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Seroprevalence of Human T-cell Lymphotropic Virus Types I/II Among Blood Donors in a Tertiary Hospital in Oman

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ABSTRACT

Objectives: Routine blood donor screening of human T-cell lymphotropic virus (HTLV) has been practiced in Oman since 2017. Limited data exists on HTLV seroprevalence among Omanis. This study aims to determine the seroprevalence of HTLV-I/II among blood donors attending a hospital-based blood bank to assess the need for a universal versus targeted screening. ***Methods***: We conducted a retrospective review of blood donors' results attending a hospital blood bank between January 2017 and February 2020. Blood samples were screened for HTLV-I/II antibodies using ARCHITECT i2000SR. Reactive samples underwent further testing by immunoblot assay (MP Diagnostics HTLV Blot 2.4). Age, gender, and nationality were assessed. All components manufactured at the blood bank undergo leukoreduction before storage. ***Results:*** A total of 24 469 first-time blood donors were screened for HTLV antibodies. Most participants were male (n = 22 186, 90.7%), and the majority were Omani (n = 22 711, 92.8%). The age range was 18 to 64 years, with a median of 32 years. The seroreactivity rate was 0.2% (43; 95% CI: 0.12–0.23). Confirmatory testing by immunoblot revealed three indeterminate results (7.9%), of which two were Omani and one non-Omani donor, and the remaining 40 seroreactive donors tested negative. ***Conclusions:*** Our study revealed zero seroprevalence of confirmed HTLV among blood donors. The continuation of universal screening for first-time donors is a standard of care. With universal leukoreduction at Sultan Qaboos University Hospital and a very low risk of HTLV in Oman's population, the need for screening regular donors can be reconsidered if these findings are confirmed on a larger scale involving other blood banks in Oman.

Human T-cell lymphotropic virus (HTLV), discovered in 1979, is the first human retrovirus belonging to the Retroviridae family.[1] The most prevalent and pathogenic HTLV types are types 1 and 2, while limited information is known about the recently discovered types 3 and 4, found in a few cases in Africa.[2] HTLV type 1 (HTLV-I) was initially identified in an American patient with cutaneous T-cell lymphoma, while HTLV type 2 (HTLV-II) was isolated two years later from a patient with variant T-cell hairy cell leukemia.[3] These viruses differ in their epidemiology and disease profiles. The most serious clinical diseases associated with HTLV-I include adult T-cell leukemia/lymphoma (ATLL) and HTLV-I-associated myelopathy (HAM).[1] Furthermore, HTLV-I has been linked to other diseases such as infective dermatitis, uveitis, and polymyositis.[1,4]

The interaction between HTLV-I and the host immune response plays a crucial role in the pathogenesis of HTLV-I-associated diseases. The virus affects the toll-like receptor-4 signaling pathway,[5] which is important for the host's innate response against bacterial infections.[6] It also triggers the secretion of interleukin-10, promoting cell proliferation in HTLV-I-infected cells through the signal transducer and activator of transcription 3 and interferon regulatory factor 4 pathways.[7] Transforming growth factor beta 1, another significant T-helper 3 immune suppressor cytokine, facilitates B-cell, and T-helper cell interaction.[8]

The programmed death 1 and programmed death ligand 1 pathway, responsible for inducing apoptosis,

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is overexpressed in HTLV-I specific CD8+ T-cells,[9] leading to T-cell exhaustion, chronic viral infection, and therapeutic failures.[10] HTLV-I-infected patients are more susceptible to tuberculosis, particularly in endemic areas, due to a dysregulated immune system response.[11] Moreover, HTLV-I infection exacerbates the clinical course of hepatitis C virus infection, contributing to the development of hepatocellular carcinoma.[12]

