Dichotomy in fatal outcomes in a large cohort of people living with HTLV in São Paulo, Brazil

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Short running title: Mortality among HTLV-1-infected in Brazil

Key Words: HTLV-1; Mortality; HAM/TSP; Brazil

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Abstract

BACKGROUND: Despite its relatively low incidence of associated diseases, HTLV-1 infection was reported to carry a significant risk of mortality in several endemic areas. HTLV-1-associated diseases, ATLL and HAM/TSP, as well as frequent co-infections with HIV, HCV and Strongyloides stercoralis were associated to increased morbidity and mortality of HTLV-1 infection. OBJECTIVE: To determine the mortality rate and its associated variables from an open cohort started in July 1997 at the HTLV Clinic, Emilio Ribas Institute (IIER), a major infectious disease hospital in São Paulo, Brazil. METHODS: Since inception up to September 2018, we admitted 975 HTLV-1-infected individuals, with a rate of 30-50 new admissions per year. All patient data, including clinical and laboratory data, were regularly updated throughout the 21-year period, using a dedicated REDCap database. The Ethical Board of IIER approved the protocol. RESULTS: During 21 years of clinical care to people living with HTLV-1 in the Sao Paulo region, we recruited 727 asymptomatic HTLV-1-infected individuals and 248 HAM/TSP patients, of which 632 remain under active follow-up. During a total of 3,800 person-years of follow-up (maximum follow-up 21.5 years, mean follow-up 6.0 years), 27 individuals died (median age of 51.5 years), of which 12 were asymptomatic, 1 ATL patient and 14 HAM/TSP patients. HAM/TSP diagnosis (but neither age nor gender) was a significant predictor of increased mortality by univariate and multivariate (HR 5.03, 95% CI [1.96-12.91], p=0.001) Cox regression models. Co-infection with HIV/HCV was an independent predictor of increased mortality (HR 15.08 95%CI [5.50-41.32], p<0.001), with AIDS-related infections as a more frequent cause of death in asymptomatic (6/13, p=0.033). HIV/HCV-negative fatal HAM/TSP cases were all female, with urinary tract infection and decubitus ulcer-associated sepsis as the main cause of death (8/14, p=0.002). CONCLUSIONS: Our data confirm high mortality in people living with HTLV-1, both in asymptomatic (2.9%) and HAM/TSP patients (7.3%). We observe a dichotomy in fatal cases, with HAM/TSP and HIV/HCV co-infection as independent risk factors for death. Our findings reveal an urgent need for public health actions, as the major causes of death, infections secondary to decubitus ulcers and AIDS-related infections, can be targeted by preventive measures.
BACKGROUND

Human T-cell Leukemia Virus-1 (HTLV-1), the first human retrovirus discovered, is the causative agent of adult T-cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy (HAM/TSP) [1,2][1], with approximately 5-10 million people infected worldwide, almost one million of them in Brazil [3]. The number of infected people may be higher, considering that only 2/3 of the world has been mapped for HTLV-1 infection [3]. After the adoption of mandatory national blood screening tests in 1993 and the observed behavioral change from intravenous to inhalation drug abuse, parental exposure to HTLV dropped [4-6]. However, our group has documented rates of 40 percent of sexual transmission [7] and of 13 percent of vertical transmission [8,9].

The incidence of ATLL and HAM/TSP varies from 0.5% to 10% among HTLV-1 infected subjects, increasing morbidity and mortality rates [10-13]. Also, treatment of co-infections, such as HIV and HCV, can be delayed due to HTLV-1 promoting an inefficacious increase in TCD4+ cells, leading to a delay in antiretroviral therapy (ART) initiation and, possibly, inefficacious HCV clearance [14-17]. In endemic countries, parasitic co-infection with Strongyloides stercoralis also increases morbidity and mortality[16].

Previous studies in Japan, French Guiana, Australia, West-Africa and the US observed variable mortality risks among HTLV-1-infected cohorts[18-22]. Despite the large variability among these populations, all studies reported that HTLV-1 by itself increased the risk for increased mortality [20,21], although confounding factors should be taken into account [11]. A recent systematic review and meta-analysis confirmed a significantly increased risk (RR 1.57) for mortality in people living with HLTV-1 [23]. Here, we report data spanning more than six years of follow-up of a cohort of people living with HTLV-1 from a single tertiary Brazilian center, regarding mortality and related risk factors.

