, de los cuales 89 (74,2%) pacientes recibieron antimicrobianos y 31 (25,8%) no lo recibieron. La media de edad fue 41,6 años. El 48,3% (n = 43) tenía entre 30 a 59 años. El 66,3% (n = 59) eran mujeres y el 47,2% (n = 42) tenían entre 1 a 3 días de estancia hospitalaria. El 50,6% (n = 45) presentaron un IMC de 25 a 29,9 kg/m², clasificado como sobrepeso. El 55,1% de los pacientes no tenían comorbilidad (n = 49), así mismo, los diagnósticos principales más frecuentes fueron shock séptico con 42,7% (n = 38), insuficiencia respiratoria con 25,8% (n = 23) y eclampsia con 16,9% (n = 15). Presentaron intervención quirúrgica el 32,6% (n = 29), de las cuales 21 fueron cesáreas, usaban catéter urinario y catéter periférico el 100% (n = 89), catéter venoso central 69,7% (n = 62) e intubación endotraqueal 71,9% (n = 64) (Tabla 1).

Durante el periodo de estudio se evaluaron hemocultivos microbiológicos a los 89 pacientes que usaron antimicrobianos, encontrándose el 13,5% (n = 12) de pacientes positivos. Los agentes más frecuentes fueron *Klebsiella pneumoniae* y *Pseudomonas aeruginosa*. Los antimicrobianos fueron indicados para shock séptico en el 42,6% de casos (n = 38) y en herida quirúrgica 30,3% (n = 27).

Tabla 1. Características clínicas y epidemiológicas de los pacientes hospitalizados en la Unidad de Cuidados Intensivos del Hospital Regional de Loreto, enero a junio 2023.

Características	Total n=89 (%)
Edad (años)	41,6 ^a
<18	9 (10,1)
18 a 29	19 (21,3)
30 a 59	43 (48,3)
60 años a más	18 (20,2)
Sexo	
Masculino	30 (33,7)
Femenino	59 (66,3)
Estancia hospitalaria (días)	8,4 ^a
1 a 3	42 (47,2)
4 a 7	26 (29,2)
Más de 7	21 (23,6)
IMC (kg/m ²)	24,6 ^a
<18,5	2 (2,2)
18,5 – 24,9	41 (46,1)
25 – 29,9	45 (50,6)
>30	1 (1,1)
Comorbilidad	
Sí	40 (44,9)
No	49 (55,1)
Diagnóstico principal	
Shock séptico	38 (42,7)
Eclampsia	15 (16,9)
Insuficiencia respiratoria	23 (25,8)
Otros	13 (14,6)
Intervención quirúrgica	
Sí	29 (32,6)
No	60 (67,4)
Tipo de intervención quirúrgica	
Ninguna	60 (67,4)
Cesárea	21 (23,6)
Histerectomía	2 (2,2)
Colecistectomía	3 (3,4)
Otros	3 (3,4)
Catéter urinario	
Sí	89 (100)
No	0 (0)
Catéter periférico	
Sí	89 (100)
No	0 (0)
Catéter venoso central	
Sí	62 (69,7)
No	27 (30,3)
Intubación endotraqueal	
Sí	64 (71,9)
No	25 (28,1)
^a Media	

Tabla 2. Características del tratamiento antimicrobiano de los pacientes hospitalizados en la Unidad de Cuidados Intensivos del Hospital Regional de Loreto, enero a junio 2023.

Características	Total n=89 (%)
Hemocultivo microbiológico	
Positivo	12 (13,5)
Negativo	77 (86,5)
Tipo de indicación	
Shock séptico	38 (42,6)
Herida quirúrgica	27 (30,3)
Neumonía	13 (14,6)
Infección del tracto urinario	6 (6,7)
Otros	5 (5,8)
Cantidad de antimicrobianos (medicamentos)	
1 a 3	83 (93,2)
4 a 7	6 (6,8)
Duración de terapia antimicrobiana (días)	8,7 ^a
1 a 3	40 (45)
4 a 6	24 (27)
7 días a más	25 (28)
^a Media	

Fueron prescritos con mayor frecuencia 1 a 3 antimicrobianos con 93,2% (n = 83) y como terapia antimicrobiana de 1 a 3 días en el 45% (n = 40) (Tabla 2).

Los casos analizados recibieron un total de 166 antimicrobianos, donde el 90,4% (n = 150) eran de tipo bactericida, el 33,1% (n = 55) pertenecían a la familia de cefalosporinas, seguido de carbapenémicos con 23,5% (n = 39) y glucopéptidos con 15,7% (n = 26). Los agentes antimicrobianos más frecuentes fueron ceftriaxona con 26,5% (n = 44), meropenem con 21,1% (n = 35) y vancomicina con 15,7% (n = 26). La vía intravenosa fue la más utilizada con 90,4% (n = 150) (Tabla 3).

DISCUSIÓN

En nuestro estudio, el 74,2% de los pacientes hospitalizados en UCI del hospital de referencia regional fueron tratados con antibióticos. Este hallazgo es congruente con que a todos los pacientes que han ingresado a UCI se les realiza hemocultivo microbiológico, lo que ayuda a identificar el agente causal específico.

Tabla 3. Uso de antimicrobianos de los pacientes hospitalizados en la Unidad de Cuidados Intensivos del Hospital Regional de Loreto, enero a junio 2023.

Características	Total n=166 (%)
Tipo de antimicrobiano	
Bacteriostático	16 (9,6)
Bactericida	150 (90,4)
Familias	
Cefalosporinas	55 (33,1)
Carbapenémicos	39 (23,5)
Glucopéptidos	26 (15,7)
Lincosamidas	18 (10,8)
Nitroimidazoles	8 (4,8)
Quinolonas	6 (3,6)
Betalactámicos	3 (1,8)
Rifamicina	2 (1,2)
Sulfonamidas	2 (1,2)
Aminoglucósidos	1 (0,6)
Otras	6 (3,6)
Agentes antimicrobianos	
Ceftriaxona	44 (26,5)
Meropenem	35 (21,1)
Vancomicina	26 (15,7)
Clindamicina	18 (10,8)
Metronidazol	8 (4,8)
Cefazolina	6 (3,6)
Ciprofloxacina	5 (3,0)
Imipenem	4 (2,4)
Cefalexina	3 (1,8)
Isoniacida	2 (1,2)
Pirazinamida	2 (1,2)
Etambutol	2 (1,2)
Rifampicina	2 (1,2)
Ceftazidima	2 (1,2)
Otros	7 (4,2)
Vía de administración	
Oral	13 (7,8)
Intramuscular	2 (1,2)
Intravenosa	150 (90,4)
Tópica	1 (0,6)

Por tal motivo, el uso correcto de antimicrobianos permite un adecuado perfil terapéutico contra organismos patógenos, permitiendo que el tratamiento sanitario sea menos largo, menos costoso y más efectivo⁽⁹⁾.

El uso de más de 3 antimicrobianos se efectuó en pacientes con diagnóstico de shock séptico, siendo la ceftriaxona

más utilizada y el que presenta una resistencia de 88% ⁽¹⁰⁾. El grupo etario de 30 a 59 años es el que recibe con mayor frecuencia prescripción antibiótica. Encontrándose similitudes con otro estudio ⁽¹¹⁾, donde los pacientes tenían 41,1 años como promedio de edad, siendo sus grupos más frecuentes los pacientes mayores entre 45 a 59 años de edad. En primera instancia, nos fijamos que las proporciones tanto de grupos como de media de edad son muy similares entre ambos estudios.

La mayor frecuencia de los pacientes hospitalizados fueron mujeres, lo cual difiere de otro estudio ⁽¹²⁾, donde la mayoría son varones. En nuestro estudio hay una mayor proporción de mujeres debido a que 23,6% de éstas fueron intervenidas por cesárea. Esto puede explicarse porque el departamento de Loreto posee el mayor promedio de recién nacidos vivos en Perú, es decir, una gran tasa de fecundidad con respecto a otros departamentos; por lo tanto se evidencia la gran proporción de intervenciones quirúrgicas por cesárea y, por consiguiente, el riesgo de infecciones puerperales, por lo que se prescribe profilaxis antibiótica quirúrgica ^(14,15). Sin embargo, las pacientes del sexo femenino con emergencias obstétricas son derivadas a la Unidad de Cuidados Intensivos de Medicina del Hospital Regional de Loreto debido a que no se cuenta con una UCI-Obstetricia que sea para la atención especializadas de dichas pacientes.

