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The Effects Of Rurality And Cost Of Transportation On Time Of Evolution And Disease Complexity At Diagnosis For Cutaneous Leishmaniasis In Colombia

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The Effects of Rurality and Cost of Transportation on Time of Evolution and Disease Complexity at Diagnosis for Cutaneous Leishmaniasis in Colombia

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Abstract

Patients in Colombia affected by cutaneous leishmaniasis (CL) face significant geopolitical and socioeconomic barriers to accessing diagnosis and treatment. This study aimed to understand how the geosocial characteristics of a patient's area of residence affect time to medical consultation and disease status at consultation. An observational cross-sectional study was performed of individuals with CL who consulted at a local clinical referral center (CIDEIM) in Cali and Tumaco, Colombia. Descriptive, bivariate, and multivariable simple and ordinal logistic regression analyses were done to examine how area of residence (urban or rural) and cost of transportation to the nearest urban center may influence complexity and time of evolution of the disease at first medical visit. Two separate disease complexity classifications – *cplexA* and *cplexB* - were created based on factors such as mucosal involvement, lymphatic dissemination, and varying number and size of lesions; a composite score of both definitions was also constructed. CL Patients who had to pay greater than $60,000 COP for transportation were more likely to have a complex disease state at consultation based on the *cplexA* criteria (aOR = 2.11 [95% CI: 1.11 – 4.02]) and had higher odds of presenting with more complex disease (ordinal logistic regression; aOR = 1.78 [95% CI: 1.09 – 2.92]). A protective association between rurality and the time of evolution for the first lesion was also seen, showing that patients who lived in rural regions were less likely to have longer wait times before consulting at CIDEIM when compared to those who lived in urban centers (aOR = 0.66 [95% CI: 0.45 – 0.97]). High cost of transportation to nearby urban centers remains a significant barrier to equitable access of medical services for CL patients living in rural Colombia. Additionally, patients with CL in living non-endemic areas suffer extended time of evolution of the disease before consulting at a local referral center, signifying a need for heighted clinical suspicion and services in urban areas.

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Introduction

Leishmaniasis is a neglected parasitic disease with a worldwide distribution, mainly affecting the impoverished and most marginalized. The global incidence for cutaneous leishmaniasis (CL) is estimated at 0.7 to 1.2 million new cases per year (1). CL is endemic in 98 countries worldwide, of which Colombia is in the top ten countries with the highest incidence. It is estimated that more than 11 million people are at risk for CL in Colombia, with the highest number of cases (52% of total cases in 2017) centered in five departments: Antioquia, Santander, Nariño, Tolima and Norte de Santander (2). Despite the fact that 77.7% of cutaneous leishmaniasis cases were reported in rural areas, the majority of the studies analyzing risk factors focus on biological and clinical correlates, often ignoring socioeconomic factors that promote a high disease burden in these areas.

CL patients in rural Colombia face significant geographical, political and economic barriers to securing high-quality diagnosis and treatment, often due to high income inequality and the threat of violence from armed conflict (1,3,4). Access to care is a prevailing health issue in terms of rural health, especially in developing countries (5,6). Previous research recognizes distance and available transportation as barriers to accessing high-quality health services but other studies have provided contradictory findings on how distance from healthcare access affects disease prevention and treatment (5–8). Increased distance from health centers has shown to be associated with increased delay from onset of symptom to diagnosis (9–11). Diagnostic delay has also been shown to be associated with increased complexity of infectious disease pathogenesis, providing a potential mechanism through which increased distance from a health center can act as a barrier to health (12–15). These findings, however, while spanning both rural and urban

regions, focus mostly on healthcare utilization in a general disease context, making the results difficult to extrapolate to CL in Colombia, for which there is a clear dearth of research into the social drivers of the disease.

