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DIRECTORA DE INVESTIGACIÓN E INNOVACIÓN EN SALUD DEL INSTITUTO NACIONAL DE SALUD

Presente

ASUNTO **INFORME DE AVANCE DE PUBLICACIONES DE INVESTIGACIONES ORIGINALES FICHA 48 – 2025**

ATENCIÓN **SUBDIRECCIÓN DE INVESTIGACIÓN – SUDIV-INS**

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Señor

M.C. Guillermo ANGULO AREVALO
Gerente Regional de Salud de Loreto

Presente

ASUNTO **INFORME DE AVANCE DE PUBLICACIONES DE INVESTIGACIONES ORIGINALES FICHA 48 – 2025**

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Señor

M.C. Jehoshua Rafael Michelangelo LOPEZ LOPEZ
Director General del Hospital Regional de Loreto

Presente

ASUNTO **INFORME DE AVANCE DE PUBLICACIONES DE INVESTIGACIONES ORIGINALES FICHA 48 – 2025**

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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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THERAPEUTIC ADVANCES in
Infectious Disease

Case Report

Ther Adv Infect Dis
2025, Vol. 12: 1–6
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Not your typical hookworm infection—a case report from the Peruvian Amazon and review of the literature

[illegible]

Abstract: Human hookworm infection is caused by the nematodes *Necator americanus*, *Ancylostoma duodenale*, and *Ancylostoma ceylanicum*. Iron deficiency anemia is the hallmark of chronic, moderate-to-heavy-intensity infections, promoting a vicious poverty cycle. Overt severe and acute life-threatening lower gastrointestinal hemorrhage is an extremely rare manifestation of hookworm infection, as well as finding multiple nematodes attached to the colonic mucosae. This rare hookworm presentation with hematochezia from the colon in a patient living with human immunodeficiency virus highlights the importance of physicians' awareness of this neglected tropical disease responsible for high morbidity and burden in healthcare systems of endemic regions.

Keywords: case report, hematochezia, HIV, hookworm, neglected tropical diseases, soil-transmitted helminthiasis

Received: 22 November 2024; revised manuscript accepted: 18 March 2025.

The nematodes *Necator americanus*, *Ancylostoma duodenale*, and *Ancylostoma ceylanicum* are the etiologic agents of human hookworm infection.[1,2] Elimination of hookworm infections has been achieved in most of the industrialized world due to improved sanitation and standards of living because of economic growth and urbanization. Nonetheless, hookworm infection continues to represent a significant burden in rural areas of tropical and subtropical regions of low and middle-income countries where poverty, poor sanitary infrastructure, and suitable soil and climate conditions coexist. Well-intended interventions such as mass drug administration (MDA) and the Water, Sanitation, and Hygiene (WASH) programs have failed to achieve the desired long-term impact on the intensity and prevalence of soil-transmitted helminthiasis (STH). Hookworm infection is considered one of the most important STH, accounting for close to 113 million cases and 540.20 thousand million lost disability-adjusted life years (DALYs) annually.[3]

Iron deficiency anemia is the hallmark of chronic, moderate-to-heavy intensity infections, promoting a vicious poverty cycle due to higher rates of low birth weight in affected communities coupled with impaired cognitive and physical development of their children and decreased productivity of their adults.[1] In the Peruvian Amazon, the situation is especially critical. A study conducted in Iquitos showed that 47.2% of pregnant women were infected with hookworms, and only 9.31% were free of any STH.[4] A high prevalence of hookworm infection shortly after MDA has also been reported in this region.[5]

Overt severe and acute gastrointestinal hemorrhage is an extremely rare manifestation of hookworm infection, as well as finding multiple nematodes in the colon. We followed the CARE

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THERAPEUTIC ADVANCES in
Infectious Disease

Volume 12

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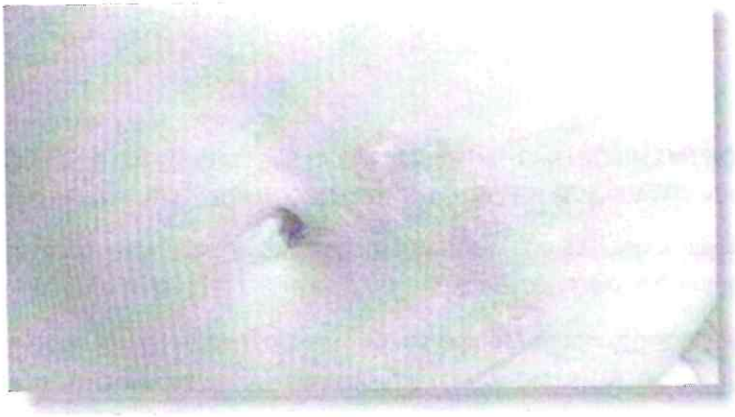

Figure 1. Hyperchromic lesions of linear shape, abdominal region.

case report guidelines[6] to describe these two rare presentations in a patient from a highly endemic area that required inpatient management causing high morbidity and a burden on the healthcare system.

Case

A 34-year-old male from Iquitos City, Department of Loreto in the Peruvian Amazon, presented with a 1-month history of excoriated pruritic lesions in the abdominal wall region that appeared after contact with sewage. Approximately 1 week after the appearance of the skin lesions, the patient developed a nonproductive cough of nocturnal predominance that lasted 8 days. Approximately 8 days before admission, he developed profuse diarrhea followed by hematochezia, for which he sought care at the Regional Hospital of Loreto, a major tertiary hospital.

His past medical history included human immunodeficiency virus (HIV) infection diagnosed 15 years ago (CD4 741 cells/mm^3; undetectable viral load) on tenofovir disoproxil fumarate, lamivudine, and efavirenz. On physical examination, blood pressure was 100/60 mmHg, heart rate was 90 beats/min, respiratory rate was 24 breaths/min, and blood oxygen saturation was 96% on room air. The skin was pale with a yellowish hue. Hyperchromatic lesions were seen on the abdominal wall (Figure 1). The rest of the physical examination was unremarkable. Laboratory findings were significant for a white blood cell count of 15,810 cells/mm^3 with 37% eosinophils (absolute: 5847 eosinophils/μL), a hemoglobin of 5.1 mg/dL with a mean corpuscular volume (MCV) of 73 fL, and a normal platelet count and coagulation parameters.

The patient was treated with intravenous fluids and a transfusion of two units of packed red blood cells. Due to the persistent hematochezia, the patient underwent a lower endoscopy that showed a friable mucosa with diffuse ulcerations as well as numerous nematodes adhered to the rectal mucosa, sigmoid, and the descending and transverse colon (Figure 2(a) and (b)).

The diagnosis of severe hookworm infection was confirmed by detecting only hookworm eggs in the stool sample at a moderate intensity (Figure 2(c)). Unfortunately, we were unable to retrieve nematodes during the colonoscopy for species identification. The patient was treated with albendazole 400 mg orally daily for 3 days. After several days of hospitalization, the patient was discharged after demonstrating favorable clinical and laboratory improvement.

Discussion

Hookworm infection is a leading cause of iron deficiency anemia in low and middle-income countries. The degree of anemia is determined by factors such as iron intake and stores, the intensity and duration of infection, and the infecting species.[4] *A. duodenale*, for example, leads to a more significant amount of blood loss (>10 times) compared to *N. americanus*.[1] The WHO classifies

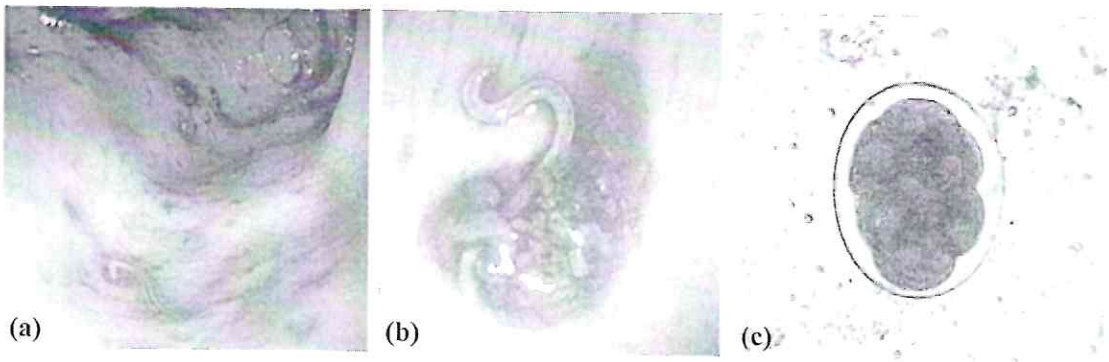

Figure 2. Lower endoscopy: (a) Transverse colon mucosa, with ulcerations and parasites anchored to the mucosa. (b) Note the parasite anchored to the colonic mucosa with perilesional reaction. (c) Hookworm egg recovered from the patient.