De manera muy similar a otros estudios, las indicaciones más frecuentes de antibióticos incluyen shock séptico, heridas quirúrgicas y neumonía. En un estudio ⁽¹¹⁾, las indicaciones incluyen shock séptico, profilaxis médico-quirúrgica, heridas quirúrgicas y neumonía. En otro estudio ⁽¹⁶⁾, las indicaciones con mayor frecuencia fueron sepsis respiratoria, infección del tracto urinario e infección abdominal. Podemos apreciar cómo las indicaciones más frecuentes fueron la sepsis y como profilaxis quirúrgica (en nuestro estudio, por profilaxis prequirúrgica en cesáreas).

En este estudio, los antibióticos más usados fueron las cefalosporinas de tercera generación y carbapenémicos, que

son antibióticos de amplio espectro utilizados contra una amplia gama de bacterias como *Streptococcus pneumoniae* ^(17,18), *Pseudomonas aeruginosa* ⁽¹⁸⁾, y cocos grampositivos ⁽¹⁹⁾ y gramnegativos ^(19,20). Además, un estudio ⁽¹⁵⁾ menciona que la profilaxis antibiótica post-cesárea con una dosis única de 1 gramo de ceftriaxona logró reducir significativamente la incidencia de endometritis clínica a 3,2%. La ampicilina y las cefalosporinas de primera y segunda generación también son buenas opciones como antibióticos profilácticos para la cesárea.

Los antibióticos más utilizados en nuestro estudio son la ceftriaxona y el meropenem. De manera similar, en un estudio ⁽⁸⁾, los antibióticos más utilizados fueron la ceftriaxona, el meropenem y la vancomicina. En otro estudio ⁽¹³⁾, los antibióticos más utilizados fueron el cefepime, la vancomicina y el meropenem. Y en otro estudio ⁽¹²⁾, los antibióticos más frecuentes fueron amoxicilina-clavulanato, piperacilina-tazobactam, ceftriaxona y levofloxacino. Se puede observar que, entre estos estudios, las cefalosporinas son las más frecuentes debido a su buen espectro antibiótico, especialmente, contra *Pseudomonas aeruginosa*, una de las infecciones intrahospitalarias más frecuentes y de mayor riesgo en las UCI ⁽¹⁴⁾.

Entre las limitaciones se puede indicar que el estudio no caracterizó el uso de antimicrobianos mediante esquemas de tratamiento y las concentraciones del fármaco en sangre. Tampoco evaluó el cumplimiento y la calidad en la prescripción de las infecciones nosocomiales. Consideramos relevante en futuros estudios considerar cual es la relación entre el uso de antimicrobianos y la respuesta terapéutica de los pacientes en UCI.

En conclusión, la mayoría de los pacientes de una unidad de cuidados intensivos requirieron antimicrobianos bactericidas de la familia de cefalosporinas y carbapenémicos, siendo la ceftriaxona y el meropenem los antimicrobianos más utilizados. Este estudio pretende visibilizar la utilización de antimicrobianos para mejorar los protocolos de tratamiento mediante la administración racional de medicamentos en pacientes críticos.

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Prevalence of HTLV-1/2 infection in pregnant women in Central and South America and the Caribbean: a systematic review and meta-analysis

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ABSTRACT

Background: Human T-lymphotropic viruses (HTLV)-1 infection is endemic in many countries of Central and South America and Caribbean (CSA&C). Neither screening nor surveillance programs exist for HTLV-1/2 infection among pregnant women in this region. Neither in Western nations with large migrant flows from HTLV-1/2 endemic regions.

Methods: Systematic review and meta-analysis of the prevalence of HTLV-1/2 infection among CSA&C pregnant women. We included studies searching EMBASE, PubMed/MEDLINE, Scopus, and Web of Science from inception to February 15, 2023. This systematic review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines.

Results: We identified a total of 620 studies. Only 41 were finally included in the meta-analysis. Most studies (61.0%) were from Brazil and Peru (14.6%). The total number of participants was 343,707. The pooled prevalence of HTLV-1/2 infection among CSA&C pregnant women was 1.30% (95% CI: 0.96-1.69) using anti-HTLV-1/2 antibody screening tests. There was a high heterogeneity ($I^2 = 98.6\%$). Confirmatory tests gave an HTLV-1 infection rate of 1.02% (95% CI: 0.75-1.33).

Conclusions: The prevalence of HTLV-1/2 infection among CSA&C pregnant women is 1.3%, most cases being HTLV-1. This rate is greater than for other microbial agents regularly checked as part of antenatal screening (such as HIV, hepatitis B, or syphilis). Thus, HTLV-1/2 antenatal testing should be mandatory among CSA&C pregnant women everywhere.

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Introduction

Human T-lymphotropic viruses 1 (HTLV-1) and 2 (HTLV-2) were the first identified retroviruses in humans. Both were originally isolated from patients with T-cell leukemias or lymphomas in the early 1980s [1–3]. Soon thereafter, HTLV-1 was associated with the

development of tropical spastic paraparesis in the Caribbean basin [4]. In contrast, HTLV-2 has only occasionally been linked to any disease since its first description [5].

Estimates for HTLV-1 are of at least 10 million people infected worldwide, with hotspots of endemicity recognized in Latin America [6], West and South Africa [7], Japan, Iran, Romania, and Australia [8]. In contrast, HTLV-2 is mostly recognized among injection drug users worldwide [9], some Amerindian tribes [10] and African pygmies [11]. A recent study reported the presence of HTLV-2 in 16

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indigenous people from the Brazilian Amazon region, highlighting the importance of breastfeeding and sexual transmissions [10].

The origin of HTLVs in South America shows at least two different branches with distinct entry timing. The major HTLV-1 entrance occurred through the east coast of Brazil at the beginning of the slave trade from the African continent, starting in the 16th century and lasting for more than 350 years. Previously, both HTLV-1 and HTLV-2 already had been introduced anciently, following human migrations from the Asian continent crossing the Behring Strait to the American continent and descending the Andes Mountains [12,13].

Both HTLV-1 and HTLV-2 are blood-borne transmitted viruses. However, because they are cell-associated, no transmissions occur following transfusion or exchange of plasma or plasma derivatives, explaining why hemophiliacs or patients on hemodialysis are not infected. By far, sexual transmission is the most frequent way of HTLV-1 spreading globally [14,15]. HTLV-1 vertical transmission mostly occurs throughout breastfeeding and overall is recognized in up to 20-25% of newborns from infected mothers [16]. Children who are not breastfed beyond 3-6 months rarely become infected with HTLV-1 [17,18]. In spite of the efficacy of shortening or avoiding breastfeeding to stop HTLV-1 vertical transmission, antenatal screening is rarely performed in pregnant women in most HTLV-1 endemic countries.

Given that large migration flows from HTLV-1 endemic regions to Europe and North America have occurred during the last decades, reports of cases of HTLV-1-associated diseases are on the rise in Western countries. Furthermore, second waves of local transmission are also recognized among Western natives having sex partners from HTLV-endemic regions. For example, Spain has a 48 million population, Latin America being the largest migrant contributor with 2.7 million [19]. A total of 482 cases of HTLV-1 infection had been reported up to the end of 2023. Of note, 66% were Latin American, and mother-to-child transmission was recognized in at least 11% of cases [20]. In the United Kingdom, a recent survey estimated that 70 newborn infections because of HTLV-1 occur annually, most mothers being from the Caribbean basin [21]. The authors concluded that cost-effective analyses would support the efficacy of HTLV-1/2 antenatal testing, at least for pregnant women from endemic regions [22].

Herein, we perform a systematic review and meta-analysis of studies conducted so far on the rate of HTLV-1/2 infection in pregnant women of Central and South America and the Caribbean (CSA&C). This information should guide recommendations for HTLV-1/2 antenatal testing in endemic regions and in Western countries with significant migrant flows from such areas.

Methods

The systematic review was prepared following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23] (PRISMA checklist in supplementary material) and the protocol was registered at PROSPERO no. CRD42022315277 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022315277).

All publications recorded in international medical databases, including PubMed/Medline, EMBASE, SCOPUS, Web of Science, Scielo, and Cochrane, were checked until July 15, 2022. The search terms were chosen from the "Medical Subject Headings" (MeSH), using a combination of keywords. The first two authors examined independently each of the articles (Supplementary Table 1). Publications considered adequate were archived using the bibliographic 'Mendeley' platform (Elsevier). The search and selection step ended up on February 15, 2023.