Globally, approximately 5–10 million individuals are infected with HTLV-I.[13] It is widespread in areas such as southwestern Japan,[2] Taiwan,[13] Sub-Saharan African countries,[3] the Caribbean basin, and South America.[2] In these regions, seroprevalence is high, reaching up to 14% of the tested population.[3,14] In endemic areas, the rate of seropositivity increases with age and can reach as high as 30–40% in individuals > 50 years old.[1] HTLV-I is also endemic in certain regions in the Middle East and India.[15] The prevalence of HTLV-I varies across different regions in Iran, ranging from 0–2.3%.[13] In Pakistan, the prevalence rate of HTLV-I among blood donors is 0.19%, while in Turkey, it is 0.0021%.[5] Saudi Arabia's studies have shown prevalence rates ranging from 0–0.006%.[2,16]

Compared to HTLV-I, HTLV-II has a more limited geographical distribution. It is endemic in Europe and North America, particularly among intravenous drug users.[1] While less pathogenic than HTLV-I, it has been linked to chronic pulmonary diseases and neurological disorders.[1] Both HTLV-I and II are transmitted through various routes, including sexual transmission, vertical transmission, breastfeeding, and parenteral transmission through transfusion or sharing infected needles.[17] In endemic areas, the seroconversion likelihood for a blood recipient who receives a contaminated blood product with HTLV-I is 40–60% within 60 days after transfusion.[5]

Transfusion is a major route of HTLV-I transmission, even in non-endemic areas. Due to the high rate of seroconversion following transfusion of contaminated blood products, especially in endemic areas, the risk of transmissible HTLV infection by blood donors is a concern. According to the World Health Organization (WHO) recommendations, HTLV I/II screening should be considered before releasing blood units.[18] The WHO advises screening blood donors for HTLV-I based on each country's epidemiological evidence. Additionally, non-endemic areas can receive migrants from HTLV-endemic regions who might pose a risk of HTLV transmission via blood transfusion.

Several endemic countries have implemented donor screening for HTLV, with Japan introducing this protocol in 1986, followed by the US and the French Caribbean in 1989.[19] Practices vary in other regions including Europe and the Middle East. For instance, Iran started the screening program in 1994, while other Gulf countries like Saudi Arabia are reviewing the necessity of stopping mandatory universal blood screening for HTLV infection due to the very low prevalence according to their studies.[3] To the best of our knowledge, only one has assessed HTLV seroprevalence in Oman. Conducted in 1997, the study showed an HTLV seroprevalence of 0.6% among blood donors (9 out of 1586) using enzyme immunoassay, with six out of nine tested reactive results being indeterminate by screening (0.4%).[20] However, the sample size was small, and the methodology used was not detailed. No other studies have been published since then.

This study sought to determine the seroprevalence of HTLV-I/II among blood donors attending the Sultan Qaboos University Hospital (SQUH) Blood Bank, evaluating the need for universal versus targeted screening of blood donors in Oman.

METHODS

This is a retrospective cross-sectional study that evaluated HTLV-I/II serological results of blood donors who donated blood at the SQUH Blood Bank. The SQUH blood bank, located in a tertiary care reference university hospital in Muscat, is an independent facility responsible for donor collection, screening, testing, and blood component manufacturing. All cellular blood components undergo leukoreduction. Donor HTLV screening was introduced at SQUH in January 2017. Records of all donors who donated blood between January 2017 and February 2020 were reviewed. Data were extracted from the hospital information system. The assessed variables included donor demographics (gender, age, nationality, and place of residency), results of HTLV-I/II screening, and any confirmatory test done.

Donor blood samples underwent HTLV-I/II antibodies using Chemiluminescent Microparticle Immunoassay (CMIA, ARCHITECT i2000SR, Abbott Diagnostics, U.S) following the manufacturer's

instructions. The sensitivity and specificity tests are 100% and ≥ 99.5%, respectively. Blood samples were considered reactive for HTLV-I/II antibodies if the signal/cutoff (S/CO) ratio was ≥ 1.0. Initial reactive samples were duplicated and retested using the same assay. Repeat reactive samples were subject to confirmation testing using HTLV- I/II Immunoblot assay (MP Diagnostics HTLV Blot 2.4, MP Biomedicals Asia Pacific Pte. Ltd), and interpretation was based on the manufacturer's instructions. The diagnosis of HTLV infection was established when both CMIA and immunoblot testing yielded reactive results. In cases of reactive HTLV screening test, donors were temporarily deferred from donation until confirmatory test results were available. Donors with confirmed positive or indeterminate results were referred to the infectious diseases team for counseling and further management.