Table 1. Reports of hookworms in the colon excluding *Ancylostoma caninum* and *Ancylostoma ceylanicum*.

Country of origin (Reference)	Age/Gender	Hemoglobin (g/dL)	Eosinophil count (cells/μL)	Infecting species	Treatment
India (15)	35-year-old male	Unable to retrieve	Unable to retrieve	*A. duodenale*	Mebendazole
Taiwan (16)	69-year-old male	13.2	Not reported	*A. duodenale*	Albendazole for 3 days
USA (17)	31-year-old male status post allogeneic stem cell transplantation	Not specified	Not specified	Not specified	Mebendazole for 4 days
South Korea (18)	32-year-old male	No anemia	5645	*A. duodenale*	Mebendazole
Indonesia (19)	66-year-old male	10	803	*A. duodenale*	Not mentioned
India (20)	62-year-old female	Not specified	Not mentioned	*A. duodenale*	Albendazole one dose
Peru (21)	34-year-old male	6.6	1560	*A. duodenale*	Mebendazole and albendazole
Peru (22)	23-year-old male	2.3	2100	Not specified	Albendazole
Colombia (23)	20-year-old male	4.9	1364	Not specified	Pamoate pyrantel
Taiwan (24)	54-year-old male	Not specified	Present, but percentage not specified	*A. duodenale*	Mebendazole for 3 days

hookworm infections as light (≤1999 eggs per gram of stool), moderate (2000–3999 eggs per gram of stool), and heavy (≥4000 eggs per gram of stool), with the severity of the anemia being directly proportional to the intensity of the infection.[7] Nevertheless, the egg count does not always accurately reflect the burden of the infection; this is especially true when only one stool sample is collected or when examination does not occur within 1 h of collection.[8]

Blood loss is primarily due to leakage around the attachment site, as opposed to direct feeding by the adult worms.[1] Hookworms secrete nematode anticoagulant peptides (NAPs), inhibiting coagulation factors such as Xa, XIa, and VIIa/tissue factor complex.[9] The enhancement of the anticoagulant effect of these peptides might be responsible for the rare reports of potentially life-threatening hematochezia in patients taking systemic anticoagulants.[10–14] Hookworm infestation of the colon is an infrequent finding, first reported in India in 2006.[15] The occasional migration and maturation of larvae in ectopic locations (i.e., outside the small intestine) is not well understood. In our case, the severity of the gastrointestinal hemorrhage and the finding of adult hookworms in the colon is an extremely rare event (Table 1).

A recent meta-analysis showed that patients living with HIV had higher odds of becoming infected with *Strongyloides stercoralis* but a lower chance of developing hookworm infection.[25] Furthermore, studies have shown that STH impairs the T_H1 immune response, which is central in controlling viral replication; however, studies examining the effect of deworming on the natural history of HIV infection have been inconclusive.[26] Our patient had been virologically suppressed with a normal CD4 cell count for many years, making it unlikely for HIV to be responsible for the nature and severity of the hookworm infection.

An unusually severe acute infection due to a high larval load could not be excluded. The patient's skin findings were suggestive of dermal itch, a reliable and universal sign indicative of larval skin penetration that can persist for 1–4 weeks.[27] His skin lesion is atypical because the pruritic erythematous rash of human hookworm infection does not commonly have the linear or serpiginous erythematous track characteristically seen with cutaneous larva migrans caused by animal hookworms.[28,29]

The time course of his symptomatology mirrors the life cycle of the helminth, further supported by the degree of eosinophilia, which typically peaks at the onset of gastrointestinal symptoms continuing until egg patency—about 6–12 weeks after infection.[1,27] The respiratory complaints in hookworm infection correlate with the migration of the larvae through the respiratory tract (i.e., Löffler syndrome).[29] Nevertheless, experimental human hookworm infections have called into question the association between hookworm larval migration in the respiratory tract and Löffler syndrome.[27,30]

In conclusion, hookworm infection continues to be a major cause of morbidity and mortality, predominantly affecting neglected communities. Atypical presentations of hookworm infections should be considered in highly endemic areas. Although great advancements have been made in understanding the intricacies of the disease, its diagnosis, and treatment, eradicating hookworm infection is unlikely to be achieved without thoughtful and sustainable investments to improve the sanitary conditions of the affected communities.

Ethics approval was not required. Verbal and written informed consent was obtained from the patient for participation.

Written informed consent for publication was obtained from the patient.

Edgar A. Ramirez-García: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

Ricci A. Chafloque-Vasquez: Investigation; Writing – review & editing.

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Andrés F. Henao-Martínez: Investigation; Supervision; Writing – review & editing.

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The corresponding author had full access to data in the study and was ultimately responsible for submitting the manuscript for publication.

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BMC Health Services Research

RESEARCH

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"The problem is not detection, it is treatment": exploring why women needing pre-cervical cancer care are lost to follow-up at the hospital in Iquitos, Peru

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Abstract

Background The objective of this study was to explore the barriers to follow-up – as well as potential ways to reduce these – of women with cervical lesions suspicious for cancer who were ineligible for primary-level treatment and needed, but did not receive, hospital-level follow-up in Iquitos, Peru.

Methods In-depth, semi-structured interviews were conducted with 18 HPV-positive women requiring hospital-level follow-up but for whom there was no documentation of completion regarding their experienced barriers to follow-up and suggestions to reduce these barriers. After thematically analyzing these patient interviews, interview findings about these topics were presented to seven doctors and five nurse-midwives at both the hospital and primary care levels. Finally, 19 health authorities and professionals discussed all findings and identified action steps for systems-level changes at a group model building workshop.

Results Patient-identified barriers to hospital care were mainly: (1) a limited patient understanding of follow-up or treatment steps (both prior to and after the hospital visit), and (2) administrative challenges to obtaining appointments or follow-up care at the hospital. Patients identified the utility of a patient navigator for this process to reduce these barriers. The healthcare professionals concurred with the barriers identified by the patients and the suggestion of a patient navigator, but further elucidated suggestions for change, including (1) differentiating referral for those with suspicion for cancer to prioritize those patients when referred to the hospital, (2) increasing information flow between the different levels of care through an integrated patient registry, and (3) improving provider education regarding HPV and the standard of care. The group model building workshop served as a space to discuss findings and action items that could potentially make these changes possible to ultimately improve the continuum of care.

Conclusions Despite an overall increase in follow-up for HPV-positive women since the implementation of the new HPV-based screen-and-treat program, women suspicious for cervical cancer are still being lost to follow-up after

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being referred to the hospital. Systems-level improvements should focus on improving information about patient flow across the continuum of care for health providers and hospital staff (who make appointments), strengthening referral systems between primary and tertiary level providers through an integrated patient registry, improving health education on HPV and screening for patients, and establishing a patient navigation system.

Keywords Loss to follow-up, HPV, Cervical cancer, Hospital-level care

Background

Despite cervical cancer being the fourth most common cancer among women worldwide, prevention and control of this disease is feasible. Many high-income countries have substantially reduced cervical cancer mortality rates, attributing their success to human papillomavirus (HPV) vaccinations [1–3], high HPV screening rates [4], and timely treatment for those who need it [5]. However, levels of success vary, with many low- and middle-income countries (LMICs) facing challenges when trying to attain these same results [6–8].

In Peru, despite implementation of policies prioritizing cervical cancer prevention since 1998, and school-based HPV vaccination campaigns since 2006, cervical cancer remains the second leading cause of cancer-related deaths among women, with an estimated mortality rate of 13.8 per 100,000 [9, 10]. In Loreto, Peru's largest state that is located within the Peruvian Amazon river basin, the cervical cancer mortality rate is the highest in the country and is 2.6 times the global average [11].

In 2013, WHO published guidelines to support a new "screen-and-treat" approach for the early detection of cervical cancer [12], thus addressing system level challenges preventing women who had received a positive HPV result from obtaining follow-up care. The premise was to provide early treatment or intervention to those at risk (i.e., HPV positive), rather than monitoring for resolution of dysplasia or HPV positivity, which risks losing contact with them. Screen-and-treat models have been shown to be effective in reducing the incidence and/or mortality of cervical cancer [13].