Few studies have looked at how rurality and transportation affect patterns of healthcare access for these patients in Colombia, or even in Latin America more broadly (16–19). A mixed-methods study on CL and gender in the country found that, due to the low fatality of the disease, individuals living in remote, rural regions feel unmotivated to seek medical care unless the disease rapidly progresses (11). Individuals with CL living in remote regions also seem to first try home herbal remedies or antibiotic creams acquired from a local pharmacy before even considering consulting at a clinic (3,11). One major shortcoming of the literature, however, is that previous studies focus solely on time of evolution of this disease in either rural or urban communities independently but have not sought to evaluate how an individual's area of residence is associated with time of evolution or complexity of disease at consultation. Additionally, previous studies have used rurality solely as binary – rural or non-rural – but have yet to further explore if their findings are consistent regardless of how far an individual in a rural area lives from an urban center.

The current study evaluates how the area of residence – urban or rural - and cost of transportation, a proxy for distance, from the patient's community to the nearest urban center may act as a barrier to health, potentially influencing time from onset of symptoms to consultation at a local referral diagnostic center and complexity of disease, with the hope of

elucidating the social factors that limit the access to diagnosis and treatment of CL in southwest Colombia.

Methods:

Study Design and Area

This cross-sectional study was conducted by drawing from a database of clinical records of patients diagnosed with CL between January 2012 and April of 2018 at the clinical referral centers of the Centro Internacional de Entrenamiento e Investigaciones Médicas (CIDEIM) in Tumaco and Cali (20).

Study Sample

Patients who met the following eligibility criteria were included: male and female individuals of any age with a confirmed diagnosis of cutaneous leishmaniasis and a date of initial consultation during the study period. Patients with an incomplete clinical history particularly regarding confirmed *Leishmania* diagnosis or lesion characteristics were excluded.

Outcome Variables:

Complexity of Disease at Diagnosis

We are interested in cost of transportation and rurality as potential barriers that may lead to diagnostic delay and more complex disease presentation at consultation. To capture disease complexity, we created two variables based on factors such as mucosal involvement, lymphatic dissemination, and varying number and size of lesions. For the *cplexA*, the following criteria had

to be satisfied to classify the case as mild: no greater than one lesion, no lesion greater than three centimeters in diameter, no evidence of lymphatic dissemination, and no evidence of muco-cutaneous lesions. For *cplexB*, we classified an individual's disease as mild if it met the following criteria: no greater than four cutaneous lesions, no lesion greater than 5 cm in diameter, no evidence of lymphatic dissemination, and no evidence of muco-cutaneous lesions. If the above-mentioned criteria were not met, the individual was classified as having more complex disease. These two variables are loosely informed by, but not adherent to, the treatment guidelines issued by the World Health Organization (WHO) and the Pan-American Health Organization (PAHO), by including those criteria related to disease complexity and excluding those that were related to viability and safety of local treatment. Both the presence of mucocutaneous lesions and evidence of lymphatic dissemination were added as they are characteristic of more complex CL in the Americas (23). Given that the criteria for *cplexB* presents a more conservative definition of complexity in which an individual cannot be classified as more complex without first also being designated as more complex under the *cplexA* criteria, we also created a three-level complexity variable as follows: mild, more complex only under *cplexA*, more complex by both *cplexA* and *cplexB* criteria.

Time of Evolution

An extended time of evolution has been demonstrated to have a positive correlation with a more complex pathology of visceral and cutaneous leishmaniasis globally (24). Time of evolution was defined as the time from patient-reported symptom onset until consultation at CIDEM. Given that the times of evolution are concentrated on the lower time scale (more than 50% report less a

time of evolution less than 2 months) and that our primary objective was to understand barriers to health access and not evaluate the natural history of the disease, time was operationalized into a four-level variable: less than 1 month, between one and up to two months, between two and three months, and greater than three months since the onset of symptoms.

Primary Independent Variables:

Area of Residence:

The area of residence of each patient was categorized as either urban or rural based on self-report.

