original reports abstract

Epidemiological Features and Outcomes of HTLV-1 Carriers Diagnosed With Cancer: A Retrospective Cohort Study in an Endemic Country

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PURPOSE Human T-lymphotropic virus type 1 (HTLV-1) is an endemic virus in Latin America that is directly linked to adult T-cell leukemia/lymphoma (ATL). Previous studies have suggested an oncogenic role of HTLV-1 in non-ATL neoplasms and have found higher mortality in HTLV-1 carriers without ATL.

METHODS In this retrospective cohort study, HTLV-1 carriers were identified through screening at a tertiary cancer center between 2006 and 2019. We compared the overall survival (OS) outcomes of patients with ATL with those with other solid or hematologic malignancies by sex stratification.

RESULTS We identified 1,934 HTLV-1 carriers diagnosed with cancer. The median age at diagnosis was 62 (range 20-114) years, 76% were female, 60% had no or elementary school education, and 50% were born in the Andean highlands. The most common non-ATL neoplasm was cervical cancer (50%) among females and non-ATL non-Hodgkin lymphoma (26%) among males. With a median follow-up of 66 months, the 5-year OS of HTLV-1 carriers with non-ATL neoplasms (26%-47% for females and 22%-34% for males) was inferior to those reported in the general population. As expected, patients with ATL had a worse prognosis (5-year OS: 10% for females and 8% for males).

CONCLUSION HTLV-1 carriers with cancer were middle age and from underprivileged settings, suggesting an undetected transmission among vulnerable populations, especially females. Survival estimates of HTLV-1 carriers with non-ATL neoplasms were lower than the regional outcomes. Future research should ascertain how the biology of HTLV-1 and health care disparities affect the outcomes of HTLV-1 carriers, as well as determine the burden of HTLV-1 infection in the cancer population to recommend screening in the outpatient setting of endemic regions.

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BACKGROUND

The human T-lymphotropic virus type 1 (HTLV-1) is an oncogenic human retrovirus whose target is CD4-positive T-cell lymphocytes.[1] HTLV-1 is associated with aggressive diseases such as adult T-cell leukemia/lymphoma (ATL) and myelopathy/tropical spastic paraparesis.[1,2] Approximately, 10-20 million people worldwide are infected with this virus; however, only a few develop HTLV-1–associated diseases.[3] HTLV-1 is endemic in Southwestern Japan, the Caribbean basin, South America, and West Africa.[1,4,5] In Peru, endemic populations include indigenous from the Andean or Amazonian regions and female sex workers.[6,7] Transmission of HTLV-1 is through breastfeeding, blood transfusion, sharing of needles, and sexual intercourse.[2]

Previous research has established the causal link between HTLV-1 infection and ATL development.[3] Other studies suggest a broader role of HTLV-1 in the oncogenesis process of non-ATL neoplasms such as lymphoma other than ATL, liver cancer, and cervical cancer.[8,9] However, these findings derive from cross-sectional and case-control studies, which are prone to bias and methodological issues. Population-based studies have identified higher all-cause mortality among non-ATL HTLV-1 carriers compared with noncarriers in Asian countries, suggesting that HTLV-1 infection is a risk factor for increased mortality.[9,10] In this exploratory research, we aimed to describe the epidemiological features and outcomes of HTLV-1 carriers with a non-ATL primary malignancy in an endemic country.

METHODS

Study Design and Population

We conducted a retrospective cohort study of patients with hematologic or solid neoplasms and with available HTLV-1 serology test results from January 2006 to

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

What are the epidemiological features and survival outcomes of Hispanic patients with cancer with human T-lymphotropic virus type 1 (HTLV-1) infection?

Knowledge Generated

Limited data exist on the demographic characteristics, frequency of solid and hematologic malignancies, and overall survival of HTLV carriers. We found that most HTLV carriers were female, coming from underprivileged settings, and with low educational levels. Most female HTLV carriers had cervical cancer, and non-Hodgkin lymphomas (besides adult T-cell leukemia/lymphoma) were the most frequent in male carriers. Survival estimates were lower than those reported in the region for the corresponding cancer diagnosis.

Relevance

This study is one of the largest cohorts among Latin American HTLV carriers with cancer. Our descriptive study suggests that HTLV transmission occurs among vulnerable populations. Future studies should determine if HTLV-1 biology or health care disparities are responsible for the lower outcomes observed and evaluate the effect of HTLV infection on treatment outcomes.

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December 2019 at the National Institute of Neoplastic Diseases (*Instituto Nacional de Enfermedades Neoplasicas*, INEN in Spanish). The INEN is a tertiary referral cancer center located in Lima, the capital city of Peru, that belongs to the public health insurance network of the Ministry of Health, which provides coverage to about 80% of insured patients.[11,12] As a national referral center, INEN receives patients from all over the country for diagnosis, management, and follow-up care. All patients were tested for HTLV infection using an enzyme-linked immunosorbent assay as part of the initial workup for cancer diagnosis. Confirmation of HTLV-1 infection via Western blot was only available in some cases given the lack of insurance coverage for such procedure and high health care cost.