An HPV-based screen-and-treat approach was successfully implemented in 2019 in primary health facilities that make up the largest health network in Iquitos, the capital of Loreto: the Micro Red Iquitos Sur (MRIS) [14]. The approach operationalized in Iquitos consisted of a visual assessment for treatment (VAT) for all women who tested positive for HPV, with thermal ablation with thermocoagulation for those eligible (no acetowhite lesions or lesions covering less than 75% of transformation zone), and referral to a specialist at the local hospital for those ineligible for thermal ablation (see Fig. 1). Although the documented loss to follow-up rate improved from 69.8 to 30% between 2019 and 2020 after the implementation of the HPV-based screen-and-treat model, mainly due to care completion at the primary level for most women, women are still being lost in the system after testing positive for HPV [15]. Unfortunately, barriers to completion of the HPV care cascade are common in other LMICs [16–18], and merit further exploration to ensure adequate management for those who are HPV positive [13].

Previous studies conducted by the Proyecto Precancer research team have examined barriers associated to loss to follow-up care, both prior to the screen-and-treat program (women with abnormal Pap smears who did not return for results or follow-up) and after the implementation of the HPV-based screen-and treat among women who tested positive for HPV but did not return for results and/or a VAT [15, 16]. The current study focuses on identifying barriers associated with loss to follow-up at a different level of care: among women who were HPV positive, received VAT, but who were ineligible for primary-level treatment with thermal ablation (e.g., due to suspicious lesions, inability to visualize transformation zone). The specific objectives of this study were to (1) explore barriers to hospital-level follow-up among HPV-positive women ineligible for thermal ablation, and (2) identify and discuss actionable solutions to reduce hospital-level loss to follow-up.

Methods

Setting

This study was carried out in Iquitos (estimated population of 400,000), the capital of Loreto, and the world's largest city accessible solely by air or water transport. Approximately 67% of Loreto's population is covered by the *Seguro Integral de Salud*, Peru's public health insurance program, which covers those living in poverty or extreme poverty. While most of the state is served by small primary health facilities, Loreto has only three public hospitals: in Iquitos, a local hospital with gynecology but no oncological services, a regional hospital with theoretical gynecology and oncological services (though the oncologist works mostly part-time, and there are no radiation services), and another hospital in the smaller city of Yurimaguas to the South, which is many away hours by boat.

The MRIS, the largest health network in Iquitos, serves roughly 127,000 people and is comprised of 17 primary level health facilities; the distance between these primary level facilities and the local hospital that receives referrals from within the MRIS varies from 4 to 56 km. The population served by the MRIS can mostly access the hospitals

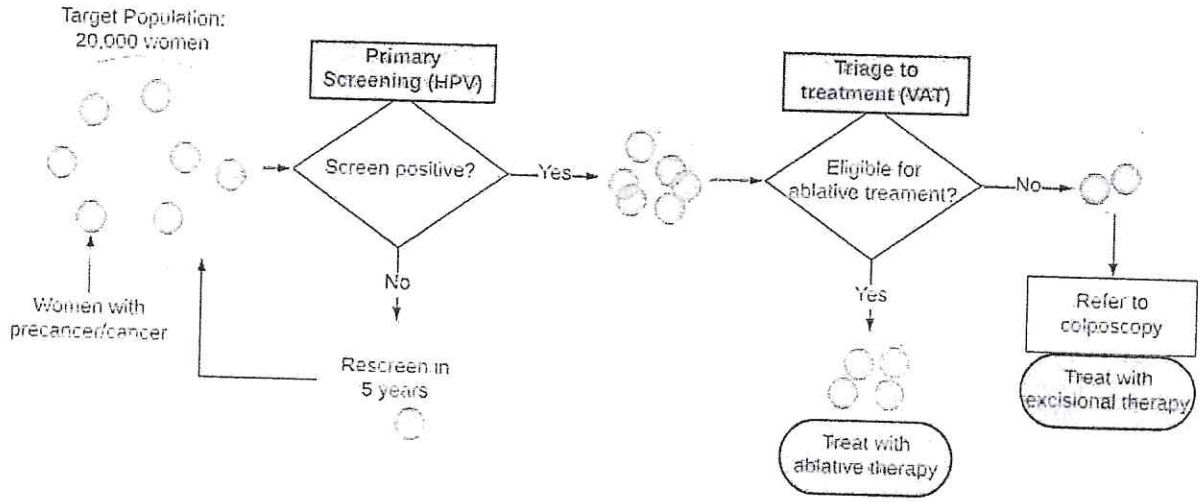

Fig. 1 Cervical cancer screen-and-treat model in MRIS, Iquitos

Table 1 Participant types/system roles and numbers

Role	Number
Phase 1: Patient Interviews	
HPV-Positive Women Lost to Follow-Up	18
Phase 2: Collaborator Interviews	
Primary-Level Physician	1
Primary-Level Midwife	2
Hospital-Level Physician	6
Hospital-Level Midwife	3
Phase 3: Group Model Building Workshop	
Primary-Level Midwife	4
Primary-Level Physician	5
Hospital-Level Midwife	1
Hospital-Level Specialist (2 Gynecologists, 2 Oncologists)	4
Administrative Assistant	1
Nurse	2
Regional Health Authority	2

via road travel (those living in urban and some peri-urban sites), and/or a combination of river and road travel (rural). As reported in previous papers [14–16], Proyecto Precáncer and local and national stakeholders launched a new HPV-based screen-and-treat cervical cancer program in 2019 within the MRIS. Approximately 20,000 women aged 30–49 within this network were eligible for this program. As a result of this new approach, there was a 3-fold increase in the number of women screened at the primary level in addition to a 37.2% increase in the number of HPV-positive women who completed the continuum of care [14].

Study design

This study was conducted in three phases. First, semi-structured interviews were conducted with 18 women who were referred to, but did not complete, hospital-level follow-up to explore the reasons why they did not receive follow-up care, as well as what they felt would have helped them obtain follow-up care. Second, we created a visual depiction of the system and its barriers from the women's perspective (see Supplemental Fig. 1) that was used as a discussion point for the semi-structured interviews with 12 health professionals working at different system levels to elicit other barriers and suggestions for change. Finally, all data was presented in a group model building workshop with key health and hospital authorities and health professionals from different levels of care with the shared goal of identifying and developing actionable system solutions to reduce these barriers (Table 1).

Patient interviews

Sampling and recruitment

Eligible interview participants were women with a positive HPV molecular test who received VAT but were deemed ineligible for thermal ablation at the primary care level, referred to a hospital for follow-up, and had no record of care completion within three months of referral. Specifically, they lacked records for one or more of the following: (1) attending a hospital appointment, (2) completing treatment after such an appointment, or (3) receiving confirmatory test results (e.g., biopsy). Women were excluded if they had evidence of treatment (e.g., at a private facility) or a negative confirmatory test.

Recruitment took place from August to September 2022. Using a registry-generated list of women without hospital follow-up, we verified care completion with nurse-midwives at primary health facilities and two hospitals based on the specified criteria. The research team then contacted or visited eligible women to invite them to participate. All 20 invited women agreed to be interviewed, but only 18 proved to be eligible, and so the data from the two ineligible women was not included

in the overall analysis (one had received follow-up not reflected in records and the other was no longer covered by the public health insurance program because she had acquired employer-based health insurance coverage).

Interview process

Interviews, conducted in Spanish during September and October 2022, took place at participants' homes, workplaces, or by phone when in-person meetings were not possible. Informed consent was obtained beforehand. Two experienced female Peruvian research assistants led semi-structured interviews, focusing on HPV screening and treatment (see Supplementary File 1). A cervical cancer screening process map guided discussions, emphasizing follow-up steps, test results, patient education, referrals, system facilitators and barriers, and recommendations for improvement (Fig. 1). All interviews were recorded, transcribed, and supported by field notes for context, though these notes were excluded from analysis.

Stakeholder interviews

Sampling and recruitment

Healthcare professionals were eligible for interviews if they were doctors (gynecologists, oncologists, primary care physicians) or nurse-midwives involved in cervical cancer prevention and control at two hospitals or two primary care facilities in Iquitos offering VAT and thermal ablation. The research team created a list to capture diverse roles across the screen-and-treat program stages. Twelve professionals (see Table 1) were recruited, and all agreed to participate. Recruitment ceased upon achieving thematic saturation across stakeholder levels regarding the cervical cancer care trajectory.