METHODS

Population

We retrospectively reviewed medical records from the HTLV-1 cohort from the outpatient clinic of “Instituto de Infectologia Emílio Ribas” (IIER), Sao Paulo city, Brazil. IIER is a public tertiary infectious disease reference hospital with an HTLV-1 outpatient service since 1997, with new patients added at a rate of approximately 30-50 patients/year[24]. The included patients were at least 18 years old and had to be tested positive to HTLV-1 through third generation EIA (Murex I/II, Abbott Murex Diagnostic, Dartford, UK), confirmed by Western-blot (Genelabs, US) and/or polymerase chain reaction (PCR) [25]. Patients with incomplete data and/or lost to follow up were excluded for this analysis.
Clinical Follow-Up

All individuals were evaluated by neurologist/infectious diseases specialists at least once in the twelve months previous to the start of data collection for this study (September 2018). Clinical variables concerning neurological, dermatological, ophthalmological, rheumatologic, urological and buccal aspects were stored in a previously validated electronic database using RedCap® [26]. People living with HTLV-1 were classified at recruitment as asymptomatic or HAM/TSP, according to the diagnostic criteria proposed by Castro-Costa et al. [27]. HAM/TSP severity was assessed by Osame motor disability scale (OMDS)[28]. The time frame for data collection was from July 1997 to December 2018.

Statistical analysis

Statistical analysis was conducted using Mann-Whitney test for nonparametric data, and Chi-square or Fisher exact test for proportions. Univariate and multivariate Cox proportional hazard analysis was performed to identify independent variables associated with the risk of death, with Wald test for hazard ratio (HR) beta coefficient. For survival analysis, the Kaplan-Meier method was used to compare the probability of survival and the median survival time, and the log-rank test to compare survival curves. Death rate was expressed in 1000 persons-year; time was measured since the start of follow-up until death. Survival analysis was performed using SPSS 21 (Statistical Package for the Social Sciences-21. Statistical Software. IBM, US).

Ethical Issues

The study was approved by IIER’s ethical board under the protocol 86806218.9.0000.0061. Signed informed consent was obtained from all participants prior to study inclusion. This study follows the principles of the Declaration of Helsinki.

RESULTS

Study Population

From July 1997 to December 2018, a total of 727 individuals diagnosed with HTLV-1 infection were recruited and classified as asymptomatic (n=479) or HAM/TSP (n=248) following complete neurological examination [27]. This is an open cohort, with new patients added at a rate of approximately 30-50 per year, also including patients with HIV and/or HCV co-infections. A total of 38 asymptomatic (7.9%) and 57 HAM/TSP cases (23.0%) were excluded from analysis due to loss of follow up, i.e. no reported visit in the last 24 months. Thus, the total cohort for the current analysis was comprised of 632 subjects (Figure 1).
We classified the cohort according to initial diagnosis at recruitment, either “HAM/TSP” or “no HAM/TSP” (Figure 1). During follow-up, two HTLV-1-infected individuals originally diagnosed as “asymptomatic” developed ATL, one of which died. Although we previously described a subset (42 of 175) of asymptomatics in the cohort which developed an “intermediate syndrome” [29], overlapping with “probable HAM/TSP” according to Castro-Costa criteria, none of these individuals originally diagnosed as “asymptomatic” progressed to clinically definite HAM/TSP and none of them died. Table 1 shows the general characteristics of the deceased individuals from the cohort, as well as the potential risk factors for mortality, including co-infection with HCV and/or HIV. The overall mortality rate was 0.7 per 100 person-years. During a total of 3,800 person-years of follow-up (mean follow-up six years), we observed 27 fatal cases (4.3%), of which thirteen were asymptomatic (2.9%) and fourteen (7.3%) were HAM/TSP patients.