Distance and Cost:

Given that a significant portion of the patient population resides in rural areas and that the geographical information regarding the *veredas* (a territorial subdivision focused primarily in rural areas) in Colombia is limited, estimates of distance through GIS information or straight-line Euclidean distances are unavailable. In their place, we used the estimated cost of transportation from every *vereda* to the urban center where each patient received their initial diagnosis of CL under the assumption that higher costs of transport are associated with a greater distance or travel time. Additionally, given that variety of transportation methods, including water- and land-based transport, used to get from rural to urban areas, cost of transportation may more accurately capture the true financial burden of seeking timely care as compared to a straight-line estimation. For patients' cost of transportation, we used values recently calculated by Berger et al (25), which were based on local health care providers' knowledge of transportation options and costs. Given the monetary denominations of Colombia, the cost of

transportation was then operationalized into a three-level variable: less than 20,000 COP, between 20,000 and 60,000 COP, and greater than 60,000 COP.

Sociodemographic and Clinical Factors

Given that the immune response is dependent on or can be influenced by various sociodemographic and clinical factors (11,26), age, sex, race, insurance type, occupation, history of previous cutaneous lesions, presence of comorbidities, and parasite species were analyzed as covariates.

Statistical analysis

We used simple descriptive statistics to describe the sociodemographic and clinical characteristics of the sample. We then examined the bivariate associations between each of our two primary independent variables of interest (urban/rural area of residence and cost of transportation) and each of the outcomes of interest (*cplexA*, *cplexB,* the composite measure of complexity, and time of evolution) using χ^2 tests. For each of the two dichotomous outcomes (*cplexA* and *cplexB*), we further used logistic regression analysis to quantify the unadjusted and adjusted associations with both area of residence and transportation cost. For the two ordinal outcomes (the 3-level composite measure of complexity and the 4-level time of evolution variable), ordered logistic regression analysis was performed. To control for potential confounders, each multivariable model included all sociodemographic and clinical variables that were associated with the respective outcome variable at the 0.20 alpha level. All analyses were conducted using SAS 9.4.

Results:

Among the 982 individuals that consulted at CIDEIM between January 2012 and April 2018 and had a laboratory-confirmed diagnosis of cutaneous leishmaniasis, 710 individuals had information on their area of residence (urban versus rural), and 315 individuals had enough detailed information regarding their address and *vereda* to estimate cost of transportation to their CIDEIM referral center (25). The sociodemographic and clinical characteristics of each analytic sample are presented in Table 1.

Table 1: Sample Characteristics

	All patients with a positive confirmed laboratory diagnosis of CL (N = 982) *	Patients with complete information about region of residence (N = 710) *	Patients with complete neighborhood and cost of transportation data (N = 315) *
Characteristic	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)
Age in years (in years)	30.7 (16.4)	30.4 (16.4)	28.3 (15.9)
Male	753 (76.7)	549 (77.3)	244 (77.5)
Afrodecendent	456 (46.4)	313 (44.1)	121 (38.4)
Public Insurance	692 (70.5)	520 (73.2)	220 (69.8)
Work in Agriculture	495 (50.4)	391 (55.1)	184 (58.4)
Presence of Comorbidities	262 (26.7)	168 (23.7)	57 (18.1)
History of Previous Lesion	83 (8.5)	50 (7.1)	19 (6.0)
L.V. panamensis †	211/253(83.6)	125/156 (80.1)	71/82 (86.6)
Live in Rural Area	576 (58.7)	576 (81.1)	223 (70.8)

* Numbers may not sum to total due to missing data

† (n/N) - given that species identification is resource-intensive, it is only available for the patients that participated in clinical trials and thus a high percentage of the sample has missing species data

The individuals with information regarding their area of residence were similar to the overall patient population. They had an average age of 30.4 years. Five hundred forty-nine were male (77.3%) and 44.1% identified as Afro-descendant. The majority of individuals worked in agriculture (55.1%), lived in a rural area (81.1%), had public insurance (73.2), and were infected

with *Leishmania (Viannia) panemensis* (80.1% out of those that had undergone species identification). Additionally, 7.1% reported a history of previous skin lesions and 23.7`% had a clinical comorbidity.

Patients for whom we had estimates of transportation costs had a mean age of 28.3 years and were majority male (77.5%), had public insurance (69.8%), lived in a rural area (70.8%) and were infected with *L. panamensis* (86.6% out of those that had undergone species identification). One hundred twenty-one individuals identified as afro-descendent (38.4%), 58.4% worked in agriculture, 6.0% reported a history of previous skin lesions and 18.1% had a clinical comorbidity.