Inclusion criteria for study selection were performed according to Population, Intervention, Comparison, Outcome (PICOS), as fol-

lows: i) Participants: pregnant women attended at antenatal sites in CSA&C; ii) Intervention: serological screening of HTLV-1/2 antibodies with subsequent confirmatory testing of initially reactive specimens; iii) Comparison: not needed; and iv) Results. Proportion of pregnant women infected with HTLV-1 or HTLV-2.

Further requirements in study design included being observational (cohorts or transversal) and specifying the number of persons included and tested. Articles had to be published in English, Portuguese, or Spanish.

Duplicated articles were identified and excluded, following the PRISMA procedure [23]. The full text of articles considered relevant was revised independently by two researchers before being considered adequate for further analyses. Differences in opinion were discussed and resolved by consensus with other investigators. All case series with less than five individuals were excluded from this analysis.

The first phase for the selection of articles to be examined was a reading of the title and abstracts. Two authors (JPS and ELG) independently reviewed their contents. Studies that did not reference HTLV, those reporting only clinical cases, those that did not include cohorts or cross-sectional studies, and those not conducted in CSA&C countries were excluded. In the second phase, all remaining articles were downloaded in full text, and a complete reading and examination were performed. We further excluded all studies that did not include confirmatory tests, were review articles, examined repeated patient populations, tested less than five patients, or did not specify how many patients included in the study tested positive for HTLV-1/2 (Figure 1). Disagreements during the first and second phases were resolved by consensus or researchers or by consulting an independent third party.

All relevant data from the articles chosen were recorded by two authors (JPS and ELG) using Excel. Another author (JMRR) checked the crude information. The following information was retrieved from the chosen articles: title, authors, publication year, study design, participants, age, ethnicity, country, education level, testing method, confirmatory assay, positive results, risk factors for transmission, HIV co-infection, and syphilis.

Two authors independently assessed the methodological quality of the studies included in the meta-analysis, using the 'Quality Assessment Tool for Case Series Studies' of the National Heart, Lung and Blood Institute (NHLBI) [24]. Disagreements were resolved by consensus or by asking an independent third party. The seven domains assessed were: bias because of confounding, bias in the selection of participants into the study, bias in the measurement of interventions, bias because of departures from intended interventions, bias because of missing data, bias in the measurement of outcomes, and bias in the selection of reported results.

Statistical analyses

All data were initially recorded in Excel (version Microsoft Office LTSC Standard 2021). All further analyses were performed using the Statsdirect software version 3.3.6 (StatsDirect Ltd Wirral, UK) (<https://www.statsdirect.com>).

A qualitative synthesis of all studies was initially performed. Then, a quantitative synthesis was then made using the Stuart-Ord method for proportion meta-analysis [25]. The estimates of HTLV-1/2 rates were graphically represented using forest plots, distinguishing HTLV-1/2 screening and confirmatory results. We used 95% CIs. The DerSimonian-Laird model was performed to assess the weight of distinct studies.

The heterogeneity between studies was assessed using the I² index with 95% confidence intervals and the Cochran Q test. The I² index ranges from 0 to 100%, considering *P*-values above 75% as too high. Publication bias was assessed using funnel plots, and

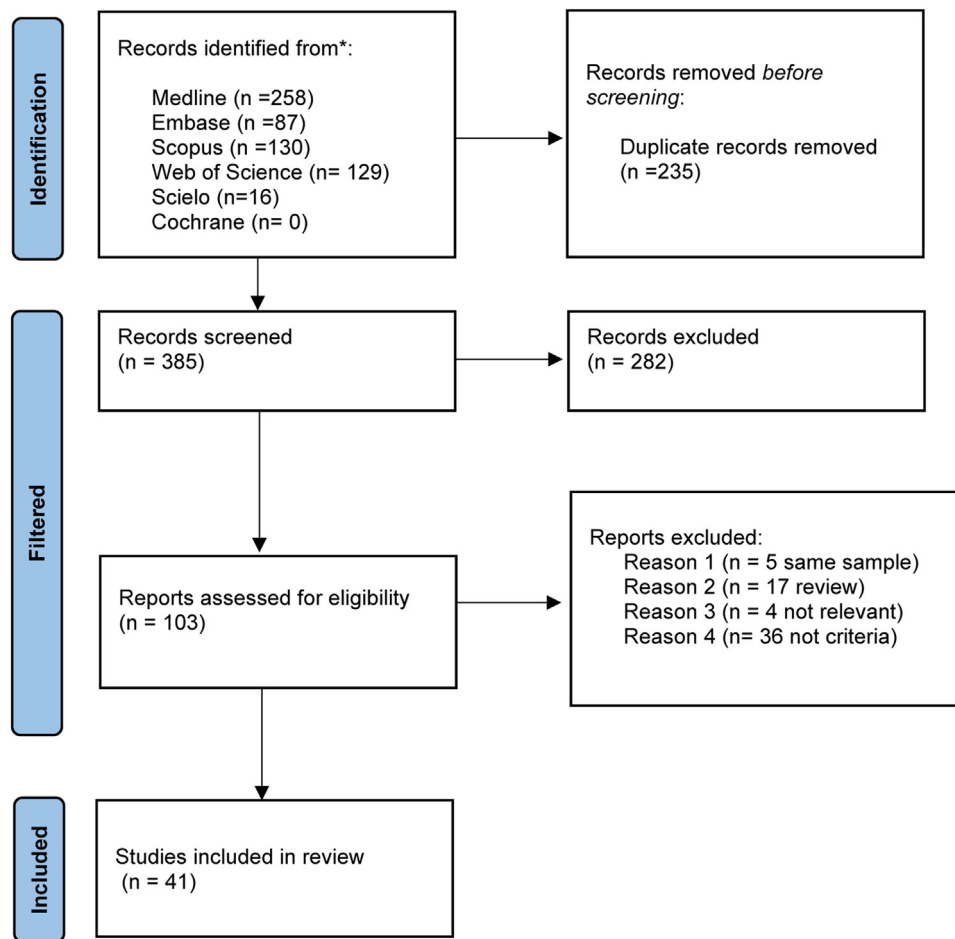


Figure 1. Flow diagram PRISMA 2020 for study selection.

^aConsider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372: n71. <http://dx.doi.org/10.1136/bmj.n71>.

HTLV, Human T-lymphotropic viruses, PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Egger and Harbord tests. Only *P*-values below 0.10 were considered adequate.

Results

A total of 620 articles were initially identified. After removing duplicates and small series, only 103 were selected. Full texts were retrieved, and further eligibility criteria were applied. Finally, 41 publications were chosen for the final meta-analysis (List of publications in Supplementary Table 2). The flow chart of the search is recorded in Figure 1.

All studies included in the meta-analysis had a transversal design and had been made in seven countries: 25 (61.0%) in Brazil, six (14.6%) in Peru, four (9.8%) in French Guiana, three (7.3%) in Argentina, two (4.9%) in Haiti, and one (2.4%) in Martinique. The main features of these studies are recorded in Table 1.

In the quality assessment, 36 studies were ranked as having good quality and five as fair quality (Supplementary Table 3).

The studies examined included a total of 343,707 pregnant women. Their mean age was 24.4 years, ranging from 12 to 50 years. The most frequent screening test for HTLV-1/2 antibodies were enzyme immunoassays (EIA) (*n* = 36; 87.8%), followed by chemiluminescence immunoassays (*n* = 4; 9.7%) and particle agglutination assay (*n* = 1; 2.4%). Besides the 1288 women who were confirmed as positive for HTLV-1, there were 189 additional

women who were HTLV-1/2 seropositive but untypeable. Only 82 were confirmed as HTLV-2 positive.

Three studies did not report any positive cases of HTLV-1/2 screening and were excluded from the quantitative synthesis. In total, 38 studies were further analyzed. Overall, the rate of HTLV-1/2 positivity in the screening test was 1.30% (95% CI: 0.96-1.69) using a model of aleatory effects (Supplementary Figure 1). It presented high heterogeneity ($I^2 = 98.6%$; 95% CI = 98.5-98.7) and high asymmetry in the funnel plot (Figure 2), confirmed using the Egger's test ($p < 0.001$) (Supplementary Table 4).