Interview process

After obtaining informed consent, interviews took place in Spanish in a private space at the participants' workplaces in February 2023. The interview guide was structured around a visual depiction of the system utilizing findings from patient interviews, with barriers occurring at six main timepoints of the continuum of care (see Supplementary File 2 and Supplementary File 3, respectively). The interviewer focused on the specific barriers that were relevant to their own roles and places of work, as well as their suggestions for addressing barriers and potential system-level changes. All interviews were recorded and transcribed. Field notes were reviewed but did not inform data analysis.

Coding and analysis

A mix of deductive and inductive codes were used to analyze all data using Dedoose. Deductive codes followed the chronological steps of the care continuum, while inductive codes were based on barriers, as well as the suggestions for change, that emerged at each step. The women's interviews were coded after completion of all 18 interviews and prior to the initiation of stakeholder interviews. Stakeholder interviews were coded after completion of all 12 collaborator interviews. For the stakeholder interviews, we created a similar codebook to the one used to analyze women's transcripts, but grouped stakeholders' suggested changes into individual-level and systems-level, further subdividing by the specific barrier the change was aimed to address. Two researchers read through and coded the transcripts, meeting after five interviews to ensure codebook was complete and to discuss coded transcripts to ensure consistency. Once researchers were coding consistently (more than 90%), one researcher coded the remainder of the interviews.

Group model building workshop

Recruitment

Key stakeholders – health authorities and professionals – in the cervical cancer prevention and control program within the MRIS were identified by members of the Proyecto Precancer team, along with the cancer coordinator of the regional Ministry of Health. The 19 invited parties included: doctors and nurse-midwives working in the gynecology and oncology departments at the two hospitals, the referring primary-care facilities, and from various rural primary-care facilities; and hospital administrators and regional health authorities. The workshop was held on February 23, 2023.

Workshop process

We started the workshop with short introductions since most individuals knew each other, followed by verbalizing our shared goal of developing the most efficient and patient-friendly cervical cancer screening and management system, and then presented interview findings to generate discussion among participants.

Following the presentation, stakeholders were divided into primary or hospital levels to address how to address barriers identified at that level. Each group was facilitated by two Proyecto Precancer team members to ensure a rich discussion that included multiple perspectives, before aiming to reach consensus on what could be done to improve the system, by whom, and how. Actionable steps were identified in each group and shared with the other group, and those present committed to making changes.

Results

Sample characteristics

Seventy women ineligible for thermal ablation were referred to the hospital, with an average age of 39.1 years (out of 58 whose ages were recorded). Referrals came from six of 17 primary care facilities, and the women

were from urban (20), peri-urban (5), and rural (26) MRIS regions (out of 51 cases with available information). We interviewed 18 women aged 30–49, with an average age of 38.8 (based on 13 recorded ages), including at least one from each of the six referring facilities. Most interviewees (15) were from urban neighborhoods in Iquitos, one from a peri-urban area outside Iquitos, and two from rural areas. Health professional details are presented in Table 1. Two main themes emerged from the interviews with patients and health care professionals: (1) limited understanding about HPV, a positive diagnosis, and the steps for follow-up (before and after reaching the hospital level), and (2) administrative challenges obtaining appointments or follow-up care at the hospital.

1 Limited understanding about HPV, a positive diagnosis, and the continuum of care

Women expressed uncertainty regarding what exactly it meant to be HPV positive and/or ineligible to receive care at the primary level; this was also reported by health professionals. The confusion and frustration women described also led to fear and distress: *"I thought I was going to die; I spent some days thinking I was going to die."*

> *I felt bad because they told me I have cancer, that I will die early... I was so upset that I stopped going to the health post, what can I do, if so much time has passed and they didn't call me [for follow-up], they wasted the whole month, they treat me like an animal, it's not right, but I got my treatment, I went to the regional hospital.*

The non-standardized trajectory of referrals also led to confusion, which perpetuated distress. Women who are HPV positive and require hospital level follow up are referred to either the gynecology unit at one of the hospitals or the oncology unit of the other; this can lead to confusion about the possibility they had cancer, or as one woman referred to oncology described:

> *In oncology, I always knew that's where people go with cancer, and I felt that I was sick, and I felt nervous and scared because one time I went there with a friend to get her mother's results who had cancer, and she told me that there [the oncology unit] is where people go with advanced cancer.*

This lack of knowledge persisted upon reaching the hospital, as many women described confusion regarding which department to visit and what to expect when finally seeing a provider. This confusion seemed to stem from a disconnect within the hospital system and the lack of clear policies at admissions about where to make the appointments: *"They said to me [at gynecology], 'How are they going to refer you to oncology if you don't have cancer? You should have come to us."*

Health professionals also recognized the communication challenges within and between the primary and tertiary levels of care. In addition to, and possibly related to, the communication challenges, health professionals identified high turnover rates of medical personnel and staff at all levels of the healthcare system as a barrier to successful engagement of women for treatment follow-up. Further, it was suggested that medical personnel at times do not have a holistic or current understanding of the new screen-to-treat program, and some are not aware that the current best clinical practices have shifted from Pap smears to molecular HPV testing that is either self-administered or performed by a healthcare professional:

> *In Loreto, doctors of any specialty that is not cancer do not know anything about cancer. They only know what cancer is, nothing more. Given that, if doctors that do not have anything to do with oncology don't know anything about cancer, imagine the knowledge level for the general population. So we have a lot of work to do in terms of training, education, re-structuring the levels of care to be able to grow and better manage this pathology.*

Women's limited understanding of next steps in their care persisted after hospital visits and diagnostic tests like colposcopy or biopsy. Some expected a call about their results but never received one, leading to fear and concern for themselves and their families. Others faced challenges accessing results or follow-up care. Over time, many women developed feelings of indignation and hopelessness. One participant expressed surprise at being contacted during the interview, as it was the first time anyone had reached out to her since undergoing additional testing following her initial positive HPV test at a health center.

Confusion was exacerbated by another issue that emerged in some interviews: dual practice (i.e., practicing medicine in both public and private systems). Specifically, women mentioned that a hospital level nurse-midwife would require them to see her at her private practice for a Pap smear or other diagnostic before she would schedule an appointment with the hospital doctor; some women stopped trying to see the hospital doctor at that point. In a few instances, women resorted to natural medicines or other "vitamins or medications" that some nurse-midwives promoted as helpful for their condition.

Overall, women expressed that they felt that the formal health system had abandoned them.

> *I went to the health post because I had to go there to make my appointment [for treatment] for the end*

of July, but when I arrived, the midwife told me that they couldn't do it because the machine was broken, but that they would let me know. So I told her, "I will come back at the end of September." She told me "Okay," but they still haven't called me, they haven't even given me my results, because the midwife told me they were going to bring some new equipment, I don't know what.

All 12 healthcare professionals recognized patients' struggles in coordinating their own care, attributing this to poor coordination between hospital units and the lack of a patient registry system.

2 Administrative challenges: multiple trips to the hospital for appointments and follow-up

While most women were eventually able to figure out how to make an appointment at the hospital through the guidance of nurse-midwives at the primary level, this process proved to be a challenge. They attributed this to a lack of familiarity with the in-person appointment-making process, miscommunication from providers about where to go or who to ask for, and the lack of support and guidance in making these appointments (i.e., in one hospital, they get seen in gynecology, in the other at oncology). Not a single participant interviewed was able to receive care upon arrival at the hospital on her first visit, and over half had to make at least three trips to the hospital before receiving care; the main reasons given for the multiple trips to the hospital were the doctor's unavailability despite having a scheduled appointment (e.g., last-minute conflict for the doctor), overbooking of appointments, the referral form expiring after two months, requiring patients get a new referral form from their primary level facility and start the process over, or the doctor or other health professionals being on strike:

The fourth time I came back, I got the appointment. [The first time] they told me that even though the doctor was there, he had to operate [and was unavailable]. They told me to come the next day. Then the next day, [I went, but] the doctor said he wasn't coming, he's coming tomorrow. And the next day, I went and they were going to see me, but the appointment that I had supposedly made was not made, so he wasn't there. The doctor was on vacation.

Women reported that repeated hospital visits led to a loss of time and money that they did not have; they felt they needed to prioritize caring for their families. Some expressed frustration with the inefficiency of the system, which delayed care and allowed their disease to progress. Many health professionals sympathized with the difficulty and time-consuming nature of making appointments, receiving care, and navigating the healthcare system:

Unfortunately, I think that we have a failed system, an inefficient system that does not work, that is not responding to demand, and unfortunately this is not just at the hospital level, but starting at the primary level. Before, you could go to a health post or a health center, get in line, and you would be seen that same day. Now, you have to go to a health center as if it were a hospital and they tell you "we have appointments in two weeks," so the supply is very little. But the issue is not just supply, but also the health centers' logistical capacity is very poor. So, if we do not improve that capacity, if we do not expand supply, the system will continue to collapse.