The medical records of the patients were identified through the electronic health record system of the INEN. We included patients age 20 years or older with a malignant pathology diagnosis. Hematologic malignancies were classified according to the 2016 WHO Classification system.[13] If a patient was diagnosed with cancer in another center, the histopathological diagnosis was reviewed and confirmed by the INEN's pathologist. Exclusion criteria were as follows: lost or destroyed medical records, incomplete or insufficient data for pathological characterization, patients with a diagnosis of carcinoma in situ, and patients with undetermined HTLV-1 serology results. All patients were linked to the National Identity and Civil Status Registry for vital status verification.

Variables

Demographic information, cancer diagnosis, and tumor staging (when applicable) are available through the electronic system. The clinical data abstraction was completed through a manual review of medical records. Variables included age, sex, region of birth, education level, Eastern Cooperative Oncology Group (ECOG) performance status, tumor staging, cancer diagnosis, and vital status. Cancer staging for solid neoplasms, Hodgkin lymphoma, and non-Hodgkin lymphomas (NHLs) was performed according to the American Joint Committee on Cancer staging system 7th edition,[14] and the Shimoyama[15] classification for ATL. Cancer diagnoses were grouped on the basis of sex-specific malignancies and whether a tumor was deemed solid or hematologic. The cancer diagnosis categories were breast and female organs, cervix, male genital organs, other solid, non-ATL hematologic malignancies, and ATL. Cervical cancer was analyzed independently, given its high prevalence in our study population.

Data Analysis

We used descriptive statistics to report the demographic and clinical characteristics. Overall survival (OS) was defined as the length of time (in months) from cancer diagnosis until death by any cause or end of the study (February 2020). We used the Kaplan-Meier method to estimate OS probabilities and the log-rank test to evaluate the difference between curves. A multivariable Cox regression was performed to model the effect of a cancer diagnosis on OS, including age group, year of diagnosis, education level, and region of birth as adjusting variables. Performance status was included as a stratifying variable in the model because of a violation of the Cox hazard assumption. These factors were included regardless of their statistical significance in the univariable analysis. All analyses were stratified by sex. We report our outcomes with adjusted hazard ratios and 95% CIs. A P value lower than .05 was considered statistically significant. All analyses were performed in the R software (R Foundation for Statistical Computing, Vienna, Austria).

Ethical Statement

This study was approved by the Institutional Review Board of the INEN. Patients' data were registered using codes (ie, 0001).

TABLE 1. Demographic and Clinical Features of HTLV-1 Carriers With a Cancer Diagnosis

Characteristic	All Patients, No. (%)	Sex, No. (%)		*P*
		Females	Males	
No. of patients	1,934	1,465	469	
Age at diagnosis, years				
Median (range)	62 (20-114)	61 (20-114)	64 (20-104)	.164
Age group, years				.028
20-39	156 (8.1)	113 (7.7)	43 (9.2)	
40-59	692 (35.8)	548 (37.4)	144 (30.7)	
≥ 60	1,086 (56.2)	804 (54.9)	282 (60.1)	
Education level				< .001
Elementary school	731 (37.8)	554 (37.8)	177 (37.7)	
High school	661 (34.2)	436 (29.8)	225 (48.0)	
College	92 (4.8)	55 (3.8)	37 (7.9)	
None	420 (21.7)	394 (26.9)	26 (5.5)	
Unknown	30 (1.6)	26 (1.8)	4 (0.9)	
Region (birth)				< .001
Coast	861 (44.5)	625 (42.7)	236 (50.3)	
Highlands	974 (50.4)	750 (51.2)	224 (47.8)	
Rainforest	99 (5.1)	90 (6.1)	9 (1.9)	
Year of diagnosis				< .001
2006-2010	411 (21.3)	272 (18.6)	139 (29.6)	
2011-2015	838 (43.3)	665 (45.4)	173 (36.9)	
2016-2019	685 (35.4)	528 (36.0)	157 (33.5)	
Cancer stage				< .001
I	119 (6.2)	104 (7.1)	15 (3.2)	
II	542 (28.0)	482 (32.9)	60 (12.8)	
III	503 (26.0)	404 (27.6)	99 (21.1)	
IV	440 (22.8)	265 (18.1)	175 (37.3)	
Not applicable[a]	56 (2.9)	34 (2.3)	22 (4.7)	
Unknown	274 (14.2)	176 (12.0)	98 (20.9)	
ECOG score				< .001
0-1	1,332 (71.5)	1,070 (75.1)	262 (59.8)	
2-4	531 (28.5)	355 (24.9)	176 (40.2)	
Unknown	71	40	31	
Cancer site diagnosis				< .001
Cervix	736 (38.1)	736 (50.2)	—	
ATL	353 (18.3)	189 (12.9)	164 (35.0)	
Non-ATL hematologic	275 (14.2)	152 (10.4)	123 (26.2)	
Breast and female organs	180 (9.3)	180 (12.3)	—	
Male genital organs	42 (2.2)	—	42 (9.0)	
Other solids	348 (18.0)	208 (14.2)	140 (29.9)	
Mortality, at 5 years	1,170 (60.5)	815 (55.6)	355 (75.7)	< .001

Abbreviations: ATL, adult T-cell leukemia/lymphoma; ECOG, Eastern Cooperative Oncology Group.
[a]Patients with leukemia.