HTLV-1/2 confirmatory tests were performed in 39 studies. The remaining two studies, both from Brazil, did not provide this information [56,64]. In 84.6% of the studies (34 of 39), a Western blot was used as confirmatory assay. polymerase chain reaction (PCR) was used in only three (7.7%) studies. In the rest, other tests were used, including Indirect Immunofluorescence (IFI) and Line Immuno Assay (Inno-LIA) HTLV I/II.

The rate of positive confirmatory results for HTLV-1 was 1.02% (95% CI: 0.75-1.33) using a model of aleatory effects (Figure 3). It depicted also a high heterogeneity ($I^2 = 98.3%$; 95% CI = 98.1-98.4) and high asymmetry in the funnel plot (Supplementary Figure 1), confirmed using the Egger's test ($p < 0.001$) (Supplementary Table 4).

Only 13 (32.5%) of studies (including 206,224 patients) reported cases of HTLV-2 infection (Table 1). These studies had been con-

Table 1
Main characteristics of studies included in the meta-analysis.

Author, year ^a	Country	Description of population	N	Median age (years)	Range (years)	Screening method	N (+)	Confirmation method	N (+)	N (+) HTLV-1	N (+) HTLV-2
Kline et al., 1991	Haiti	Women from Haiti as part of a perinatal study	1100	-	-	EIA	59	WB & RIPA	59	59	0
Wignall et al., 1992	Peru	Women attended in prenatal clinics in Lima (July 1987 to May 1988)	510	25.5	18-42	EIA	16	WB & RIPA	16	16	0
Allain et al., 1992	Haiti	Pregnant women who attended the hospital for prenatal care in three rural populations in northern Haiti (1988 and 1989)	500	25	15-49	EIA	11	WB & RIPA	11	11	0
Tuppin et al., 1995	French Guiana	Pregnant women belonging to different ethnic groups (July 1991 to June 1993)	1716	-	31-35	EIA	75	WB	68	68	0
Dos Santos et al., 1995	Brazil	Pregnant women referred to the public health laboratory of the state of Bahia for prenatal examination (November 1990 to June 1991)	1025	-	Categories (<21, 21-30 & >31)	EIA	15	WB	10	7	-
Loureiro et al., 1995	Brazil	Pregnant women	1000	-	14-40	EIA	16	WB	5	0	0
Broutet et al., 1996	Brazil	Six selected population groups, including pregnant women recruited from public health centers and hospitals (July 1993 to February 1994)	814	-	-	EIA	3	WB	2	1	1
Zurita et al., 1997	Peru	Pregnant women	211	-	15-49	EIA	5	WB	5	5	0
Mansuy et al., 1999	Martinique	Pregnant women receiving prenatal care at the Department of Maternity & Child Protection (August 1995 to January 1996)	467	26	15-49	EIA	9	WB	9	9	0
Tortevoye et al., 2000	French Guiana	Pregnant women from the regional public gynecology & obstetrics unit in Saint Laurent (July 1991 to June 1997)	3834	-	-	EIA	144	WB	144	144	0
Bittencourt et al., 2001	Brazil	Pregnant women who attended the prenatal care unit of a state maternity hospital in the city of Salvador (January 1996 to September 1998)	6754	26	Categories (14-20, 21-30 & 31-42)	EIA	61	WB & PCR	59	57	2
Carles et al., 2004	French Guiana	Pregnant women who gave birth in St. Laurent (July 1991 to June 1993)	1727	-	Categories (<21, 21-25, 26-30, 31-35 & >36)	EIA	75	WB	75	75	0
Juscamaíta et al., 2004	Peru	Pregnant women attending prenatal care and women at risk of sexually transmitted infections at the Regional Hospital of Ayacucho (November 2002 to February 2003)	602	-	Categories (<20, 20-29, 30-39 & >40)	EIA	6	WB	3	3	0
Olbrich-Neto & Meira, 2004	Brazil	Embarazadas atendidas en Unidades Básicas de Salud del municipio de Botucatu.	913	-	-	EIA	2	WB	2	1	1
Figueiró-Filho et al., 2005	Brazil	Pregnant women attended Basic Health Units in the municipality of Botucatu	32512	-	Categories (15-19, 20-29, 30-39 & 40-49)	EIA	37	WB & PCR	29	0	0
Tortevoye et al., 2005	French Guiana	Pregnant women who attended the sole regional public gynecology and obstetrics unit at the Saint Laurent du Maroni hospital (July 1991 to June 2001)	6331	27	Categories (<21, 21-25, 26-30, 31-35 & >36)	EIA	218	WB	218	218	0
Alarcon et al., 2006	Peru	Women who sought care at the Maternal Perinatal Specialized Institute (IMP) (August 1996 and April 1997)	2492	25.5	Categories (<20, 20-30 & >30)	EIA	42	WB	32	32	0

(continued on next page)

Table 1 (continued)

Author, year ^a	Country	Description of population	N	Median age (years)	Range (years)	Screening method	N (+)	Confirmation method	N (+)	N (+) HTLV-1	N (+) HTLV-2
Oliveira & Avelino, 2006	Brazil	All pregnant women attended all prenatal care units of the Municipal Health Department of Goiânia (September 2003 to December 2004)	15485	-	Categories (<30, & ≥30)	EIA	19	PCR	16	16	0
Eirin et al., 2007	Argentina	Pregnant women who attended two public hospitals in Buenos Aires and Neuquén	1867	-		EIA	3	WB	3	1	2
Trenchi et al., 2007	Argentina	Pregnant women registered in the public health service of the province of Córdoba (year 2000)	3143	-	-	PAA & IFA	171	WB	6	3	0
Fabbro et al., 2008	Brazil	Women seeking prenatal care in the Program for the Protection of Pregnant Women in the State of Mato Grosso do Sul	116689	27	14-44	EIA	153	WB & PCR	150	133	17
Magalhães et al., 2008	Brazil	Pregnant women beyond 10 weeks of gestation in Cruz das Almas were randomly selected (June to October 2005).	408	-	14-32	EIA	4	WB	4	4	0
Ydy et al., 2009	Brazil	Puerperal women admitted at three public maternity hospitals affiliated with the Unified Health System in Cuiabá (April to September 2006)	2965	23.9	13-44	EIA	9	WB	7	6	1
Mello et al., 2009	Brazil	Pregnant women from the maternity ward of Vitória Mercy Hospital and the External Patient Referral Unit of the Municipality of Serra	447	24.8	12-44	EIA	6	IFA & MEIA	1	0	0
Souza et al., 2009	Brazil	Pregnant women were assisted during prenatal care in three public services in São Luis (February to December 2008).	2044	-	18-45	EIA	7	WB & PCR	7	4	3
Ribeiro et al., 2010	Brazil	Mothers and newborns. Samples collected on filter papers (September to November 2007)	55293	-	-	EIA	53	WB	42	40	2
Filho et al., 2010	Brazil	Consecutively attended pregnant women from the spontaneous demand of Faculdade de Medicina do Triângulo Mineiro (March to September 2008)	618	23.9	13-43	EIA	0	PCR	0	0	0
Sequeira et al., 2012	Brazil	Pregnant women interviewed during prenatal consultations at health units in 19 municipalities that entered the Maternal and Child Health program (February to November 2008)	13382	-	Categories (15-19, 20-39, & 40-49)	EIA	43	WB	41	39	1
Blas et al., 2013	Peru	Women from the Shipibo-Konibo ethnic group (July to December 2010)	1253	-	15-39	EIA	121	WB	121	74	47
Berini et al., 2013	Argentina	Pregnant women over 18 years old who attended prenatal consultations consecutively in five public hospitals	2403	-	>18	EIA	6	WB & PCR	6	3	3
Mello et al., 2014	Brazil	Women attended the prenatal units of the two regional hospitals (Ilheus and Itabuna) (November 2008 to May 2010)	2766	-	Categories (9-19, 20-29 & >30)	EIA	34	WB	29	29	0
Monteiro et al., 2014	Brazil	Pregnant women admitted for delivery at two public hospitals in the metropolitan area of Rio de Janeiro (November 2012 to April 2013)	1204	-	Categories (<24 & ≥ 25)	CMIA.	10	WB	8	7	1
Moura et al., 2015	Brazil	Pregnant women seeking care in the Universal Health System of Maceió during their first prenatal check-up (June 2007 to May 2012)	54798	23.3	15-35	EIA	129	WB	118	0	0

(continued on next page)

Table 1 (continued)