Unadjusted and adjusted associations of both area of residence and cost of transportation with complexity of disease based on *cplexA* criteria are shown in Table 2. Overall, 74.6% of patients were categorized as having more complex disease at initial consultation based on this definition. Having to pay more than $60,000 COP for transportation from a patient's *vereda* of residence to the nearest urban center was associated with a significantly higher odds of being classified as more complex compared with those who had to pay less than $20,000 COP (unadjusted OR = 1.91 [95% CI: 1.04 – 3.49]). The significant association persisted even after adjusting for potential cofounders (adjusted OR = 2.11 [95% CI: 1.11 – 4.02]. Rural residence was associated with lower odds of more complex disease at diagnosis; however, the association was not statistically significant at the 0.05 level but it was marginally significant at the 0.1 level (p = 0.080).

Table 2: Association of Area of Residence and Cost of Transportation with Disease Complexity based *cplexA* Criteria								
	N	n (%) with more complex cutaneous leishmaniasis based on *cplexA* criteria	Unadjusted OR (95%)			Adjusted* OR (95%)		
Area of Residence (N = 700)								
Urban	130	101 (77.7)	REF			REF		
Rural	570	398 (69.8)	0.67	(0.42,	1.04)	0.65	(0.40,	1.05)
Cost of Transportation in Colombian Pesos (N = 314)								
< 20,000	155	105 (67.7)	REF			REF		
20,000 - 60,000	64	40 (62.5)	0.79	(0.43,	1.46)	0.89	(0.46,	1.71)
>60,000	95	76 (80.0)	**1.91**	**(1.04,**	**3.49)**	**2.11**	**(1.11,**	**4.02)**
* Adjusted for race, sex, presence of comorbidities, and history of a previous lesion for Area of Residence model (N = 664); Adjusted for age, sex, and the presence of comorbidities for Cost of Transportation model (N = 301)								

As shown in Table 3, 35.9% of patients were categorized as more complex at initial consultation using the *cplexB* criteria. Patients with transportation costs of less than $20,000 COP were the least likely to be diagnosed with more complex disease; however, the association between greater costs and *cplexB*-defined disease complexity did not reach statistical significance, nor did the association between rural residence and lower odds of more complex disease.

Table 3: Association of Area of Residence and Cost of Transportation with Disease Complexity based on *cplexB* Criteria								
	N	n (%) with more complex cutaneous leishmaniasis based on *cplexB* criteria	Unadjusted OR (95%)			Adjusted* OR (95%)		
Area of Residence (N = 694)								
Urban	129	53 (41.1)	REF			REF		
Rural	565	192 (34.0)	0.74	(0.50,	1.09)	0.75	(0.50,	1.14)
Cost of Transportation in Colombian Pesos (N = 309)								
< 20,000	152	37 (24.3)	REF			REF		
20,000 - 60,000	63	20 (31.8)	1.45	(0.76,	2.76)	1.44	(0.77,	2.70)
>60,000	94	28 (29.8)	1.32	(0.74,	2.35)	1.52	(0.76,	3.01)
* Adjusted for race and the presence of comorbidities for Area of Residence model (N = 661); Adjusted for age, sex, and insurance for Cost of Transportation model (N = 281)								

Crude analyses showed that individuals with a rural residence and those with transportation costs less than $20,000 COP were the least likely to be diagnosed with more complex disease but the association was not significant at the 0.05 level (Table 4). After adjusting for covariates, however, individuals who had to pay an estimated cost of transportation greater than $60,000 COP were found to have a significantly higher odds of having more complex disease than those individuals who have to pay less (adjusted OR = 1.78 [95% CI: 1.09 – 2.92]).