3 Suggestions for reducing barriers

At the end of all 18 patient interviews, interviewers provided education on HPV, cervical cancer, and the continuum of care in Iquitos. For women needing follow-up appointments, interviewers coordinated the appointments and provided guidance on logistics. All participants expressed that such assistance would be highly beneficial throughout their care journey. One participant stated:

It would be easier to have a designated member of the health facility, and someone there that would know if and when the patient had to come to each facility. It would also be helpful if there was someone, maybe a health professional, who we could call and follow up with. This would be helpful because then the patient would not have to do all that.

Health professionals also suggested the benefit of a patient navigator, including one that could be available by phone. Many also recommended that a friend or relative accompany the patient at appointments, with the idea that an extra set of ears would help capture results and the next steps of care.

It would help if the health center had a phone number that patients could call to know if they have to go back to the heath center, or if there was a health professional that they could call for follow-up. That way the patient would not have to do all of this, to travel to the hospital, wait up to six months and still not have their test result. Because what are you supposed to say to the patient? Once you get your biopsy, come back in six months? I can't say that. That's not a viable option. There should be a better solution. There should be a phone number to call,

that's my recommendation, so that after the doctor sees you, if there is follow-up pending or you have to make another appointment, you call that number, and they tell you if they will be able to see you.

Health professionals proposed three other changes that would they felt would reduce patients' barriers to getting follow-up care. They acknowledged the lack of an integrated patient registry as a barrier, and noted that such a registry would improve information flow between the different levels of care. They also recognized that for various reasons, including staff turnover and lack of proper communication channels, some hospital staff may make appointments for patients in the wrong service, simply because they do not know better. Finally, there was agreement that one could not expect women to know much about HPV and its continuum of care when health professionals and hospital staff were also lacking education on this, and suggested provider education on this topic and on the new screen-and-treat model.

Group model building: actionable items for change

The identified barriers and suggestions for change were presented at the group model building workshop with health professionals held in February 2023. Stakeholders then divided into two groups based on their expertise for further discussion of these topics. Discussion themes and key action steps from the workshop are presented in this section.

1 Prioritization of patients with a high risk of cancer

The health professionals all agreed that HPV-positive women who are ineligible for primary-level treatment due to suspicion for cancer need to be prioritized when referred to the hospital. Suggestions included updating the referral form for these patients, to include an "urgent box" that can be checked, or asking the provider making the referral to call one nurse-midwife directly to ensure that patient was prioritized at the time of making an appointment. This latter suggestion was shared among all present to ensure a do-able action that could be carried out immediately since all key stakeholders were at the workshop.

As this topic was explored, hospital professionals discussed the speed at which they could intervene with a patient with suspected cancer. Initially, the oncologist mentioned being able to operate on urgent cases within days. Further clarification led to the reflection that, prior to any surgical intervention, the patient needed to be cleared by cardiology and obtain some blood tests, and that sometimes there are delays involved with these additional steps. For example, there may be no appointments in cardiology at the end of a month, requiring the patient to return at the start of a month for available appointments which might be weeks away. The head of oncology recognized this was an unnecessary and dangerous delay, and committed to speaking to the head of cardiology to find ways to speed up pre-surgical appointments.

2 Increasing communication between levels of care, including via a patient registry

Many collaborators expressed the importance of a direct provider-to provider referral process to ensure that each of the levels of care has some awareness of the referral. They described how this would be more effective than sending the patient with a slip of paper to a provider without notifying that provider. WhatsApp groups were also highlighted as an effective way for nurse-midwives to communicate between the different levels of care.

Stakeholders from all levels of care discussed the lack of an integrated patient registry, making patient management nearly impossible. They suggested that the registry should include information such as the types of tests performed, the results, follow-up appointments attended, and treatment recommended and received, among others. The patient registry discussion led to the discussion of a patient navigator, since this would help guide patients as well. The cancer coordinator present explained Peru's REF-CON (*referencia y contrareferencia*) system, which was designed to assist providers in patient follow-up. Specifically, the REF-CON system is meant to be used by primary level providers to send patients to tertiary level care ("REF" for reference), and then by tertiary level providers to inform the primary level what was done and the needed follow up ("CON" or counter-reference). This small group decided it would be more efficient to evaluate the REF-CON system's effectiveness for the cervical cancer prevention and control system than to try to create a new system. One doctor recommended adding a feature that would create an alert or notification for the nurse-midwife when a patient did not initiate or continue treatment, so that the nurse-midwife could contact the patient to reschedule her appointment. Despite a commitment to testing this system that is already familiar to most, the cancer coordinator left their position within weeks, and this effort did not proceed.

3 The utility of patient navigation

Multiple models for patient navigation were discussed based on systems that the healthcare professionals had seen in other departments or facilities. The models included using volunteers and health workers as navigators who could provide education, advice, and logistical plans for patients in terms of next steps of care. For example, when the Proyecto Precancer interviewer found patients who had been lost to follow-up to explore their barriers, she provided information and assisted women

in making appointments. Both the women and health professionals commented on the value of such a person in the system, while recognizing the difficulty to fund such a role. Another option discussed was the possibility of having a health professional running a telephone line to track and follow up with patients and be available to them for orientation or education.

This discussion sparked a conversation among stakeholders about a person who had once assisted indigenous people from remote areas of the rainforest to navigate the hospital system when needed. They thought this patient navigator worked for a non-governmental organization (no one was sure who paid for his role) and would become involved when there was a referral from an indigenous community where individuals are less connected to the health system and may not speak Spanish. Discussion of this person triggered enthusiasm that the hospital – at some point in the past – had such a patient navigator, and that it could be possible to create such a role. The two hospital administrators committed to learning more from their colleagues to find out who paid for the patient navigator and to explore the feasibility of onboarding patient navigators.

4 Improving provider knowledge regarding HPV and continuum of care

Finally, during the workshop, stakeholders recognized that providers needed to improve their own knowledge regarding HPV screening and treatment and the need for a uniform continuum of care that providers and health administrators recognize. Two recommendations were made in this regard: (1) developing curricula (including on the continuum of care) on HPV-related training for OBGYN residents, medical students, and nurse-midwife students, and (2) enforcing a uniform continuum of care and appropriate triage system for managing patients at the hospital level. On this second issue, some professionals recognize that some colleagues engage in dual practice, and feel they are unable to address it directly without consequences for themselves. They also recognize that constant turnover in their administration requires a better orientation system that ensures that those scheduling appointments and handling patient care are aware of the expected procedures for the continuum of care in their facility.

Discussion

Many of the barriers identified in the health system in Iquitos are not uncommon. LMICs like Rwanda, Kenya, and Ethiopia all struggle with high loss to follow-up for women with HPV or cervical cancer due to similar factors such as long travel distances, lack of patient registry systems, inadequate patient navigation, poor understanding of HPV, transportation costs, household obligations, fear of treatment, and delays in medical services [17–19]. Each country has specific barriers, including decentralized healthcare in Rwanda, cultural and logistical challenges in Kenya, and delays and costs in Ethiopia [17–19]. However, following the implementation of a new HPV-based screen-and-treat model in this unique setting in Latin America, where stakeholder engagement in the decisions and steps was high and "fresh," our data suggested that loss to follow-up at the hospital-level among HPV-positive women remained high. Given the consequences of loss to follow-up for these high-risk patients, it was important to explore and discuss this loss for future tailored responses.

Our findings have policy, programmatic, and research implications. First, developing and implementing training programs for providers would address the women's lack of a clear understanding of their disease and the healthcare system, by first training the providers involved in teaching them. These trainings must not only focus on content, but also teach providers how to convey information in a way that matches their patient's health literacy level. This could include visual tools, such as a flowchart with instructions of the patient's next stage of care or provision of written material. Health literacy trainings for physicians has improved health outcomes for patients in several different countries, from the United States [20] to Iran [21]. Health literacy training programs that are tailored to the health care system at hand and that keep in mind the socioeconomic and cultural contexts of the patients are also recommended by the CDC to improve health outcomes [22].