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RESULTS

Demographic and Clinical Characteristics

From 2006 to 2019, we identified 1,934 HTLV-1 carriers with cancer diagnoses. Table 1 shows the demographic and clinical characteristics. The median age at diagnosis for all patients was 62 (range 20-114) years, and 75.7% were females. One fifth of the individuals did not attain any education (21.7%), and half were born in the highlands (50.4%). Advanced disease (cancer stage III-IV), when applicable, was observed in 48.8% of the total population. Compared with males, most females had no education (26.9% *v* 5.5%, $P < .001$) and were diagnosed in early cancer stages (40.0% *v* 16.0%, $P < .001$).

Cancer Diagnosis Distribution

Cervical cancer (49.9%) was the most frequent neoplasm among female carriers, followed by ATL (12.9%) and breast cancer (5.6%). For males, the most common neoplasms were ATL (35.0%), non-ATL NHL (17.7%), and tumors of the genital organs (9.0%) (Table 1). Of the 42 males with genital tumors, 27 had prostate cancer, 14 had penile cancer, and one individual had testicular cancer. Figure 1 shows a significant difference in the distribution of cancer diagnosis for females (Fig 1A; $P < .001$) and males (Fig 1B; $P < .001$) by age group. Cervical cancer was the most prevalent diagnosis among females across all age groups while ATL diagnosis tends to decrease from 19% in the 20-39 age group to 11% in females age 60 years and older. In contrast, ATL was the most common diagnosis for male carriers in the age groups 20-39 years (42%) and 40-59 years (49%), but the prevalence of ATL decreased to 27% among males age 60 years and older. Non-ATL hematologic malignancies had a prevalence of approximately 30% across all age groups for males. Detailed distribution by age group for each sex is provided in Appendix Table A1.

Survival Outcomes

The median follow-up time (reverse Kaplan-Meier method) was 66 months (95% CI, 62 to 74) for all patients, 65 months for females (95% CI, 60 to 72), and 75 months for males (95% CI, 58 to 98). A total of 1,170 deaths were observed in all patients within 5 years after diagnosis (815 in females and 355 in males). The 5-year OS for females was 28% and for males was 10%. Figure 2 depicts the Kaplan-Meier curves for age group (Figs 2A 2B), region of birth (Figs 2A 2B), and ECOG score (Figs 2A 2B) by sex stratification. Females age 20-39 years experienced the lowest survival rates compared with those age 40-59 or 60 years and older (27% *v* 42% *v* 36%, respectively; $P = .006$). Although nonstatistically significant, the 5-year OS rates among males age 20-39 years were 28% compared with 16% and 20% for those age 40-59 or 60 years and older, respectively ($P = .089$). OS estimates by region of birth were similar for both males ($P = .440$) and females ($P = .530$). An ECOG score of ≥ 2 was associated with a worse OS compared with a score of 0-1 among females (15% *v* 46%; $P < .0001$) and males (13% *v* 25%; $P < .0001$).

Figure 3 provides the 5-year OS curves by cancer site diagnosis for females (Fig 3A) and males (Fig 3B). Patients with an ATL diagnosis experienced the worst 5-year outcomes among females (OS: 10%, median OS: 6 months; $P < .0001$) and males (OS: 8%, median OS: 5 months; $P < .0001$). In females, cervical cancer and breast and female organ tumors had the highest 5-year OS (47% for both) compared with non-ATL hematologic malignancies or other solid tumors (29% and 26%, respectively, $P < .0001$). In males, sex-specific genital tumors had the highest 5-year OS (34%), followed by non-ATL hematologic malignancies (27%) and other solid tumors (22%; $P < .0001$). When survival comparison between sexes was applied, there was no statistically significant difference in outcomes at 5 years

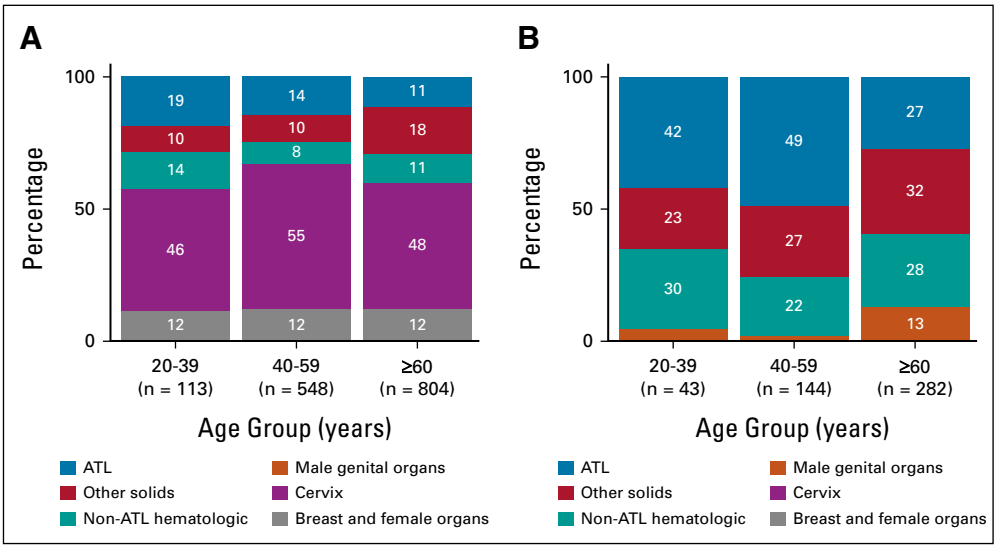


FIG 1. Cancer site diagnosis distribution for (A) females and (B) males by age group among HTLV-1 carriers. Values < 10% were suppressed. The total percentage might not add up to 100 because of rounding issues. ATL, adult T-cell leukemia/lymphoma.