Table 4: Association of Area of Residence and Cost of Transportation with Composite Complexity Score

	N	n (%) who had a low complexity	n (%) who had a moderate complexity	n (%) who had a higher complexity	Unadjusted OR (95%)	Adjusted* OR (95%)
Area of Residence (N = 694)						
Urban	129	29 (22.5)	47 (36.4)	53 (41.1)	REF	REF
Rural	565	172 (30.4)	201 (35.6)	192 (34.0)	0.71 (0.50, 1.01)	0.72 (0.50, 1.05)
Cost of Transportation in Colombian Pesos (N = 308)						
< 20,000	152	50 (32.9)	65 (42.8)	37 (24.3)	REF	REF
20,000 - 60,000	63	24 (38.1)	19 (30.2)	20 (31.6)	1.04 (0.60, 1.79)	1.22 (0.69, 2.15)
>60,000	93	19 (20.2)	47 (50.0)	28 (29.8)	1.54 (0.95, 2.49)	**1.78 (1.09, 2.92)**

* Ordinal logistic regression; Adjusted for sex, race, and the presence of comorbidities for Area of Residence model (N = 661); Adjusted for sex and the presence of comorbidities for Cost of Transportation model (N = 297)

Table 5 shows the unadjusted and adjusted associations of both area of residence and cost of transportation with time of evolution of the patient's first lesion. Living in a rural area was found to be associated with a 35% decreased likelihood of having a longer time of evolution when compared with those who lived in urban areas (unadjusted OR = 0.65 [95% CI: 0.46– 0.92]), and the protective effect persisted after controlling for potential confounders (adjusted OR = 0.66 [95% CI: 0.45 – 0.97]). Individuals who had to pay less than $20,000 COP for transportation

were found to be the least likely to have a higher time of evolution, but the association did not reach statistical significance.

Table 5: Association of Area of Residence and Cost of Transportation with Time of Evolution											
	N	n (%) who had a time of evolution of <1 month for their first lesion	n (%) who had a time of evolution from 1 - <2 months for their first lesion	n (%) who had a time of evolution from 2 – 3 months for their first lesion	n (%) who had a time of evolution of > 3 months for their first lesion	Unadjusted OR (95%)			Adjusted* OR (95%)		
Area of Residence (N = 699)											
Urban	134	15 (11.2)	33 (24.6)	44 (32.8)	42 (31.3)	REF			REF		
Rural	565	20 (5.3)	239 (42.3)	183 (32.4)	113 (20.0)	**0.65**	**(0.46,**	**0.92)**	**0.66**	**(0.45,**	**0.97)**
Cost of Transportation in Colombian Pesos (N = 308)											
< 20,000	152	6 (4.0)	81 (53.3)	45 (29.6)	20 (13.2)	REF			REF		
20,000 - 60,000	63	2 (3.2)	27 (42.9)	19 (30.2)	15 (23.8)	1.63	(0.95,	2.82)	1.36	(0.73,	2.56)
>60,000	93	7 (7.5)	36 (38.7)	29 (31.2)	21 (22.6)	1.48	(0.91,	2.40)	1.38	(0.77,	2.50)
* Ordinal logistic regression; Adjusted for age, race, sex, work, insurance, and the presence of comorbidities for the Area of Residence model (N = 645); Adjusted for age, sex, race, insurance, and the presence of comorbidities for the Cost of Transportation model (N = 271)											

Upon stratifying the results by the two cities where CIDEIM is present, Cali and Tumaco, the aforementioned effects remained consistent – an apparent association between increased disease complexity and higher cost of transportation and a protective association between rurality and time of evolution), especially for Tumaco where the majority of the patients in our sample sought medical consultation (data not shown).

Discussion

Using data from a local clinical referral center (CIDEIM) in southwest Colombia, this study found that there was a positive association between cost of transportation from a patient's *vereda* to the nearest urban center and an increased likelihood of more complex cutaneous leishmaniasis at first clinical consultation. CL Patients who had to pay greater than $60,000 COP for transportation were more likely to be classified as having more complex disease based on the *cplexA* criteria and had higher odds of presenting with more complex disease. Contrary to our expectation, however, a protective association between rurality and the time of evolution for the first lesion was also seen, showing that patients who lived in rural regions were less likely to have longer wait times before consulting at CIDEIM when compared to those who lived in urban centers. While not statistically significant, a similar protective association between rurality and complexity was seen, where patients living in a rural residence were less likely to be diagnosed with more complex disease when compared to those with urban residence.