A minimum calculated sample size of approximately 23 000 blood donors was required. The sample size calculation was based on the following assumptions: the previous local prevalence of HTLV-I in Oman (0.6%),[20] a precision of 0.1% and a confidence level of 95%. Seroprevalence data were derived from all blood donor test results. Statistical analysis was performed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Categorized variables were described as percentages. Prevalence was calculated as a percentage with 95% CI.

Ethical approval was obtained from the Medical Research Ethics Committee at the College of Medicine and Health Sciences, Sultan Qaboos University (MREC#1786).

RESULTS

A total of 24 469 first-time blood donors were included in the study. The age range of the donors was between 18 and 64 years with a median age of 32 years. The majority of the donors were males (22 186; 90.7%) and Omani (22 718; 92.8%). The demographic characteristics of the blood donors are summarized in Table 1.

Out of the 24 469 screened blood donors, 43 were repeatedly reactive for HTLV by CMIA (0.2%; 95% CI: 0.12–0.23). The S/CO ratio of reactive samples ranged from 1.00 to 34.50, with a median of 1.9 [Table 2]. The majority of seroreactive donors were male (39; 90.7%). The age range was between 19 and 48 years with a median of 27 years. Most of these donors were Omani (n = 39; 90.7%) while four were non-Omani (9.3%) [Table 2].

Table 1: Demographic characteristics of the blood donors.

Variables	Number	Percentage
Gender		
Male	22 186	90.7
Female	2282	9.3
Age group, years		
18–20	2794	11.4
21–30	11 107	45.4
31–40	7569	30.9
41–50	2564	10.5
> 50	436	1.8
Nationality		
Omani	22 718	92.8
Non-Omani	1751	7.2

Table 2: Demographic characteristics of human T-cell lymphotropic virus-I/II seroreactive blood donors.

Variables	Number	Percentage
Gender		
Male	39	90.7
Female	4	9.3
Age group, years		
19–25	19	44.2
26–35	18	41.9
36–48	6	14.0
Nationality		
Omani	39	90.7
Non-Omani	4	9.3

Repeatedly reactive samples underwent further testing using an immunoblot confirmatory assay. Out of the 43 reactive screening samples, 40 (93.0%) were negative, and three (7.0%) were indeterminate by immunoblot [Table 3]. The indeterminate group consisted of one Omani male, one Omani female, and one non-Omani male donor. Two indeterminate profiles showed only one envelope band (GD21/rgp46-II) and one showed two envelope bands (GD21 and rgp46-II) with CMIA S/CO ratios of 1.09, 1.55, and 2.33, respectively. Considering the absence of confirmed HTLV I/II infection in this cohort, the overall HTLV-I/II virus seroprevalence was 0.0% among all donors.

Table 3: Human T-cell lymphotropic virus (HTLV-I/II) screening and immunoblot results.

HTLV-I/II Screening		HTLV-I/II Western blot		
Signal-to-cutoff value	Number	Positive	Indeterminate	Negative
1–5	38	-	3	35
5–10	3	-	-	3
> 10	2	-	-	2

DISCUSSION

This study represents the largest assessment of HTLV-I/II infection seroprevalence among blood donors in Oman. The results showed a seroprevalence of confirmed HTLV-I/II infection at 0.0%. None of the seroreactive Omani blood donors on initial screening were confirmed positive by the immunoblot except for the three indeterminate results. Factors such as cross-reactivity to other retroviruses, defective HTLV-I/II, antibody reaction to *Plasmodium falciparum,* or delayed seroconversion could contribute to these indeterminate results.[21] Molecular testing using polymerase chain reaction is required to clarify these indeterminate results and confirm the presence of HTLV I/II. However, this test was unavailable in our study center.