Author, year ^a	Country	Description of population	N	Median age (years)	Range (years)	Screening method	N (+)	Confirmation method	N (+)	N (+) HTLV-1	N (+) HTLV-2
Guerra et al., 2018	Brazil	Adolescent pregnant girls who attended prenatal care at the Specialized Unit for Maternal-Child and Adolescent Care (November 2009 to February 2010)	324	15.8	12-18	EIA	0	PCR	2	0	0
Mata et al., 2018	Brazil	Women of reproductive age in the urban area of Oiapoque	216	-	Categories (0-15, 16-20, 21-30, 31-40, 41-50)	EIA	0	WB	0	0	0
Costa et al., 2018	Brazil	Pregnant mothers who attended the Women's Reference Care Center (Maternidade Santa Helena) in the city of Ilhéus (July 2009 to July 2010).	511	-	13-44	EIA	6	WB & PCR	6	0	0
Medeiros et al., 2018	Brazil	Pregnant women attending a high-risk prenatal care unit at Clinical Hospital/Federal University of Paraná (August 2015 to August 2016)	643	-	18-47	CMIA	4	PCR	2	1	1
Barmpas et al., 2019	Brazil	Pregnant women attending a high-risk prenatal care unit at Clinical Hospital/Federal University of Paraná (August 2015 to August 2016)	1628	-	Categories (<=24 & >24)	CMIA	14	WB	12	0	0
Mendes et al., 2020	Brazil	Pregnant volunteers who were selected by free choice during the prenatal period at LACEN-MA (February 2015 to May 2017)	713	24.3	15-43	CMIA	5	WB & PCR	5	5	0
Vargas et al., 2020	Brazil	Parturient attended at two public maternity hospitals in Salvador, Bahia (April 2016 to June 2017)	2099	27.3	14-46	EIA	10	WB & PCR	9	0	0
Ramos et al., 2021	Peru	Pregnant women attending health centers in the city of Iquitos (May and June 2019)	300	26	≥18	EIA	5	WB & PCR	5	5	0

^a List of publications in Supplementary Table 2.N, number; EIA, enzyme immunoassay; CMIA, chemiluminescence immunoassay; PAA, particle agglutination assay; IFA, indirect immunofluorescence assay; MEIA, microparticle enzyme immunoassay; WB, western blot; RIPA, radioimmunoprecipitation assay; PCR, polymerase chain reaction.

ducted in Brazil, Argentina, and Peru. None in the Caribbean or Central America. The rate of positive confirmatory results for HTLV-2 was 0.14% (95% CI: 0.06-0.25) using a model of aleatory effects (Figure 4). It had a high heterogenicity ($I^2 = 94.2\%$; 95% CI = 92.2-95.4) and high asymmetry in the funnel plot (Supplementary Figure 1), confirmed using the Egger's test ($p = 0.02$) (Supplementary Table 4).

Discussion

In this systematic review and meta-analysis of HTLV-1/2 infection among pregnant women in CSA&C, we reported an overall prevalence rate of 1.02% (95% CI: 0.75-1.33) for HTLV-1 and of 0.14% (95% CI: 0.06-0.25) for HTLV-2. These rates significantly differ from those reported in a recent systematic review conducted on pregnant women in Brazil on studies published until mid-2020 [26], which found prevalence rates of 0.32% for HTLV-1 and 0.4% for HTLV-2 were found. The authors acknowledged a geographical split of HTLV-1 predominating in the north whereas HTLV-2 predominated in the southern regions.

In a study conducted in the late 90s among ethnic minorities living in South America [25], high rates of HTLV-1 were seen among the Peruvian Aymara (1.6%), the Bolivian Aymara (5.3%) and Quechua (4.5%), the Argentine Puna (2.3%), and the Chilean Ata-

cama (4.1%). In contrast, HTLV-2 was highly prevalent among the Brazilian Kayapo (57.9%), the Paraguayan Chaco (16.4%), the Chilean Alacalf (34.8%), and Yahgan (9.1%). Accordingly, the authors concluded that there was a geographic clustering of HTLV-1 foci in the Andes highlands and of HTLV-2 foci in the lowlands of South America.

In our study, high rates of HTLV-1 (1%) were uniformly noticed in all studies conducted on pregnant women in Caribbean countries, such as Haiti, Martinique, and French Guiana. Interestingly, none reported a single case of HTLV-2 infection. In contrast, we recorded pregnant women with HTLV-2 infection in Brazil and Argentina, generally with low rates and nearly always below those seen for HTLV-1 in these countries. Intriguingly, one exception was one study conducted on pregnant women from the Shipibo-Konibo ethnic minority living in the Peruvian Andes, which reported a 4% rate of HTLV-2 along with a 7% of HTLV-1 infection (Blas et al., 2013 in Table 1)

There was a high heterogeneity between studies included in our meta-analysis. Accordingly, HTLV-1/2 rates differed substantially. A large proportion of women examined belonged to special populations, including ethnic minorities, rural areas, and well-known highly HTLV-1/2 prevalent regions. In contrast, a few studies included women from urban areas with null or low Amerindian ancestry. As expected, in the latter studies HTLV-1/2 prevalence rates

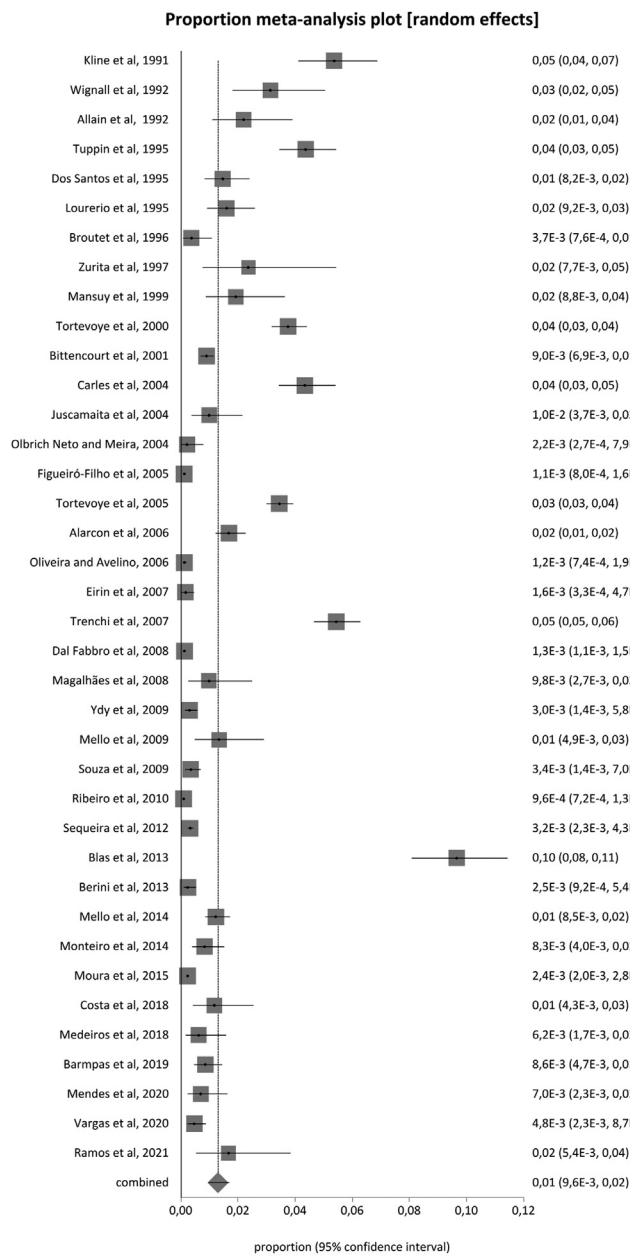


Figure 2. Pooled prevalence of HTLV-1/2 positivity in the screening test. HTLV, Human T-lymphotropic viruses.

were significantly lower. In some studies, from Brazil (Table 1: Filho et al., 2010, Guerra et al., 2018 and Mata et al., 2018), no pregnant women with HTLV-1/2 infection were found.

An interesting finding in our study refers to the relatively good performance of HTLV-1/2 screening assays, with an average 90% confirmation of initially seroreactive samples. The fact that the study population was expected to depict moderate to high rates of HTLV infection could explain this finding. Most concerns about false positive rates came from studies performed in low-risk populations in non-endemic regions, such as blood donors in Europe or North America [27].