The overall mean age of death was 52.0 years, which was not significantly different between cases with (54.6 years, range 38-78) and without (49.4 years, range 40-68) HAM/TSP diagnosis (Table 1, p=0.23). We observed an overall 0.8:1 female/male ratio among all fatal cases, but an increased 2:1 female ratio for the fatal HAM/TSP cases, although this difference was not statistically significant (Table 1, p=0.17). The main causes of death were infectious, predominated by sepsis and urinary tract infections (UTI) in the whole cohort, as well as among those without HAM/TSP diagnosis. However, the main cause of death among HAM/TSP patients was decubitus pressure ulcers (8/14, 57.1%), which was absent in asymptomatic fatal cases (Table 1, p=0.002). On the other hand, among the HIV/HCV co-infected individuals, the main causes of death (6/13, 46.2%) were sepsis and AIDS-related infections (cryptococcal meningitis and Toxoplasmosis encephalitis), the latter being significantly higher (p=0.033) among fatal cases without HAM/TSP (Table 1). Of the three fatal cases with neoplasia in the cohort, two were linked to oncogenic viruses: one female ATL patient and one male patient (HCV-positive) with hepatocarcinoma.

Survival analysis and Cox proportional hazard analysis

As evident from Kaplan-Meier curves (Fig. 2), the estimated survival time was significantly lower for fatal cases with HAM/TSP diagnosis at recruitment (median survival 16 years) vs. those without HAM/TSP diagnosis (19 years, p=0.038, log-rank test).

Of note, neither age (HR 1.59, 95% CI 0.73-3.45, p=0.24) nor gender (HR 1.93 95% CI 0.91-4.13, p=0.089 Wald test) were significantly associated to risk of death by univariate Cox regression.
analysis (Table 2). However, HAM/TSP diagnosis (HR 2.19 95% CI 1.02-4.68, p=0.043), HCV infection (HR 5.19 95%CI 2.44-11.07, p<0.001), HIV infection (HR 5.12 95%CI 2.39-10.96, p<0.001) and HCV+HIV co-infection (HR 7.48 95%CI 3.46-16.16, p<0.001) were identified as significant predictors of increased mortality by univariate Cox regression (Table 2).

In multivariate Cox regression models (Table 3), gender was retained but was not found to be an independent predictor (HR 1.16 95% CI 0.51-2.64, p=0.13). However, both HAM//TSP diagnosis (HR 5.03, 95% CI [1.96-12.91], p=0.001) and co-infection with HIV+HCV (HR 15.08 95%CI [5.50-41.32], p<0.001) were identified as independent predictors of the risk of death in our cohort (Table 3).

**DISCUSSION**

This open cohort currently has over two decades of continuous follow-up, making it one of the longest running cohorts worldwide to study the clinical outcomes of HTLV-1 infection. During the submission of this manuscript, a systematic review and meta-analysis was published, demonstrating a significantly increased risk (RR 1.57) for mortality in people living with HTLV-1 [23]. Although our cohort recruitment strategy did not include a control group without HTLV-1 infection, our study confirms high mortality (4.7%) and a young age at death (52 years) for HTLV-1-infected individuals.

Several factors might help explain shortened survival among people living with HTLV-1, such as immune senescence and telomere exhaustion triggered during the chronic infection [30]. In addition, lifestyle, socio-economic conditions, and psychological factors may have an additional influence on these outcomes [31]. Surprisingly, neither age nor gender, the major factors determining survival in the general population as well as most in most cohort studies of people living with HTLV-1 [11,18,20-22,32,33], significantly predicted mortality in either univariate or multivariate Cox regression models in our cohort. Comparable to other HTLV-1 cohorts and a recent meta-analysis [23], neoplasia without viral etiology was infrequent among our fatal cases (one lung carcinoma), while two cases could be linked to oncogenic viruses (one ATL case and one HCV-positive hepatocarcinoma). However, we identified HAM/TSP diagnosis at recruitment and HIV/HCV co-infection as risk factors for premature death in our cohort.