While previous studies have attempted to understand barriers to CL diagnosis in rural regions of Latin America (11,17,27,28), to our knowledge, the current study is the first to examine how distance from an urban center, here estimated through cost of transportation, is associated with time of evolution and complexity of disease at first visit to a local CL referral clinic. We uncover a threshold effect, in which we only see a significant association between cost of transportation and complexity of disease when patients need to pay greater than $60,000 COP. Assuming that high cost is associated with either farther distances away from the urban center or a more expensive mode of transportation (i.e. marine vs land transport), our results highlight that

transportation is still a significant barrier to equitable health access in individuals living in rural Colombia.

Interestingly, while we see a significant association with cost of transportation and complexity using the *cplexA* criteria, the association using *cplexB* guidelines did not reach statistical significance. A consistent trend, however, is still seen throughout: patients with less than $20,000 COP in transportation costs have the lowest odds of being diagnosed with more complex disease. Given that *cplexB* gives a more conservative definition of complexity, the cases identified using this criterion are implied to be of high complexity while the *cplexA* criteria captures moderate disease as well. The observed difference in statistical significance might be explained through this differential complexity classification: individuals with moderate disease, (*cplexA*) might not be motivated to consult a referral clinic at the nearest urban center if their cost of transportation exceeds $60,000 COP but individuals with more complex CL (*cplexB*) would be more willing to seek diagnosis and treatment, regardless of the cost. Ordinal logistic regression of the complexity score created as a composite of both criteria revealed that CL patients that had transportation costs that exceeded $60,000 COP had higher odds of being more complex at time of consultation, supporting the idea that mostly individuals with more complex disease would be willing to seek diagnosis and treatment despite the high cost.

Despite the few numbers of articles on CL and time of evolution, the majority of the literature mentions rurality and associated factors – low trust in medical institution, the use of alternative or home remedies, lack of urgency due to the non-fatal nature of the disease, the need for multiple, costly hospital visits for treatment – as strong contributors to the high time of evolution

seen in Colombian CL patients (11,17,27,29). The current study presents a contradictory perspective: compared to those patients living in urban centers, patients living in rural areas had significantly lower odds of longer evolution times for their first lesion. Similarly, patients living in a rural residence were also less likely to be diagnosed with more complex disease, although the association did not reach statistical significance. Given that the majority of CL cases occur in rural regions and that in Colombia the disease is often pejoratively associated with remote guerilla militants, urban centers are viewed as non-endemic regions for CL. While endemic areas bare a higher disease burden, the lack of health professionals trained in a particular disease diagnostic or the lack of clinical suspicion in non-endemic regions has shown to be associated with increased diagnostic delay (30–33). Thus, in Colombia, individuals in urban centers might be susceptible to diagnostic delay and longer times of evolution due to lack of clinical suspicion of the disease in non-endemic regions of the country.

While CL is primarily considered a rural disease as infection usually occurs through zoonotic transmission from either canine or sylvatic reservoir hosts, rapid deforestation and urbanization in Latin America is bringing many people into contact with zoonotic *Leishmania* hosts and with *Phlebotomus* sand flies (the insect vector for CL) (34). In Colombia, both rapid urbanization and forced human migration as a result of armed conflict and drug trafficking has promoted an increase in CL cases in the country (4). As cities continue to expand into previously forested regions, the country may see an increase in CL cases in urban centers. Given the results of this study, local governments and health departments may need to expand clinical diagnostic capacity in order to prevent significant diagnostic delays.

Interestingly, despite longer time of evolution being associated with higher disease complexity (15,35,36), the current study fails to find a significant association between area of residence and CL complexity at time of consultation, regardless of the guidelines used to classify the disease as complex. The potential reasons – both clinical and social – are many, given the multiple risk factors that may influence disease progression (15,26,28). Given that the outcome of CL is highly dependent on the host's immune system (23,37), however, one potential explanation might be higher prevalence of malnutrition, which has been shown to suppress the immune system and promote lesion persistence (38–41), in patients living in rural areas compared to those living in urban centers (42,43). Malnutrition might be modifying the association between area of residence and complexity but careful additional investigation is needed.