Limitations

We should acknowledge several caveats in our meta-analysis. Firstly, we could not find any study from continental Central America that fitted the inclusion criteria, so such a region was not

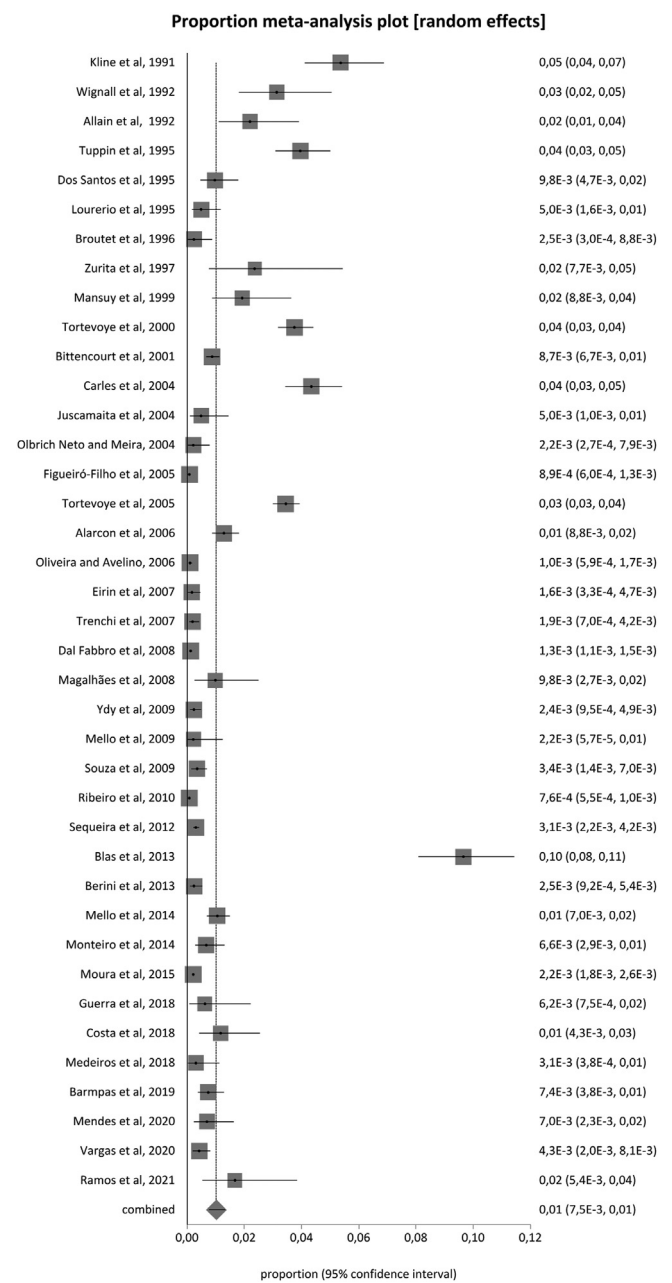


Figure 3. Pooled prevalence of positive confirmatory results for HTLV-1. HTLV, Human T-lymphotropic viruses.

represented in this systematic review. Of note, only studies from four countries in South America and another four in the Caribbean basin were examined. Again, misrepresentations of other countries could influence our results. Secondly, the reliability of HTLV-1/2 assays was quite variable comparing distinct tests and periods, as previously highlighted by others [28]. Although we considered both screening results along with confirmatory results, a substantial proportion of women gave HTLV-1/2 positive results on immunoblot that were untypable. Because PCR was not performed, these serological results should be interpreted cautiously. In this regard, misdiagnosis of HTLV-1 and in less extent of HTLV-2 might have occurred to some extent. Both in the pooled analysis of the screening and confirmatory results, asymmetrical funnel plots can be observed (Supplementary Figs 1-C). This is explained by the fact that prevalence results below 0 are not possible. Therefore, neither the plots nor the results of the bias tests necessarily indicate pub-

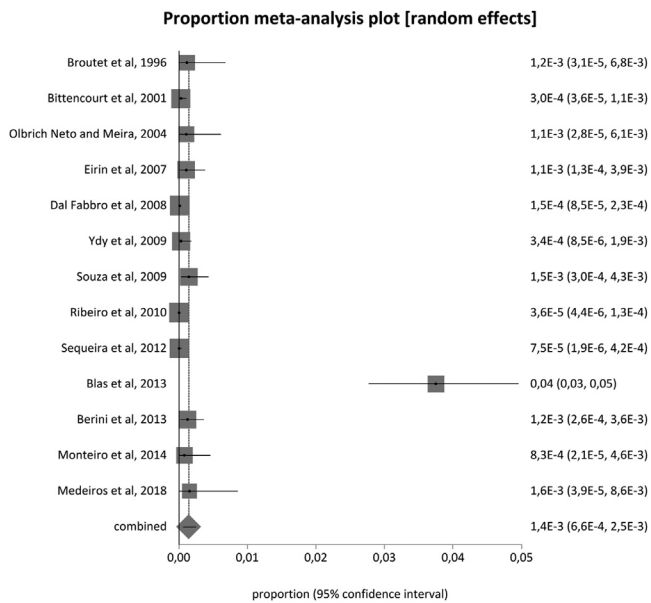


Figure 4. Pooled prevalence of positive confirmatory results for HTLV-2. HTLV, Human T-lymphotropic viruses.

lication bias [29]. In contrast, we attribute the high heterogeneity found not only to the intrinsic differences between the studies but also to the fact of counting and pooled estimates <10% and a high number of studies. The last observation is that the prevalence of newborns testing positive for HTLV-1/2 was not evaluated, even though the original study design was intended to investigate these results. Conducting studies such as the present systematic review and meta-analysis is important for evaluating the prevalence of vertical HTLV transmission.

Conclusions

This meta-analysis and systematic review show a 1.3% rate of HTLV-1/2 infection among pregnant women in CSA&C. This figure is greater than rates for HIV, syphilis, or hepatitis B, for all of which there is a clear recommendation for antenatal testing. Thus, our results support the introduction of HTLV-1/2 screening of pregnant women from CSA&C everywhere. This recommendation is particularly relevant for endemic regions but also extends to Western countries with a significant CSA&C migrant population.

Declarations of competing interest

The authors have no competing interest to declare.

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Ethical approval

The meta-analysis study is exempt from ethics approval, as the study authors collected and synthesized data from previously published studies.

Authors contributions

Study design: J.M. Ramos-Rincón and E. de-Miguel-Balsa.

Data collection: J.P Sánchez-Núñez, E. Lorenzo-Garrido, S. Otero-Rodríguez, J.C. Celis-Salinas, C. de-Mendoza and M. Casapia-Morales.

Data analysis: E. de-Miguel-Balsa, and A. Giménez-Richarte.

Writing: J.P Sánchez-Núñez, E. de-Miguel-Balsa, V. Soriano and J.M. Ramos-Rincón.

Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107018.

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Hemorrhagic erucism due to *Lonomia* spp. in Peru – A call for action

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ABSTRACT

Envenomation due to exposure to caterpillars is an emerging public health problem. A life-threatening bleeding diathesis has been described in South America after exposure to *Lonomia obliqua* or *L. acheolus*. Deforestation, forest degradation, and global warming might increase the frequency of human exposure to these insects. Prompt recognition and administration of antivenom are crucial to ensure a favorable outcome.

1. Introduction

The order Lepidoptera, comprising moths and butterflies, is considered one of the most diverse insect groups. Caterpillars, the worm-like larval forms, have evolved defensive mechanisms against their natural predators. These consist of bared setae, hollow plume-like sharp hairs connected to poison sacs that release poison when they pierce the skin [1,2]. Caterpillar envenomation in humans can be classified clinically as (a) erucism, (b) lepidopterism, (c) dendrolimiasis, (d) ophthalmia nodosa, and (e) consumptive coagulopathy with secondary fibrinolysis [3]. Lepidopterism refers to the reactions from moths or butterflies, while erucism refers to any response to caterpillars [4].

Caterpillar exposure is infrequent and most often affects children or field workers such as farmers or fishermen. Seasonal outbreaks have been documented and usually coincide with the synchronous hatching of eggs or the dispersal of their setae by the wind [1,5]. Local and self-limiting reactions are the most frequently described clinical manifestations. These are characterized by mild to severe burning pain that develops shortly after exposure, localized edema, and erythema. Severe, systemic, and potentially life-threatening reactions are almost

exclusively related to exposure to *Lonomia* spp. This type of erucism, also known as lonomism, is geographically restricted to South America and manifests as a hemorrhagic diathesis [4,6].