To our knowledge, this is the first large cohort study describing HAM/TSP as a major and independent risk factor for mortality among people living with HTLV-1. Moreover, the major causes of death among HAM/TSP patients in our Brazilian cohort differ from those described previously in
HAM/TSP cohorts in the UK (n=48) and Martinique (n=123), both with a similar long-term follow-up [10,34]. This might be due in part to different definitions of death related to HAM/TSP, namely “pneumonia with respiratory failure, and severe HAM with disseminated inflammation” [34] and “bedridden patients who developed sepsis, pneumonia, nephritis, or pulmonary embolism” [10]. While pneumonia and respiratory disease were not found among fatal cases in our cohort, sepsis occurred at a frequency similar to the Martinique HAM/TSP cohort but did not differ between fatal cases with or without HAM/TSP (Table 1).

In contrast, we identified decubitus pressure ulcers, in the absence or presence of (secondary) sepsis, as a major cause of death in HAM/TSP patients. Pressure ulcers and urinary tract infections (UTIs) are frequent, recurrent, and lifelong for patients with neurological impairment [35,36]. A high prevalence of pressure ulcers, especially in those suffering from chronic diseases, has previously been associated to immobility and/or spasticity [36-39]. Hence, the level of disability might be a possible predictor of mortality, since most (78.6%) of the fatal HAM/TSP cases presented with OMDS over five points (data not shown). Our study provides new insight into the long-term care of people living with HTLV-1, and HAM/TSP patients in particular. Considering the importance of UTI and decubitus ulcers in fatal cases, home visits by a dedicated ‘home care team’, as happened infrequently in this cohort, should be reinforced. Thus, more emphasis should be given to nursing and rehabilitation to prevent UTI and decubitus wounds, especially for HAM/TSP patients with increased disability (OMDS >5).

In addition, HIV/HCV co-infection was identified as a second, independent predictor of mortality among people living with HTLV-1. Notably, a large proportion of these fatal cases were due to AIDS-related infectious complications (cryptococcal meningitis and Toxoplasmosis encephalitis), in spite of free access to antiretroviral therapy (ART) in Brazil for over two decades. HTLV-1/HIV co-infected individuals in our cohort displayed fourfold higher mortality rates (2.6 per 100 person-years) as compared to recent data from an HIV cohort also located in metropolitan Sao Paulo (0.6 per 100 person-years [40]. These mortality rates are strikingly similar to a recent publication comparing HTLV-1/HIV co-infected patients (3.0 per 100 person-years) with HIV mono-infected patients (1.3 per 100 person-years) in Salvador-Bahia, Northeast Brazil [17]. However, Brites et al. demonstrated that the decreased survival observed in HTLV-1/HIV co-infected patients was normalized in those with early and successful ART [17].

We acknowledge several limitations in our study, most of which are inherent to the long period of follow-up (>20 years) and the low socio-economic conditions of our population. First, eight percent of asymptomatics and 23% of HAM/TSP patients were lost to follow-up, despite our efforts
to trace them in the community. However, if we use the 95% CI to extrapolate the 2.9% (95% CI 1.6-4.8%) mortality in individuals without HAM/TSP and the 7.3% (95% CI 4.1%-12.0%) mortality in HAM/TSP patients, we can assume another 1-2 and 2-7 fatal cases might have been missed among individuals without and with HAM/TSP, respectively. Although we cannot exclude the possibility that these missing cases might have migrated to another state or region in Brazil, this is highly unlikely for the HAM/TSP cases, considering their limited mobility and low socio-economic conditions. Second, we do not have data on other important risk factors for mortality, such as smoking, alcohol consumption and BMI (body mass index).

However, these factors are more strongly associated to the major causes of death in the general population, namely cardiovascular disease, cancer and respiratory diseases, which were not among the major causes of death in our cohort. However, a recent study found increased HIV-related mortality associated with lower BMI [41], so this might represent a possible confounding factor in the minor subset (15% of our cohort) HIV co-infected individuals which are over-represented among fatal cases (55%). Third, low income and living outside the large Metropolitan area of São Paulo (the largest city in the Southern hemisphere with an estimated 12 million inhabitants), poses a major hurdle for people living with HTLV-1, and HAM/TSP patients in particular, to comply with yearly visits and hence may influence our results through increased loss of follow-up. The profound economic crisis in Brazil over the last five years might have aggravated this [42], for example, the unemployment rate rose from seven percent in 2014 to 13% of the working population in 2017 [43]. Fourth, we do not have data on adherence to antiretroviral therapy (ART) among HIV-co-infected individuals in our cohort.