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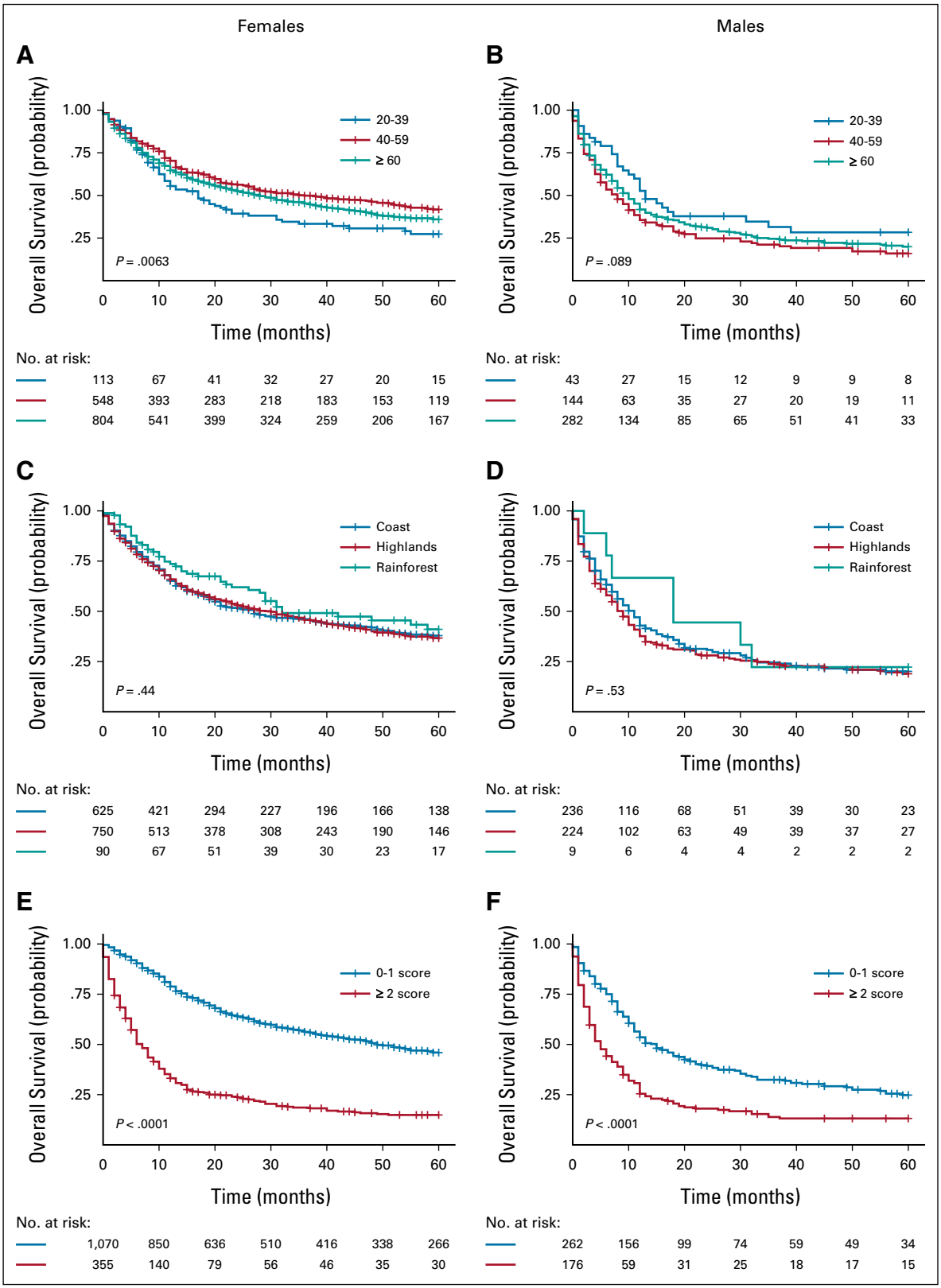


FIG 2. Five-year overall survival analysis of HTLV-1 carriers with a cancer diagnosis. (A, C, and E) Kaplan-Meier curves for females by age group, region of birth, and ECOG score. (B, D, and F) Kaplan-Meier curves for males by age group, region of birth, and ECOG score. ECOG, Eastern Cooperative Oncology Group.