We herein report the first case of hemorrhagic erucism in Loreto, in the Amazon of Peru, highlighting the importance of a timely diagnosis and treatment for the attainment of a favorable outcome.

2. Exemplary case

A 34-year-old American woman, living in Peru for several months for work-related reasons, accidentally touched an army of caterpillars while climbing a tree (Fig. 1). She experienced immediate paresthesia and severe stabbing and burning pain in her right palm with radiation to her forearm. Twenty-four hours later, the patient noticed bleeding from an old abrasion on her right foot. A few hours later, she noted painless ecchymosis in her arms, the right axillary, and the right iliac crest region. She was hospitalized three days after contact with the caterpillars due to vaginal bleeding, worsening generalized ecchymosis, and headache.

On physical examination, she had multiple and large hematomas in her upper and lower extremities and torso, with the largest in the right

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axillary region measuring 8×10 cm and over the right iliac crest measuring 15×5 cm (Fig. 2). Laboratory findings were significant for a hemoglobin of 9.5 g/dl; platelets count of $121,000 \text{ mm}^3$, thrombin time greater than 50 s, and an unmeasurable international normalized ratio (INR) and fibrinogen levels.

The patient was treated with Lonomia antivenom obtained from Colombia's National Institute of Health. Due to the persistence of severe headaches and abnormal coagulation studies, the patient was transferred to a reference hospital in the capital city of Lima. In that facility, the patient was treated with additional vials of antivenom and a transfusion of cryoprecipitate, which led to the resolution of bleeding and normalization of the coagulation parameters.

3. Discussion

Caterpillar-induced bleeding due *L. achelous* was first reported in Venezuela in 1967 [7]. Only two species have been conclusively linked to envenomation accidents. *L. achelous*, found in the Amazonian regions of Brazil, Colombia, Venezuela, Ecuador, Peru, and the French Guiana, and *L. obliqua*, restricted to the southern portions of Brazil, Paraguay, and Argentina. Other species are nevertheless likely responsible for human envenomation [6,8,9]. Although Peru has the highest diversity of the region with 19 recorded species, few cases of lononism have been described [6]. A total of six cases of hemorrhagic erucism have been reported in Peru, with three reported from the department of Junin, two from Huánuco, and one in a Canadian traveler who acquired the disease in the northeastern region of the country [10–12] (Table 1).

The mechanism of action of the venom of *L. obliqua* consists of two toxin procoagulants: a factor X activator known as Losac or Stuart factor activator and a prothrombin activator named Lopap. Fibrinolysis results from the exuberant formation of fibrin due to thrombin generation [17]. Lonomin II and V, the most important toxins of *L. achelous*, have a direct

fibrinolytic activity and degrade coagulation factor XIII, respectively [17,18]. In addition, the procoagulant effect of the *L. obliqua* toxin is maximized by venom-induced platelet dysfunction [19]. Furthermore, a cellular and humoral response leads to the release of substances such as bradykinin, prostaglandins, metalloproteases, hyaluronidases, tumor necrosis alpha, interleukin-6, and other molecules that contribute to the pro-inflammatory action of the venom [20,21]. The lethal dose of *L. obliqua* venom in mice is about 10 mg/kg body weight [17].

Despite the difference between the toxin's mechanism of action, the clinical manifestations of envenomation are indistinguishable between the species and range from local cutaneous reactions to a life-threatening systemic hemorrhagic syndrome. The cutaneous manifestations typically present immediately or up to 72 h after contact with the caterpillar. Hemorrhage can present 1 h to ten days after exposure and predominantly affects the mucous membranes and soft tissues but can also affect vital organs such as the brain and the lungs [12,20,22]. The development of acute kidney injury is associated with delayed presentation to care and portends a guarded prognosis [23,24]. This has been almost exclusively reported after envenomation with *L. obliqua* and is attributed to ischemia, a direct toxin effect on the kidney, and the deposition of fibrin in the glomeruli [25,26]. Importantly, renal dysfunction can be permanent in survivors [24].

Cases typically present with normal platelet, hemoglobin count, and liver function tests, differentiating lononism from other causes of hemorrhagic fever in the tropics, such as yellow fever and dengue. Prolonged prothrombin, partial thromboplastin, and thrombin times associated with low to undetectable fibrinogen levels and increased fibrin degradation products are characteristic. The degree of hypofibrinogenemia correlates with the severity of the hemorrhagic manifestations and can be used to monitor the effectiveness of treatment [25].

Treatment consists of administering antifibrinolytics such as ϵ -aminocaproic acid at a dose of 30 mg/kg followed by 15 mg/kg every 4 h

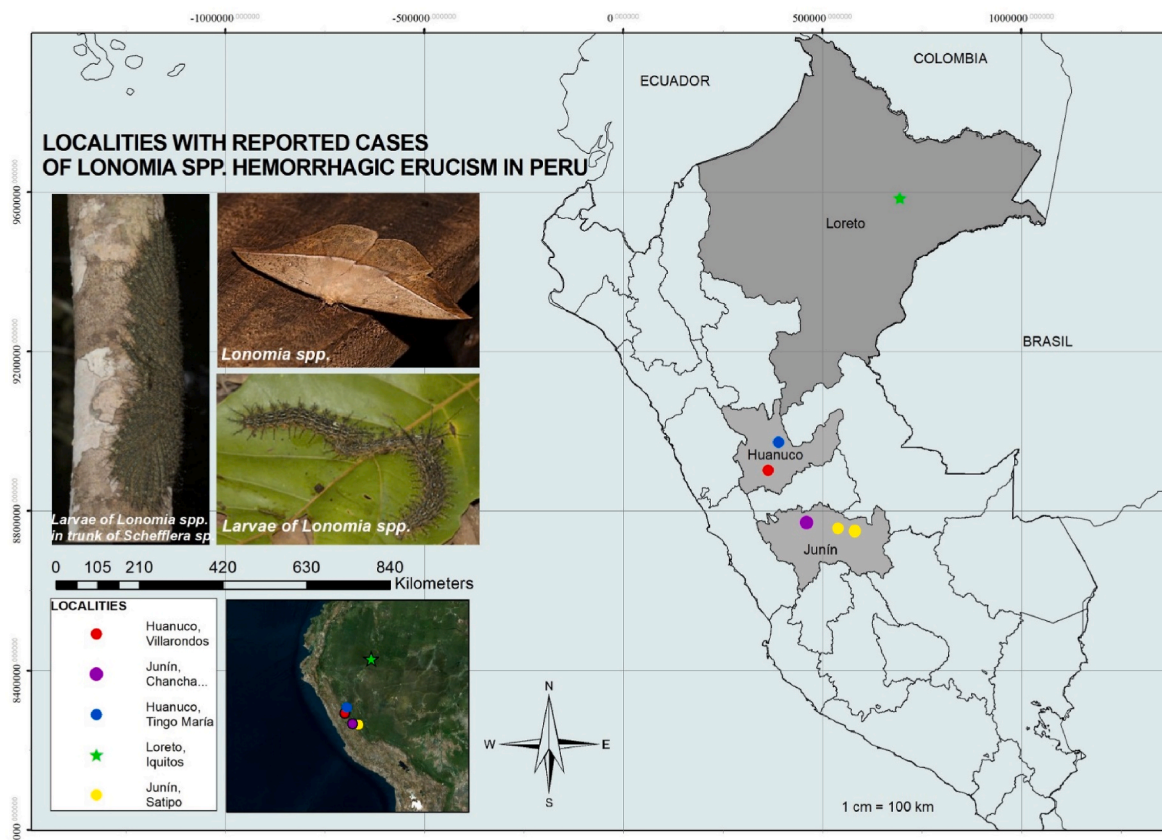


Fig. 1. *Lonomia* spp. encountered by our patient (A and B). The gregarious nature (A) may lead to contact with large number of caterpillars exposing individuals to a considerable amount of venom. Adult *Lonomia* moth (C). The maps illustrate the location of the cases of lononism reported in Peru.