Second, a telephone-based patient navigation system could support women in scheduling appointments, accessing their results, and navigating the healthcare system as a whole [23, 24]. To compensate providers for "giving out results" (a specific code in the system), the current system requires that women take the primary level referral to the hospital in person to make an appointment, then go to an appointment, then return to the hospital to pick up a paper copy of their results to make a follow up appointment, and so on. The burden is on the woman. A new remote health service provided via computers, phones, and other digitized systems, called Telesalud, has been gaining momentum in some of the larger health centers [25], and some alternate phone and message-based systems were used during the COVID-19 pandemic. Could it be possible to create a new system code for providing results over the phone while still allowing the health facility to be compensated for this activity?

Third, in Iquitos, new technology has rapidly entered people's daily lives, where many have access to both phones and the internet, at least in and close to the city. People commonly use platforms like Facebook,

Instagram, or WhatsApp to communicate and get their information. These platforms could be an invaluable tool to support HPV-positive patients in navigating the health system in Peru by providing an accessible way to get information while using the technology they already have at their fingertips [26]. On the other hand, the digital divide could lead to even less support for the most vulnerable who do not have consistent access to phones and/or internet connections, or who are not computer literate. To ensure that further inequities do not arise, these mobile-based solutions should supplement, not replace, the current system that requires patients to pick up their results in person. Further research is needed to explore and pilot patient navigation models for this population.

The final implication concerns the high turnover rates of medical personnel and staff, resulting in them not having a holistic understanding of the new screen-and-treat system (and likely other clinical practices or procedures). Health professional societies, such as the Colegio Medico del Peru, must develop systems for updating their personnel on current information on HPV and its treatment, whether through development or approval of new courses or classes on topics like HPV and its treatment to their members. Furthermore, having virtual onboarding and training systems for new health staff (which supposedly exist, but are not actually put into practice) could be beneficial for efficiently dealing with the high turnover rates. Availability of such material online would reduce the time and effort to train individuals regularly. This would also ensure that healthcare professionals have access to updated information, as currently most providers travel to Lima for training purposes.

Limitations

This study was conducted in the MRIS network, selected due to its centralized location and its comparatively efficient documentation system. The barriers and suggestions for change may not be applicable to other regions of Peru or Loreto due to differing structural and geographic barriers. For example, most women living in the MRIS – which is in or near Iquitos – speak Spanish, whereas women from more remote regions likely face additional linguistic and cultural barriers, particularly if indigenous. Additionally, we conducted a limited number of interviews (aiming for saturation), but over-represented the more urban areas of the MRIS because our research team was only able to locate three of the approximately 20 eligible women who lived in rural areas. The women we did interview were themselves difficult to find (approximately 1.5–3 h to find each woman) because many had moved and/or had changed their telephone numbers. When a woman did not answer the phone, our research team went to her last recorded address. If that woman no longer lived at that address, our research team asked neighbors for updated contact information to locate her. While we did not find all of these women, we were able to locate many, but ultimately, our findings reveal the significant barriers causing loss to follow-up while living within hours of the hospitals, and this would only be worse for women living further away. The time required to find each woman also depicted another reality for this system: it would be difficult to task a health worker to follow up with missing patients under these circumstances in this setting. Another limitation was incomplete data. Our registry uses primary data forms and when information is missing, it is updated via a physical search through clinical records, but the system is not perfect. Although interviews with healthcare professionals were conducted in the workplace and could result in some feeling careful about what they reported, these interviews were conducted in private offices and our research team had been working closely with the professionals over several years, so we believe this established trust led to honest answers. Finally, many of the women interviewed discussed the barriers they faced when getting care at the hospital in the context of COVID- 19. While COVID- 19 was unprecedented and may have caused further fragmentation of care, we were unable to determine which, if any, barriers were heightened by COVID- 19. Despite these limitations, major patterns emerged in our interviews and workshop regarding barriers to accessing tertiary level care and future suggestions for change.

Conclusion

Despite an increase in follow-up for HPV-positive women overall since implementation of the new HPV-based screen-and-treat approach in Loreto, women who are at a higher risk of developing cervical cancer are still being lost after their referral to the hospital level for care. Factors associated with the loss to follow-up included the lack of understanding of next steps of care and about HPV, as well as the challenging processes to make appointment and obtain follow-up care at the hospital. System improvements should focus on developing an integrated registry that can be accessed by primary and tertiary level providers, testing and implementing a patient navigation system for women, and improving dissemination of health education and administrative processes via internal hospital processes, as well as health programs, professional societies, and virtual programs.

Abbreviations

LMICs	Low- and middle-income countries
HPV	Human papillomavirus
MRIS	Micro Red Iquitos Sur
REF-CON	Referencia y contrareferencia
VAT	Visual assessment for treatment

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Authors' contributions

A.C.B., V.P.S., and G.M.S. conceived and designed this study. V.P.S., C.H., E.J.R.L., R.M., J.B., R.P.R., L.D.C., K.G.D., L.W., R.L.L., and J.V.V. contributed to the data collection and curation. A.C.B., R.T., L.N., and V.P.S. contributed to data analysis, drafted the manuscript, and made substantial edits. L.N., V.P.S., G.M.S., and J.K.T. edited the final version. All authors read and approved the final manuscript.

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Data availability

The dataset supporting the conclusions of this article is available upon reasonable request and with the participants' permission, pursuant to the terms of the IRB approval.

Declarations

Ethics approval and consent to participate

Our study adhered to the Declaration of Helsinki. Ethics approval for this study was obtained from the institutional review boards at: Asociación Benéfica PRISMA (CE0251.09), Tulane University School of Public Health and Tropical Medicine (reference number 891039), the University of Maryland School of Medicine (IRB#061614), Hospital Regional Loreto (ID- 002-CIEI- 2017), and Hospital Apoyo Iquitos (065-ID-ETHICS COMMITTEE HICGG- 2018). As approved by these IRB committees, all participants provided verbal and written informed consent to participate.

Consent for publication

Not applicable.

Competing interests

V.P.S., on behalf of the Proyecto Precancer, received discounted prices and/or donated supplies from Copan and Cepheid. The authors declare that they have no other competing interests.

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Publisher's Note

CASE REPORT

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 insights 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 verrucous 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

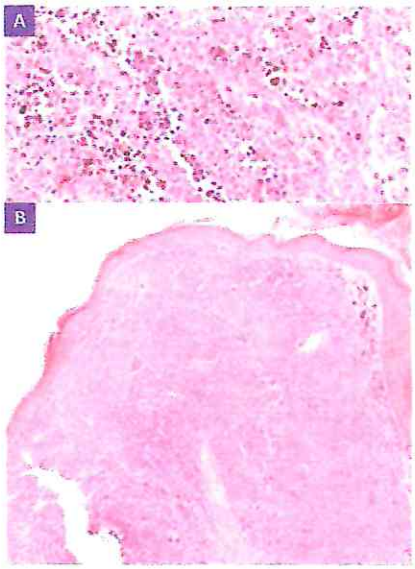

Figure 4. A. HHigh resolution image showing polymorphic tumor cells, increased mitotic activity, perinuclear halo and intracytoplasmic brown pigment (40X, H&E). **B.** High resolution image depicting nodular collection of melanocytes (20X, H&E).

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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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.

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 derivates, 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 follows: 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