Although all HIV-infected individuals are offered ART as standard-of-care without any cost, as part of Brazil’s public health policy, the high percentage of AIDS-related deaths in our cohort point at low adherence and/or delayed treatment initiation. Collectively, this study reveals the urgent need for public health measures targeted at preventing premature death in people living with HTLV-1. For HAM/TSP patients, both a high loss to follow-up (23%) and UTI or pressure ulcer-related fatal infections indicate the dire need for targeted home interventions. For HTLV-1/HIV co-infected individuals, early access to ART and strategies to increase treatment adherence should be prioritized. In both cases, low socio-economic status continues as a major hurdle to reduce morbidity and mortality among people living with HTLV-1, reinforcing the need for its recognition as a neglected disease [34]. In conclusion, this study underscores high mortality among people living with HTLV-1 in Sao Paulo, Brazil, and identifies HAM/TSP diagnosis and HIV/HCV co-infection as independent risk factors for death.
Acknowledgments

We would like to thank all the interns of the IIER Neurology program, the patients and their relatives for their participation. Funding was obtained from Fapesp (Grant to JC), CNPq (Scholarship to JC), FFM (support to JC), KU Leuven (“Vaast Leysen Leerstoel voor Infectieziekten in Ontwikkelingslanden”, Grant to JVW).

FIGURE LEGENDS:

Figure 1: Description of the outcomes of the cohort of people living with HTLV-1 in São Paulo city, Brazil.

“No HAM/TSP” includes all HTLV-1-infected individuals classified as “asymptomatic” during complete neurological examination at recruitment, two of which later developed ATL during follow-up (one fatal case). §Missing cases are those who did not visit the clinic in the last two years and those without complete clinical records.

Figure 2: Estimated survival time, according to clinical diagnosis at recruitment (HAM/TSP or asymptomatic)

REFERENCES


23. Schierhout, G.; McGregor, S.; Gessain, A.; Einsiedel, L.; Martinello, M.; Kaldor, J. Association between HTLV-1 infection and adverse health outcomes: a systematic review and meta-


Figure 1: Description of the outcomes of the cohort of people living with HTLV-1 in São Paulo city, Brazil.

“HAM/TSP” and “No HAM/TSP” indicate HTLV-1-infected individuals diagnosed with HAM/TSP at recruitment, or classified as “asymptomatic” during complete neurological examination at recruitment, two of which developed ATL during follow-up (one fatal case). §Missing cases are those who did not visit the clinic in the last two years and those without complete clinical records.
Figure 2: Estimated survival time, according to clinical diagnosis at recruitment (HAM/TSP or asymptomatic)