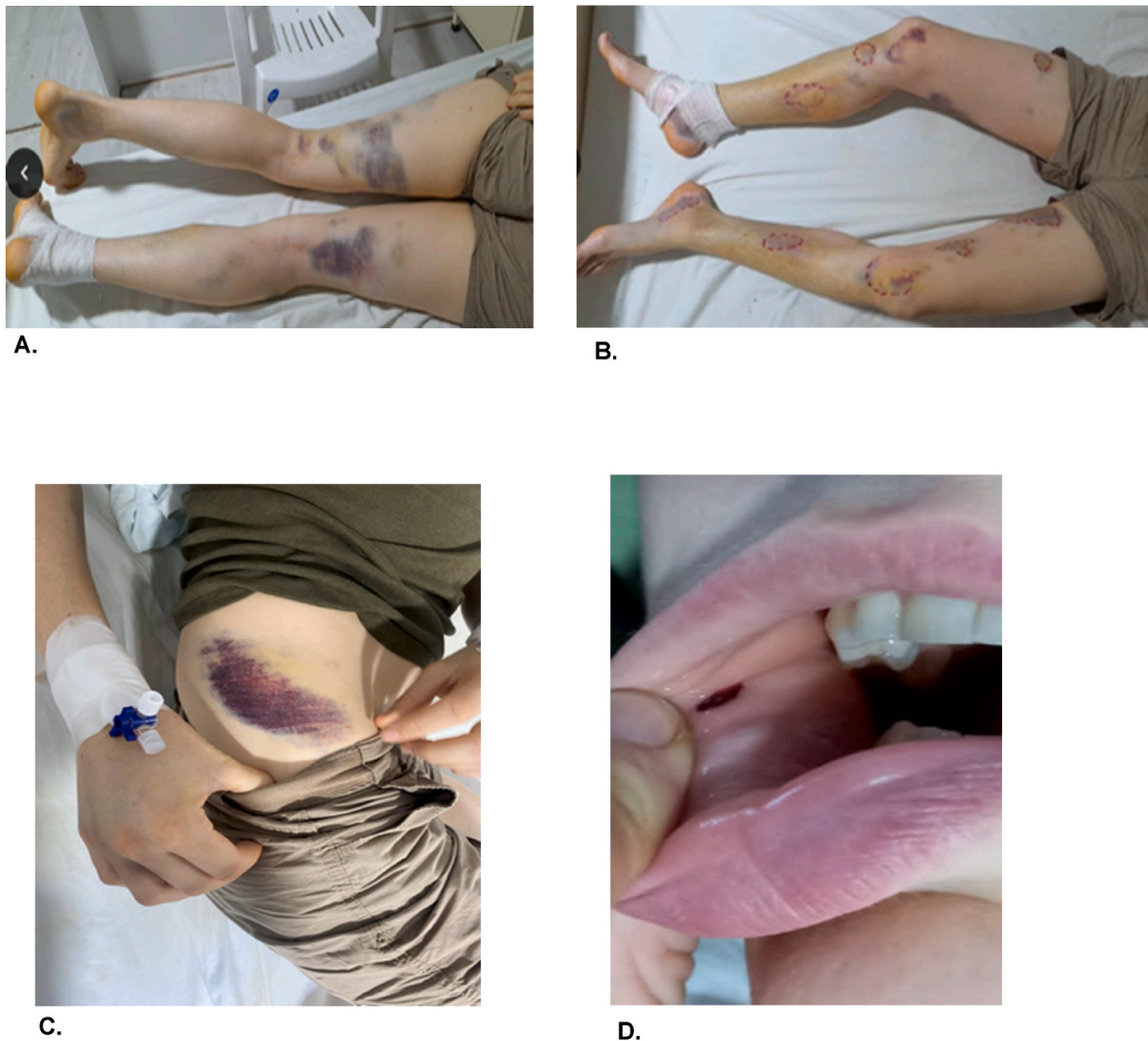


Fig. 2. Hemorrhagic manifestations present at admission involving both of her legs (A and B), right iliac crest (C), and the oral mucosa (D).

until normalization of the coagulation parameters. More importantly, whole blood or fresh frozen plasma is contraindicated as it can exacerbate consumptive coagulopathy [18]. Antivenim was first developed by the Butantan Institute in Brazil in 1996 and is effective when administered 12–24 h after envenomation. It is indicated when there is evidence of bleeding, with doses varying between five and ten vials depending on the severity of presentation. Each 10 ml vial contains heterologous F (ab')₂, neutralizing approximately 3.5 mg of *L. obliqua* venom [8,27,28]. The lethality in the absence of treatment is approximately 1.5–2%, three to four times that of snakebites [24]. The antivenim can be obtained from the Butantan Institute in Sao Paulo, Brazil, or the National Institute of Health of Colombia. Contact information: <https://en.butantan.gov.br/about-envenoming.php> and <https://www.ins.gov.co/Direcciones/Produccion/Paginas/Suero-antiofidico-polivalente.aspx>, respectively.

We describe the first cases of lonomism from the Amazon Region of Loreto in Peru and the second travel-related case in the literature. The only described travel-related case involved a Canadian citizen who had visited Peru and unfortunately died as a result of the envenomation [12]. According to biologists from the Loreto Regional Hospital and based on their appearance, the *Lonomia* species responsible for the envenomation in our case was likely other than *L. obliqua* or *L. acheoulus*. Unfortunately, we did not have a specimen for further identification and analysis.

Lonomism is likely an underappreciated condition in many of the

Peruvian Amazon's local indigenous and riverine communities due to their difficulty in accessing healthcare facilities [8]. Deforestation and human encroachment in the fringes of biodiversity-rich areas increase the risk of interaction between populations and wildlife. Occupational and accidental exposure to caterpillars is thus predicted to occur as their distribution increases in areas closer to populated areas due to the loss of their natural habitat and attraction to the lights of human settlements, increasing the potential for occupational exposure [6,29]. The burden of erucism in rural tropical areas is undoubtedly underestimated, underscoring the need to improve surveillance of an emerging public health problem in the Americas [2,6,23,30].

4. Conclusion

More reported cases of caterpillar-induced hemorrhage are expected as deforestation, forest degradation, and global warming continue to go unchecked. It is, therefore, essential for healthcare professionals around the globe to be acquainted with this emerging public health problem. Prompt recognition and administration of antivenom are crucial to ensure a favorable outcome. There is an urgent need for countries at risk of lonomism to develop and maintain a national stockpile of the life-saving antivenim. Hemorrhagic erucism should be considered in the differential diagnosis of hemorrhagic syndromes in the tropics.

Table 1
Reported cases of Lonomism in Peru.

Year of the Incident (ref.)	Locality	Gender	Age (years)	Clinical Manifestations, Treatment, and Outcome
2006 [13]	Satipo, Junín	Female	32	Presentation: generalizing pain, nausea, vomiting, ecchymosis, gingivorrhagia Treatment: supportive. No antivenom used Outcome: full recovery
2007 [14]	Chanchamayo Junín	Female	12	Presentation: pain at the inoculation site, vomiting, headache, epistaxis, and ecchymosis. Treatment: blood transfusion and transfer to reference hospital Outcome: unknown
2008 [12]	Northeastern Peru	Female	22	Presentation: headache, ecchymosis, acute kidney injury, respiratory distress due to alveolar distress, microangiopathic hemolytic anemia, and disseminated intravascular coagulation Treatment: supportive, invasive mechanical ventilation, and antivenom Outcome: death
2010 [10]	Villarondos, Huánuco	Female	5	Presentation: vomiting, fever, epistaxis, hematemesis, gingivorrhagia, ecchymosis Treatment: supportive requiring admission to the intensive care unit, and antivenin Outcome: full recovery.
2014 [15]	Tingo María, Huánuco	Male	10	Presentation: pain at the inoculation site, right hip pain, shortness of breath, hemarthrosis, hemopericardium, acute gastrointestinal bleeding, hematuria Treatment: supportive requiring admission to the intensive care unit. Antivenin Outcome: full recovery
2020 [16]	Satipo, Junín	Male	48	Presentation: pain at the inoculation site, headache, abdominal pain, ecchymosis, gingivorrhagia and intracranial hemorrhage Treatment: supportive and antivenin Outcome: full recovery

CRedit authorship contribution statement

Edgar A. Ramírez García: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Maria José Valentina Canchanya-Olimar:** Writing – original draft, Investigation. **Mariana Rojas del Águila:** Writing – original draft, Methodology, Data curation. **Nelson Iván Agudelo Higuíta:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Andrés F. Henao-Martínez:** Writing – review & editing, Writing – original draft. **Carlos Franco-Paredes:** Writing – review & editing. **Luis A. Marcos:** Writing – review & editing, Conceptualization. **Juan C. Celis Salinas:** Writing – review & editing. **Martín Casapia Morales:** Writing – review & editing, Writing – original draft.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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