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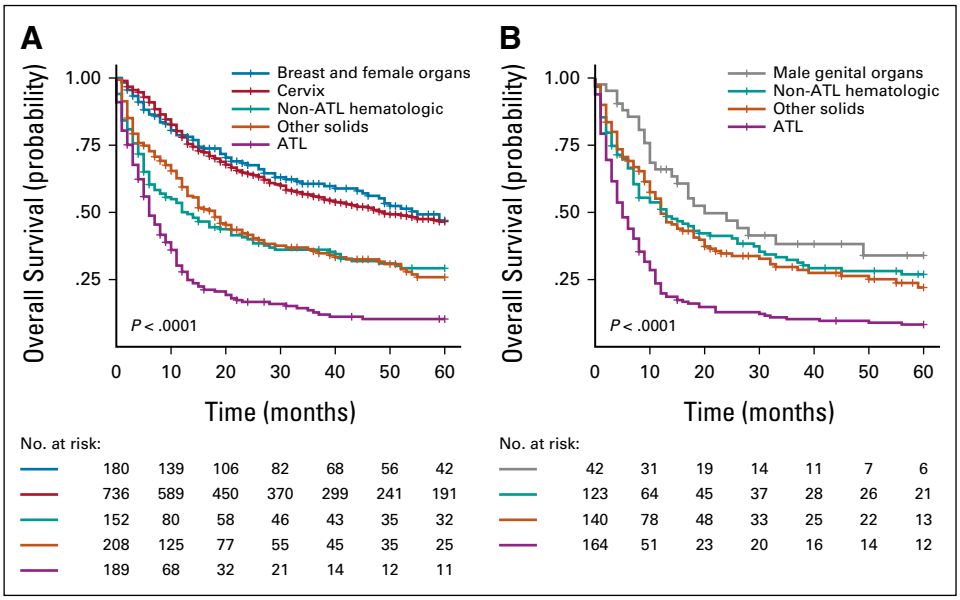


FIG 3. Five-year overall survival Kaplan-Meier curves of HTLV-1 carriers according to cancer site diagnosis for (A) females and (B) males. ATL, adult T-cell leukemia/lymphoma.

for the major and detailed cancer site diagnosis grouping (Table 2).

We performed a multivariable Cox analysis stratified by sex to evaluate the effect of HTLV-1 infection on patients with a cancer diagnosis. The risk of all-cause mortality was worse among patients with ATL compared with patients with other solid or hematologic malignancies after adjusting for age, year of cancer diagnosis, education level, and region of birth (Table 3).

DISCUSSION

To our knowledge, this cohort is the first to describe the epidemiological characteristics and outcomes of Latin American HTLV-1 carriers with a non-ATL neoplasm. Most HTLV-1 carriers were middle age and from underprivileged settings in Peru, underscoring a considerable undetected transmission in this cancer population. Cervical cancer was diagnosed in half of the females while NHL was most frequent among males after ATL. Patients with ATL had the worst survival outcomes, suggesting that HTLV-1 infection appeared not to compromise OS as much as those that developed ATL. However, controversy remains on the potential oncogenic role of HTLV-1 in non-ATL neoplasms and if HTLV-1 infection negatively affects outcomes of patients with non-ATL hematologic or solid neoplasms.

Given the high endemicity of HTLV-1 in Peru, local clinical guidelines recommend screening in blood donors and patients receiving systemic anticancer therapy.[4,16] However, HTLV-1 screening is performed differentially among health care practitioners. Our cohort includes patients treated at the Department of Medical Oncology of the INEN, which performs routine HTLV-1 testing during the diagnosis workup as a standard of care. Therefore, the observed distribution of non-ATL neoplasms might reflect the cancer population from this medical unit. For instance, although breast cancer is the most common neoplasm among Peruvian women, we only found a prevalence of 6%.[17] Breast cancer is generally treated by surgeons in our center, explaining some of the prevalence discrepancies between this cohort and the overall Peruvian cancer population.

Half of the females in this cohort were diagnosed with cervical cancer. Transmission of HTLV-1 occurs through unprotected sexual intercourse, such as the human papillomavirus (HPV).[1,18] A dual and undetected sexual transmission might have been the main route for HTLV-1 spread among females. This transmission mechanism is frequent among underserved and marginalized populations.[1,8,19] Most patients had no or little education and half were from the highlands, both factors associated with unprivileged settings in Peru.[20] Our outcomes are in line with previous studies. In Brazil, the prevalence of HPV infection was significantly higher among HTLV-1–infected women (44%). Similarly, one study found an association between HPV and HTLV-1 infections in a Peruvian Amazonian Community.[8] The high frequency of females with HTLV infection in this study suggests that the use of barrier contraceptive methods, such as condoms, could prevent the development of HTLV and HPV coinfection. However, additional studies should corroborate this assumption.