Kaplan Meier survival curve

Estimated survival

Years after first HTLV-1 positive serology

p=0.038 (Log Rank test)
Table 1. Risk factors for mortality in the HTLV-1 cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>HTLV-1 N (%) (n=27)</th>
<th>Asymptomatic N(%) (n=13)</th>
<th>HAM/TSP N(%) (n=14)</th>
<th>OR</th>
<th>CI 95%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>52.2 (10.5)</td>
<td>49.4 (9.2)</td>
<td>54.6</td>
<td>0.231*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>51.5</td>
<td>47</td>
<td>54.5</td>
<td>0.291*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male</td>
<td>15 (55.6)</td>
<td>9 (69.2)</td>
<td>6 (42.9)</td>
<td>2.667</td>
<td>0.973-</td>
<td>0.168*</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>12 (44.4)</td>
<td>4 (30.8)</td>
<td>8 (57.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Co-infected</strong></td>
<td>HIV</td>
<td>4 (14.8)</td>
<td>2 (15.4)</td>
<td>2 (14.3)</td>
<td>1.543</td>
<td>0.943-</td>
<td>0.389*</td>
</tr>
<tr>
<td></td>
<td>HCV</td>
<td>4 (14.8)</td>
<td>1 (7.7)</td>
<td>3 (21.4)</td>
<td>2.087</td>
<td>0.936-</td>
<td>0.315*</td>
</tr>
<tr>
<td></td>
<td>HCV/HIV</td>
<td>11 (40.7)</td>
<td>9 (69.2)</td>
<td>2 (14.3)</td>
<td>2.521</td>
<td>1.141-</td>
<td>0.003*</td>
</tr>
<tr>
<td><strong>Cause of death</strong>*</td>
<td>Neoplasia§§</td>
<td>3 (11.1)</td>
<td>2 (15.4)</td>
<td>1 (7.1)</td>
<td>1.625</td>
<td>0.315-</td>
<td>0.596*</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>10 (37.0)</td>
<td>6 (46.2)</td>
<td>4 (28.6)</td>
<td>1.471</td>
<td>0.624-</td>
<td>0.440*</td>
</tr>
<tr>
<td></td>
<td>Decubitus Ulcers</td>
<td>8 (29.6)</td>
<td>------</td>
<td>8 (57.1)</td>
<td>1.543</td>
<td>0.943-</td>
<td>0.389*</td>
</tr>
<tr>
<td></td>
<td>Urinary Tract Infection</td>
<td>10 (37.0)</td>
<td>4 (30.8)</td>
<td>7 (50.0)</td>
<td>1.688</td>
<td>0.548-</td>
<td>0.236*</td>
</tr>
<tr>
<td></td>
<td>AIDS-related§</td>
<td>7 (25.9)</td>
<td>6 (46.2)</td>
<td>1 (7.1)</td>
<td>4.550</td>
<td>0.721-</td>
<td>0.033*</td>
</tr>
</tbody>
</table>

* Mann-Whitney test/ Median test  ** Fisher test  *** Patients may have more than one cause of death diagnosis in their medical record.; §§ Neoplasia: one case was ATLL, one case hepatocarcinoma and one case lung cancer; §Cryptococcal meningitis/ Toxoplasmosis Encephalitis
Table 2. Univariate Cox proportional hazard analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Survivors N (%) (n=605)</th>
<th>Fatal cases N (%) (n=27)</th>
<th>HR</th>
<th>CI 95%</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≤ 52 (mean)</td>
<td>51.9 (13.8)</td>
<td>52.2 (10.5)</td>
<td>1.307</td>
<td>0.597-2.859</td>
<td>0.503</td>
</tr>
<tr>
<td></td>
<td>≤ 53 (median)</td>
<td>53</td>
<td>51.5</td>
<td>1.589</td>
<td>0.731-3.454</td>
<td>0.242</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>233 (38.5)</td>
<td>15 (55.6)</td>
<td>1.933</td>
<td>0.905-4.130</td>
<td>0.089</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>372 (61.5)</td>
<td>12 (44.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-infection</td>
<td>HCV</td>
<td>67 (11.1)</td>
<td>4 (14.8)</td>
<td>5.194</td>
<td>2.438-11.065</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
<td>80 (13.2)</td>
<td>4 (14.8)</td>
<td>5.117</td>
<td>2.388-10.963</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td></td>
<td>HCV/HIV</td>
<td>26 (4.3)</td>
<td>11 (40.7)</td>
<td>7.476</td>
<td>3.458-16.161</td>
<td>1</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>HAM/TS P</td>
<td>177 (29.3)</td>
<td>14 (51.9)</td>
<td>2.188</td>
<td>1.023-4.678</td>
<td>0.043</td>
</tr>
</tbody>
</table>

<sup>a</sup> Wald test
Table 3. Multivariate Cox proportional hazard analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-infection</td>
<td>HCV/HIV</td>
<td>15.076</td>
<td>5.501-41.318</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>HAM/TSP</td>
<td>5.030</td>
<td>1.959-12.911</td>
<td>0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>1.161</td>
<td>0.510-2.643</td>
<td>0.129</td>
</tr>
</tbody>
</table>

*Wald test*