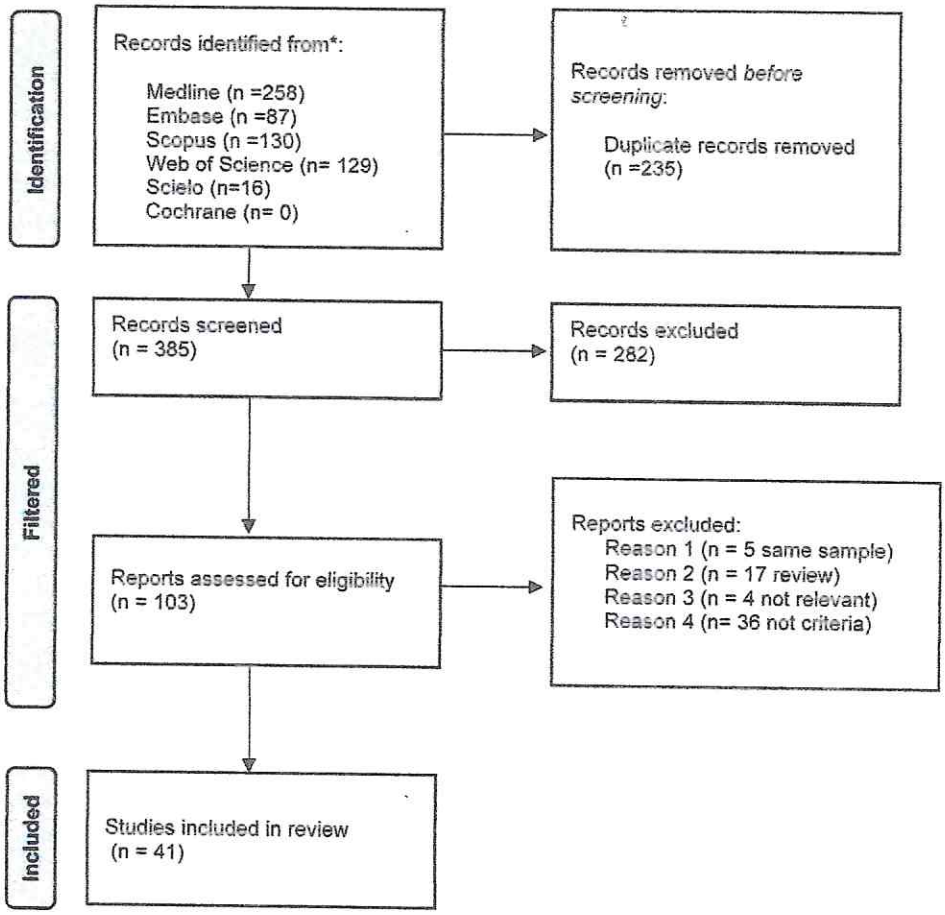

Figure 1. Flow diagram PRISMA 2020 for study selection.
[a]Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, 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 heterogenicity (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 heterogenicity (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	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	-
Lourerio et al., 1995	Brazil	Pregnant women	1000	-	14-40	EIA	16	WB	5	0	0
Brouiet 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
Juscamaita 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	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 Su	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

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Table 1 (*continued*)

Author, year	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 Atacama (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

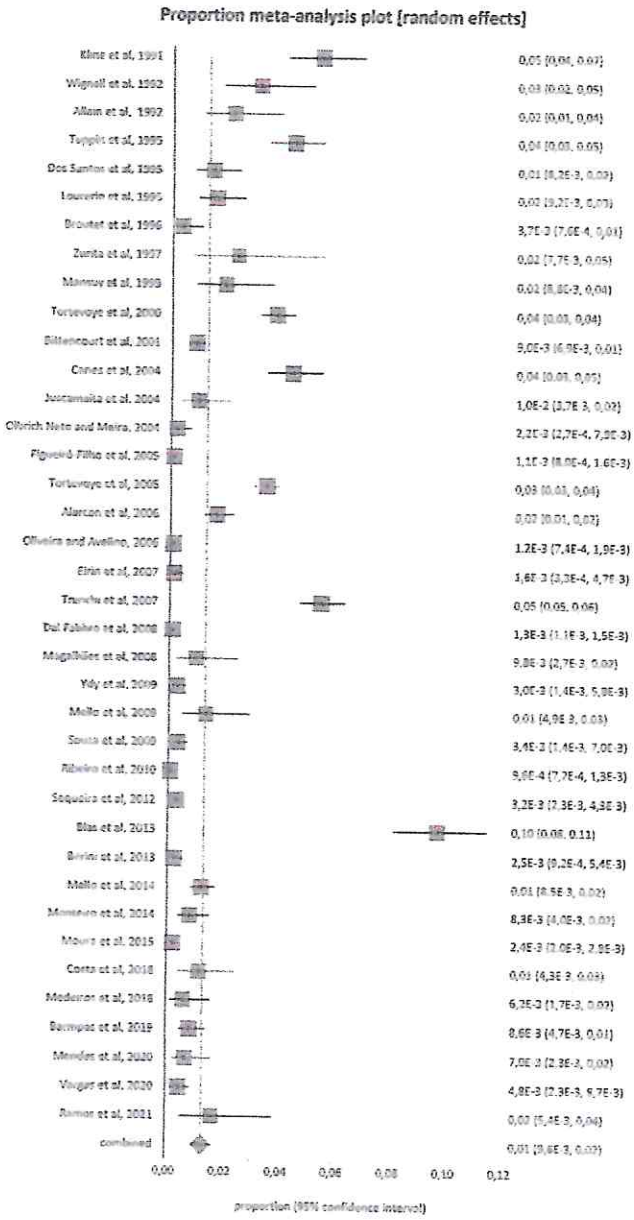

Figure 2. Pooled prevalence of HTLV-1/2 positivity in the screening test. HTLV, Human T-lymphotropic viruses.

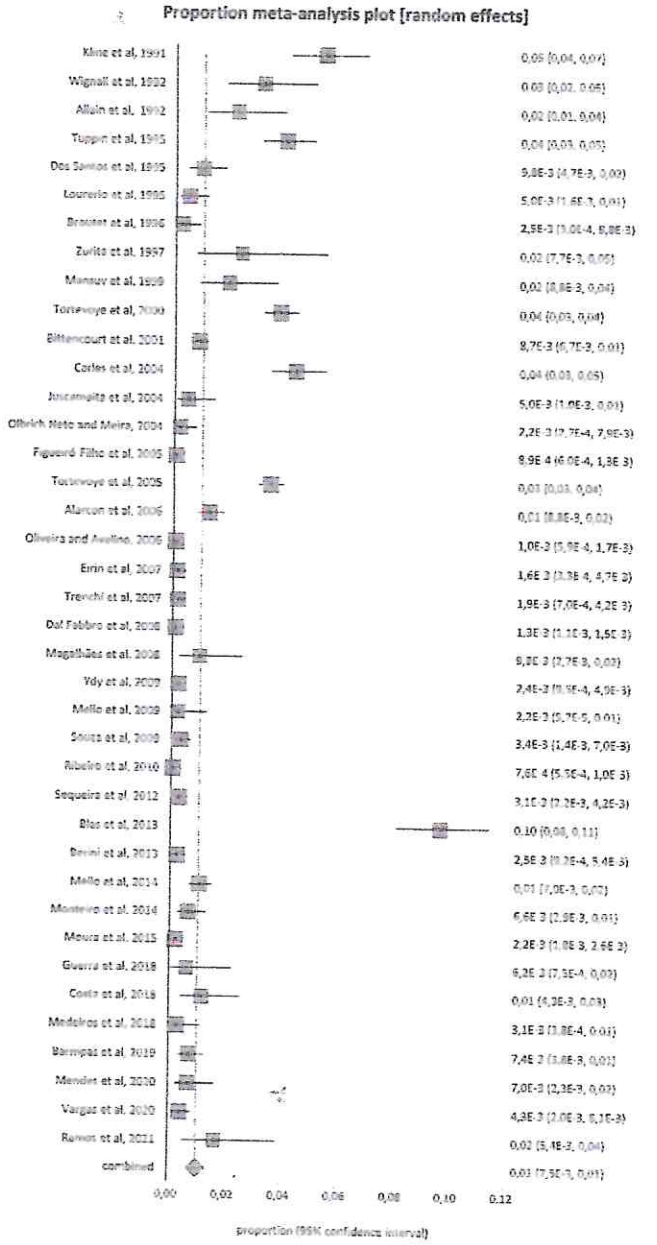

Figure 3. Pooled prevalence of positive confirmatory results for HTLV-1. HTLV, Human T-lymphotropic viruses.

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 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-

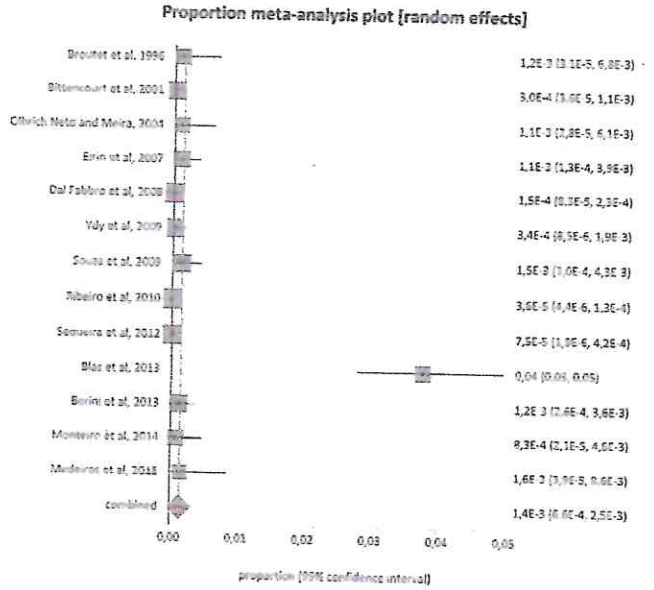

Figure 4. Pooled prevalence of positive confirmatory results for HTLV-2. HTLV, Human T-lymphotropic viruses.