The rainforest is a region with high prevalence and mortality rates of cervical cancer.[20] Most of our patients with cervical cancer were from the coast or the highlands. Therefore, we believe that our estimates likely underrepresent the real burden of HTLV-1 infection in patients with cervical cancer. The synergistic process between HTLV-1 and HPV remains to be studied. It is unknown whether HTLV might have generated an immunosuppressive status suitable for the development of HPV-associated cervical cancer and if

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TABLE 2. Major and Detailed Cancer Diagnosis Distribution, 5-Year OS, and 5-Year Median OS, Unless Otherwise Specified by Sex

	Females (n = 1,465)			Males (n = 469)			
Cancer Site Diagnosis	No. (%)[a]	OS (95% CI)	Median Survival (95% CI)	No. (%)[a]	OS (95% CI)	Median Survival (95% CI)	*P*
Major grouping							
Cervix	736 (50.2)	47 (43 to 51)	49 (41 to NR)	—	—	—	—
ATL	189 (12.9)	10 (6 to 17)	6 (5 to 8)	164 (35.0)	8 (5 to 14)	5 (4 to 7)	.190
Non-ATL hematologic	152 (10.4)	29 (22 to 38)	13 (8 to 23)	123 (26.2)	27 (20 to 37)	13 (8 to 26)	.860
Breast and female organs	180 (12.3)	47 (39 to 57)	55 (45 to NR)	—	—	—	—
Male genital organs	—	—	—	42 (9.0)	34 (21 to 54)	20 (15 to NR)	—
Other solids	208 (14.2)	26 (20 to 34)	18 (13 to 24)	140 (29.9)	22 (15 to 32)	12 (10 to 19)	.220
Detailed grouping							
Cervix	736 (50.2)	47 (43 to 51)	49 (41 to NR)	—	—	—	—
ATL	189 (12.9)	10 (6 to 17)	6 (5 to 8)	164 (35.0)	8 (5 to 14)	5 (4 to 7)	.190
NHL	107 (7.3)	30 (22 to 41)	15 (10 to 25)	83 (17.7)	31 (22 to 43)	10 (7 to 21)	.620
Female reproductive, others	98 (6.7)	40 (30 to 53)	34 (24 to NR)	—	—	—	—
Breast	82 (5.6)	56 (44 to 72)	NR (54 to NR)	—	—	—	—
Lower GI	40 (2.7)	39 (23 to 65)	42 (16 to NR)	21 (4.5)	25 (12 to 54)	18 (12 to NR)	.190
Leukemias, MDS	34 (2.3)	20 (10 to 39)	6 (4 to 17)	24 (5.1)	21 (9 to 49)	8 (3 to 39)	.780
Upper GI	25 (1.7)	15 (5 to 48)	15 (10 to 53)	25 (5.3)	12 (4 to 41)	11 (2 to 15)	.300
Male genital organs	—	—	—	42 (9.0)	34 (21 to 54)	20 (15 to NR)	
Sarcoma	19 (1.3)	62 (43 to 89)	NR (13 to NR)	18 (3.8)	48 (29 to 79)	37 (12 to NR)	.520
Head and neck	21 (1.4)	19 (7 to 51)	20 (17 to NR)	14 (3.0)	9 (1 to 59)	9 (5 to NR)	.160
Urinary tract	16 (1.1)	7 (1 to 44)	12 (11 to 49)	12 (2.6)	58 (36 to 94)	NR (10 to NR)	.100
Hodgkin lymphoma	11 (0.8)	48 (23 to 98)	48 (3 to NR)	16 (3.4)	16 (5 to 57)	33 (30 to NR)	.340
Skin and melanoma[b]	12 (0.8)	0 (0)	24 (8 to NR)	15 (3.2)	22 (8 to 59)	21 (10 to NR)	.420
Hepatobiliary system[c]	18 (1.2)	9 (2 to 57)	3 (2 to NR)	8 (1.7)	0 (0)	4 (4 to NR)	.670
Others	57 (3.9)	29 (17 to 47)	13 (7 to 52)	27 (5.8)	13 (3 to 63)	10 (4 to NR)	.420

Abbreviations: ATL, adult T-cell leukemia/lymphoma; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; NR, not reached; OS, overall survival.

[a]Percentages might not add up to 100 because of rounding issues.

[b]OS outcomes could only be estimated until 37 months for females.

[c]OS outcomes could only be estimated until 45 months for females and 12 months for males.

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HTLV infection negatively affects treatment response and outcomes among this population.

Survival outcomes in this cohort for the most common non-ATL cancer diagnoses were inferior compared with those reported in the regional cancer population. The CONCORD study identified that the 5-year OS among females from South America with cervical or breast cancer is above 60% and 70%, respectively. Furthermore, the estimates for Peruvian females were 57% for cervical cancer and 85% for breast cancer,[21] higher than the 47% and 56% survival rates in this cohort, respectively. In addition, previous studies have reported a 5-year OS of 40%-50% for aggressive NHL,[22,23] higher than the approximately 30% for males and females carriers. Our findings suggest worse outcomes among HTLV-1–infected individuals compared with their noncarrier counterparts. However, few data exist to support the assumption that HTLV-1 infection might lead to poor survival estimates. Direct comparison with previous studies should be interpreted with caution given the difference in the population characteristics or the methodology approach for outcomes estimation. Future studies should validate the findings of this cohort, accounting for the nuance in clinical features and treatment approaches for each cancer site.