In contrast to the previously reported data by Knox-Macaulay et al,[20] from 1997, which indicated an HTLV-I seropositivity of 0.6% (9 out of 1586) by enzyme immunoassay and 0.4% (6 indeterminate results out of 9) by immunoblot, none of these cases were confirmed as positive. The difference in reactivity rates could be attributed to the variation in sample size between the two studies and the substantial improvement in the overall performance of current screening and confirmatory assays compared to those used in the past. The reactivity rate of CMIA screening at 0.2% might also result from the high sensitivity of the kit used in this study, potentially leading to false-positive outcomes.

In general, many studies conducted in the Arabian Peninsula reported very low or zero seroprevalence rates of HTLV-I/II infection. In several studies involving blood donors to determine HTLV-I/II seroprevalence, the seroreactive group was predominantly male due to a higher proportion of male donors compared to females in these studies.[2,3,5,8,15] Saudi Arabia, for example, extensively studied HTLV-I/II prevalence among blood donors.[2,3,16,22] A study involving 107 419 blood donors revealed a CMIA reactivity of 0.088%, with no confirmations by immunoblot.[3] Similarly, several reports from different tertiary hospitals in Saudi Arabia demonstrated a zero prevalence of HTLV-I/II,[2,22] consistent with our study findings. On the other hand, a study in Kuwait involving 46 039 volunteer blood donors indicated an overall HTLV-I positive donation frequency of 1:7212 among Kuwaiti nationals and 1:1500 among Indians, supporting the mandatory screening of donated blood for HTLV-I. Notably, one Omani male in this study tested positive for HTLV-I by Western blot out of 21 other positive donors.[23]

HTLV-I infection is endemic in northeastern Iran, particularly in Mashhad, where the population prevalence is 2.12%.[24] A study that evaluated 1 864 489 blood donations from seven Iranian blood transfusion centers over five years revealed an overall HTLV-I prevalence of 0.098% with a descending trend over the years.[13] This decline was attributed to an improved donor selection process and the permanent deferral of previously seropositive donors from donating blood.[13] The seroprevalence of HTLV-I/II among blood donors in Lebanon and Turkey was reported to be 0.028% and 0%, respectively.[25,26] No publications on the prevalence rate of HTLV-I/II could be found in other countries in the region.

However, our study has some limitations. It was conducted in a single center where blood donors mainly come from the Muscat Governorate. Therefore, potential differences in seroprevalence among donors from different regions in the country could not be assessed. Additionally, the ethnicity of the non-Omani donors in our study cohort was not assessed. We employed a convenient and healthy population to study the prevalence rate of viral infection, which could introduce selection bias and might not fully reflect the actual prevalence in the general population, including other high-risk groups. Nevertheless, this study is the largest to assess the seroprevalence of HTLV-I/II among Omani donors. To determine a precise seroprevalence of HTLV-I/II in Oman, a large

multi-center study involving other blood banks across the country is necessary. Moreover, a confirmatory assay such as polymerase chain reaction for proviral DNA is needed to confirm the significance of the indeterminate results.

CONCLUSION

Our study has revealed a seroprevalence of confirmed HTLV-I/II infection of zero among blood donors in our center. This suggests that HTLV might not pose a significant public health concern in Oman. However, it is crucial to continue the universal screening of first-time donors as a standard of care. Additionally, monitoring HTLV seroprevalence is important, as it can change over time. Given the presence of universal leukoreduction at SQUH and the very low risk of HTLV in Oman's population, consideration might be given to discontinuing the screening of regular donors after confirming our findings on a larger scale involving other blood banks in different regions of Oman.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

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