This study had the following limitations. Due to the lack of geographical information and clear political definitions of *veredas*, neither straight-line Euclidean distance nor distance of roads traveled could be determined. Since neither distance travelled nor direct costing of transportation is routinely collected from patients, we had to approximate distance from each *vereda* to the nearest urban center using estimated travel costs found in Berger et al (25). While these estimates fail to account for variability in transportation methods, differences in routes, and individual variation, the approximate transportation costs were estimated by healthcare professionals using local knowledge and experience and are thus considered to be highly informed on the basis of preferred route, diversity of mode of transportation, and local variation in costs. In regards to the outcome variables, currently, to our knowledge, there is no validated complexity score for cutaneous leishmaniasis. In order to quantify complexity, however, we used the treatment guidelines for local therapy set by PAHO and the WHO as a general starting point, with some

notable distinctions. We only included those criteria related to disease complexity and excluding those that were related to viability and safety of local treatment. For example, both the WHO and PAHO count lesions on the face and joints as ineligible for local treatment. Given that this consideration is due to the potential risk of complication from local therapies such as thermotherapy and cryotherapy at these locations and not with complexity or chronicity, we decided to exclude them from the criteria. A similar rationale was applied with the criterion for availability for follow- up. Since the *Leishmania* species found in Colombia are also capable of inducing mucocutaneous lesions as well as capable of disseminating through the lymphatic tract, both presence of mucocutaneus lesions and lymphatic dissemination were included as part of the complexity criteria. We created a complexity score by combining the two criteria as a substitute for a validated score but confirmatory evaluations should be done if a validated scale is created. Additionally, only 347 individuals in our sample had undergone testing for parasite species identification due to the time-intensive methodology and high cost. Despite this limitation, we found no significant association of complexity or time of evolution with parasite species, even when accounting for the missing data as an additional category in the variable. In the individuals that did have information regarding parasite species, we found that greater than eighty percent were infected with *L. panamensis*, which matches with the observed species distribution found throughout the country (2). In addition to cost of transportation, there exist many different factors that might influence an individual's willingness to seek medical attention and ease of transport, including remoteness, different modes of transportation, lack of roads, violence, drug trafficking, etc. Future studies should work to uncover and address the other equally important influences that act as barriers to equitable health for patients in rural Colombia. This research is also an observational cross-sectional study using routine clinical data not specifically collected for the

purpose of this investigation, meaning that causality cannot be inferred. Additionally, the quality of self-reported variables could not be verified.

While the current study examines cost of transportation as it relates to time of evolution and complexity at first medical visit, transportation cost should also be examined in relation to treatment access, delay, and adherence for CL patients in rural regions. The current standard of care for CL is a twenty-day injection regimen with meglumine antimoniate that requires the patients to visit a clinic daily. A recent study conducted by Berger et al. (25) estimated that the mean cost-per-cure from a patient perspective was $443 USD due to transportation, food, lodging, medical and child care, which represents a significant cost given the monthly minimum wage of about $260 USD (44). Future studies should address how a higher cost of transportation might affect a patient's willingness to seek and remain on treatment with meglumine antimoniate and potentially with miltefosine, an equally efficacious oral medication that has recently been incorporated into the standard of care in Colombia after being shown to be a potential alternative (45,46).

In conclusion, our analysis revealed that a high cost of transportation to an urban center is associated with increased likelihood of higher disease complexity at the time of first consultation at a local referral center for patients with CL in rural Colombia. Our findings further demonstrate that CL patients living in urban regions often present a higher time of evolution for the disease and more complex disease at consultation, setting the basis for future research into the potential causes for this phenomenon and underscoring the need for higher clinical suspicion and diagnostic capabilities in rapidly-urbanizing regions currently classified as non-endemic for CL.

Our study highlights that transportation in rural regions still remains a significant barrier to equitable health access for CL patients in Colombia and warrants further investigation into interventions that might improve diagnostic and treatment services for these individuals and communities.

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