Other factors, including health care disparities and limited availability of cancer therapies, may explain the poor outcomes. Peru faces barriers to effective cancer care delivery, such as geographical barriers to access health care, long waits for medical checks, and treatment delays.[24] Although Peru is under a health care decentralization process since

TABLE 3. Univariate and Multivariate Cox Regression Analysis of Overall Survival Among HTLV-1 Carriers With a Cancer Diagnosis Stratified by Sex

	Females			Males		
Characteristic	**No. (%)**	**HR (95% CI)**	**aHR (95% CI)**	**No. (%)**	**HR (95% CI)**	**aHR (95% CI)**
Age group, years						
20-39	113 (7.7)	Reference	Reference	43 (9.2)	Reference	Reference
40-59	548 (37.3)	0.68 (0.52 to 0.88)	0.70 (0.53 to 0.91)	144 (30.7)	1.54 (1.03 to 2.32)	1.33 (0.87 to 2.03)
≥60	804 (54.9)	0.80 (0.62 to 1.02)	0.69 (0.52 to 0.90)	282 (60.1)	1.32 (0.89 to 1.94)	1.31 (0.87 to 1.98)
Year of diagnosis						
2006-2010	272 (18.6)	Reference	Reference	139 (29.6)	Reference	Reference
2011-2015	665 (45.4)	0.98 (0.82 to 1.18)	1.22 (1.01 to 1.48)	173 (36.9)	0.89 (0.69 to 1.14)	1.19 (0.90 to 1.58)
2016-2019	528 (36.0)	0.92 (0.75 to 1.13)	1.13 (0.91 to 1.39)	157 (33.5)	1.00 (0.77 to 1.31)	1.54 (1.13 to 2.12)
Education level						
College	55 (3.8)	Reference	Reference	37 (7.9)	Reference	Reference
Elementary school	554 (37.8)	0.97 (0.68 to 1.40)	1.16 (0.79 to 1.70)	177 (37.7)	1.47 (0.95 to 2.27)	1.63 (1.04 to 2.56)
High school	436 (29.8)	0.96 (0.66 to 1.39)	1.02 (0.70 to 1.51)	225 (48.0)	1.27 (0.83 to 1.95)	1.32 (0.85 to 2.06)
Unknown/none	420 (28.6)	1.01 (0.70 to 1.47)	1.14 (0.77 to 1.70)	30 (6.4)	1.38 (0.78 to 2.42)	1.39 (0.76 to 2.55)
Region (birth)						
Coast	625 (42.7)	Reference	Reference	236 (50.3)	Reference	Reference
Highlands/rainforest	840 (57.3)	0.99 (0.86 to 1.14)	1.03 (0.89 to 1.20)	233 (49.7)	1.08 (0.88 to 1.33)	1.08 (0.86 to 1.35)
Cancer site diagnosis						
ATL	189 (12.9)	Reference	Reference	164 (35.0)	Reference	Reference
Other solids	208 (14.2)	0.47 (0.37 to 0.59)	0.50 (0.39 to 0.63)	140 (29.9)	0.51 (0.39 to 0.66)	0.41 (0.30 to 0.56)
Non-ATL hematologic	152 (10.4)	0.50 (0.39 to 0.64)	0.57 (0.44 to 0.75)	123 (26.2)	0.49 (0.38 to 0.64)	0.46 (0.34 to 0.61)
Cervix	736 (50.2)	0.25 (0.20 to 0.30)	0.35 (0.28 to 0.43)	—	—	—
Breast and female organs	180 (12.3)	0.24 (0.18 to 0.31)	0.32 (0.24 to 0.43)	—	—	—
Male genital organs	—	—	—	42 (9.0)	0.35 (0.23 to 0.54)	0.32 (0.20 to 0.51)

NOTE. ECOG performance status was included as a stratified variable in the model because of proportional hazard assumption violation.
Abbreviations: aHR, adjusted hazard ratio; ATL, adult T-cell leukemia/lymphoma; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

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2002,[25] most of the oncology workforce and tertiary centers are located in certain metropolitan urban cities, which impairs the health care access to individuals living in rural communities. Moreover, access to novel treatments, such as molecular or target therapies, is lacking.[26,27] Our population was generally low educated and from disadvantaged settings. Therefore, health care disparities and limited access to treatment in this vulnerable population might be responsible for the poor outcomes in this study compared with previous reports. However, additional research is warranted to determine if HTLV-1 infection increases the risk of treatment failure or mortality in cancer populations.

The pattern of cancer diagnoses according to the age group could explain the difference in OS between both sexes. Females age 20-39 years had a higher frequency of hematologic malignancies, which are associated with lower survival compared with other solid neoplasms such as breast and cervical cancer.[21] For males, the survival curves between young and older individuals are consistent with previous reports among patients with aggressive hematologic malignancies.[28,29] Furthermore, previous studies suggest that patients from the highlands or the rainforest have higher mortality.[30,31] However, we found similar survival estimates regardless of the region of birth. This outcome supports our assumption that health care disparities are a relevant factor for the poor survival rates in our population.

Our study has some limitations. This is a retrospective analysis from a single tertiary cancer center, and missing data is a concern. Nevertheless, we identified a low missing data percentage. In addition, we linked the patient's records to the National Identity and Civil Status Registry for vital status verification. We were unable to determine the prevalence of HTLV among all patients managed at the INEN. Screening for HTLV was implemented differentially between the Departments of the INEN since the early 2000s. Therefore, the distribution of cancer diagnoses in our population likely reflects the patients treated in the Department of Medical Oncology. However, we attempt to reduce bias by selecting a period where patients were screened irrespective of their demographics and clinical

features. Furthermore, confirmatory tests are not routinely available because of their high cost.