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 SCA&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-Rodriguez, J.C. Celis-Salinas, C. de-Mendoza and M. Casapia-Morales.

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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, accidently 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 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 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 lonomism 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 lonomism 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

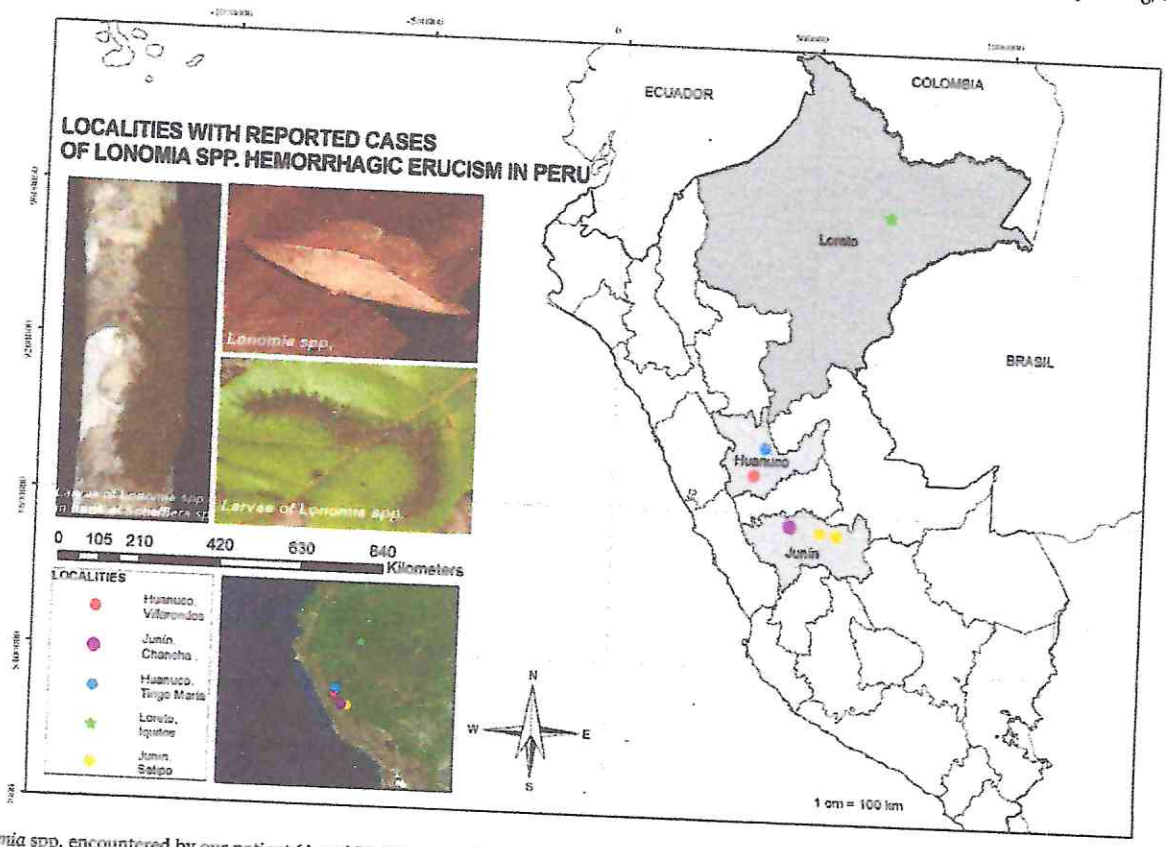

Fig. 1. *Lonomia* spp. encountered by our patient (A and B). The gregarious nature (A) may lead to contact with large number of caterpillars exposing individuals to a considerable amount of venom. Adult Lonomia moth (C). The maps illustrate the location of the cases of lononism reported in Peru.

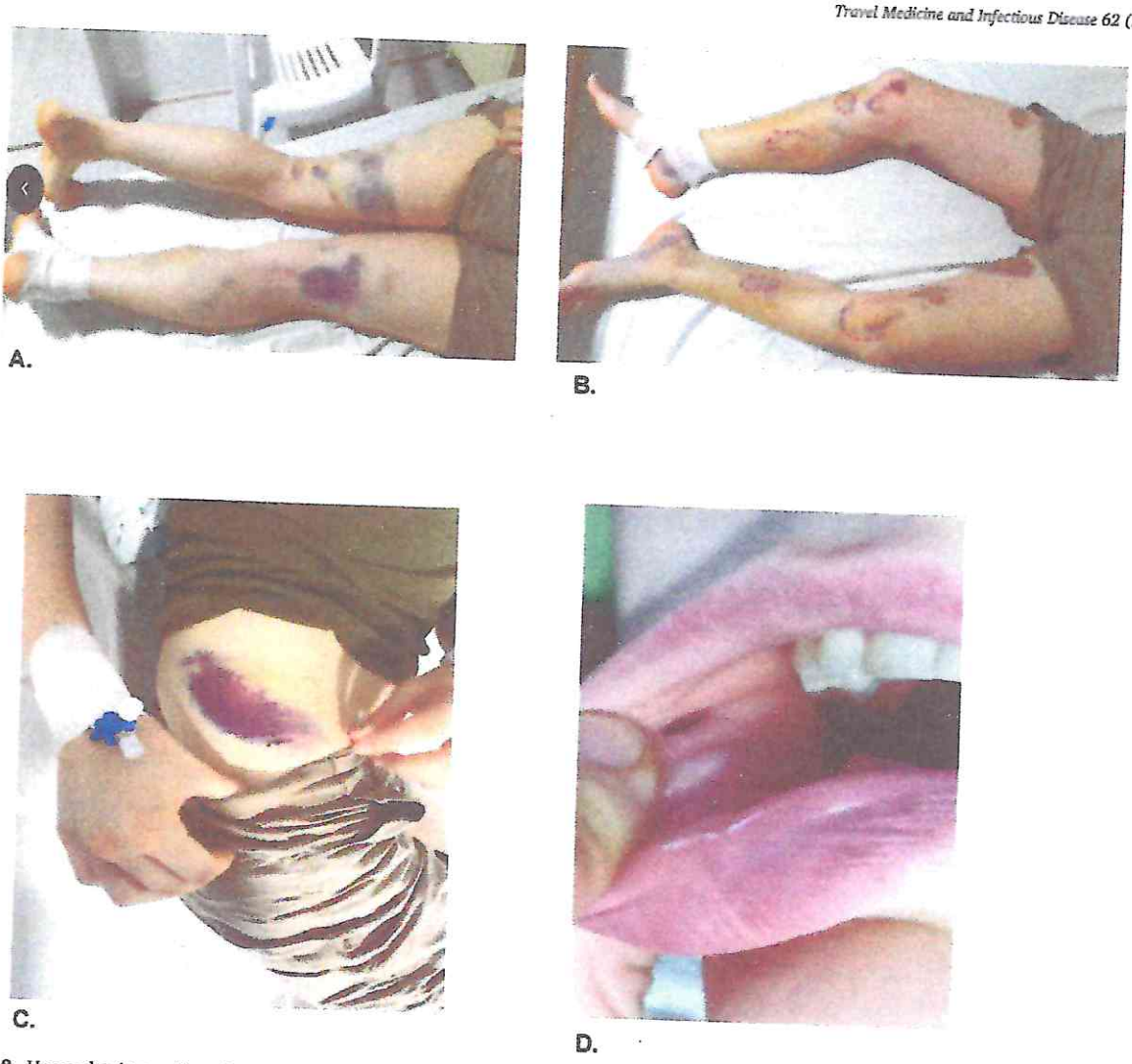

Fig. 2. Hemorrhagic manifestations present at admission involving both of her legs (A and B), right iliac crest (C), and the oral mucosa (D).

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 antivenin 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-us/contact.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 antivenin. 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 [ ]	Satipo, Junín	Female	32	**Presentation:** generalizing pain, nausea, vomiting ecchymosis, gingivorrhagia **Treatment:** supportive. No antivenom used **Outcome:** full recovery
2007 [ ]	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 [ ]	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 [ ]	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 [ ]	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 [ ]	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 Higuita:** 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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ORIGINAL BREVE

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 trasmisión 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/m²)	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

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)

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.

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 [15], 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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