We acknowledge that patients living in far-away provinces might not have been referred to the INEN or decided not to travel for cancer management because of the high out-of-pocket cost. Therefore, patients from these provinces were probably not captured in the database of this center. In addition, testing for Epstein-Barr virus is not implemented routinely at the INEN, limiting reliable prevalence and outcomes estimations in our cohort.

This study represents one of the largest cohorts of HTLV carriers with a confirmatory cancer diagnosis in an endemic country. HTLV screening practices in our setting allow us to provide a clinical profile and report survival rates of cancer patients with HTLV infection, reducing selection bias and providing more reliable real-world outcomes for this unique cancer population. These results might not be replicable among settings without a systematic implementation of HTLV screening. However, our findings may reflect the outcomes among several Latin American countries with similar ethnic diversity and health systems to Peru.

In conclusion, HTLV-1 carriers with a cancer diagnosis were generally middle age, had poor outcomes, and were from resource-constrained settings, highlighting an undetected transmission among vulnerable populations. Survival rates for patients with non-ATL neoplasms were lower compared with those in the regional cancer population. The poor outcomes among patients with non-ATL neoplasms might be associated with health care disparities and barriers to accessing prompt treatment in the HTLV-1–infected population. Patients with ATL had the worst survival; however, controversy remains if a synergic role between oncogenic viruses, such as HPV, affects treatment outcomes in patients with non-ATL cancer. Our findings describe the burden of HTLV-1 in a diverse cancer population and support the development of public health efforts to control this virus. Future studies should evaluate the population-based serology distribution of HTLV-1 among cancer populations to measure the effect of HTLV-1 infection on patient outcomes and to provide robust evidence on the feasibility of HTLV-1 screening in the outpatient cancer setting in endemic regions.

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DATA SHARING STATEMENT

Deidentified data can be shared on reasonable request.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Detailed Cancer Diagnosis Distribution by Sex and Age Group Among HTLV-1 Carriers

	Females			
		Age Group, No. (%)		
Cancer Site Diagnosis	All Patients, No. (%)	20-39	40-59	≥60
No. of patients	1,465	113	548	804
Cervix	736 (50.2)	52 (46.0)	302 (55.1)	382 (47.5)
ATL	189 (12.9)	21 (18.6)	79 (14.4)	89 (11.1)
Non-Hodgkin lymphoma	107 (7.3)	5 (4.4)	32 (5.8)	70 (8.7)
Female reproductive, others	98 (6.7)	3 (2.7)	24 (4.4)	71 (8.8)
Breast	82 (5.6)	10 (8.8)	43 (7.8)	29 (3.6)
Lower GI	40 (2.7)	1 (0.9)	9 (1.6)	30 (3.7)
Leukemias, MDS	34 (2.3)	7 (6.2)	11 (2.0)	16 (2.0)
Upper GI	25 (1.7)	3 (2.7)	6 (1.1)	16 (2.0)
Head and neck	21 (1.4)	0 (0.0)	4 (0.7)	17 (2.1)
Sarcoma	19 (1.3)	3 (2.7)	8 (1.5)	8 (1.0)
Hepatobiliary system	18 (1.2)	1 (0.9)	6 (1.1)	11 (1.4)
Urinary tract	16 (1.1)	0 (0.0)	3 (0.5)	13 (1.6)
Skin and melanoma	12 (0.8)	0 (0.0)	0 (0.0)	12 (1.5)
Hodgkin lymphoma	11 (0.8)	4 (3.5)	3 (0.5)	4 (0.5)
Others	57 (3.9)	3 (2.7)	18 (3.3)	36 (4.5)

	Males			
		Age Group, No. (%)		
Cancer Site Diagnosis	All Patients, No. (%)	20-39	40-59	≥60
No. of patients	469	43	144	282
ATL	164 (35.0)	18 (41.9)	70 (48.6)	76 (27.0)
Non-Hodgkin lymphoma	83 (17.7)	6 (14.0)	18 (12.5)	59 (20.9)
Male genital organs	42 (9.0)	2 (4.7)	3 (2.1)	37 (13.1)
Upper GI	25 (5.3)	1 (2.3)	6 (4.2)	18 (6.4)
Leukemias, MDS	24 (5.1)	4 (9.3)	10 (6.9)	10 (3.5)
Lower GI	21 (4.5)	2 (4.7)	6 (4.2)	13 (4.6)
Sarcoma	18 (3.8)	4 (9.3)	6 (4.2)	8 (2.8)
Hodgkin lymphoma	16 (3.4)	3 (7.0)	4 (2.8)	9 (3.2)
Skin and melanoma	15 (3.2)	0 (0.0)	2 (1.4)	13 (4.6)
Head and neck	14 (3.0)	0 (0.0)	5 (3.5)	9 (3.2)
Urinary tract	12 (2.6)	0 (0.0)	3 (2.1)	9 (3.2)
Hepatobiliary system	8 (1.7)	1 (2.3)	3 (2.1)	4 (1.4)
Others	27 (5.8)	2 (4.7)	8 (5.6)	17 (6.0)

Abbreviations: ATL, adult T-cell leukemia/lymphoma; MDS, myelodysplastic syndrome.

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