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Original Article

Prevalence of Hepatitis B, Hepatitis C, and HIV in Multiply Transfused Sickle Cell Disease Patients from Oman

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Abstract. ***Background*: In Oman, the prevalence of hepatitis B (HBV) infection is 5.8%, with 2.8–7.1% HBV carriers. Hepatitis C (HCV) prevalence among Omanis is 0.41%. A total of 2917 human immunodeficiency virus (HIV) infections were notified among Omanis by 2017. This study was performed as there was no data on the prevalence of HIV, HBV and HCV in sickle cell disease (SCD) patients from Oman.**
Study Design and Methods: **In this retrospective, cross-sectional study, medical records of all SCD patients who attended our hospital between 2011 to 2017 were retrieved from the hospital information system. Following approval by the local medical research and ethics committee, data on HIV, HBV, and HCV exposure were recorded to estimate the prevalence.**
Results: **Among a total of 1000 SCD patients (491 males and 509 females), twenty-three (2.3%) patients showed positive serology for hepatitis B surface antigen (HbsAg), of whom sixteen (1.6%) were HBV DNA positive. 126 (12.6%) had anti-HCV antibodies (anti-HCV), of whom fifty-two (5.2%) were HCV RNA positive. None of the patients had positive serology for HIV. A normal liver was observed on abdominal ultrasound in 788 (78.8%) patients, whereas 208 (20.8%) had hepatomegaly, and 4 (0.4%) had liver cirrhosis. Thirty-six (3.6%) patients died, but in only two patients, the mortality was due to cirrhosis of liver.**
Conclusions: **This study provides the first comprehensive data on the prevalence of HBV and HCV infections among Omani SCD patients exposed to blood transfusions. Reassuringly, no case with HIV was observed.**

Keywords: Prevalence; Hepatitis; HBV; HCV; HIV; Infection.

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Introduction. Sickle-cell disease (SCD) is a monogenic disorder characterized by a mutation in the beta-globin gene, where glutamic acid is replaced by valine, resulting in the polymerization of Hb and formation of Hb S, with many devastating clinical manifestations.[1-2] It is not only affecting red cells but also evolving into multi-system involvement. Although the mutation of the sickle gene originated in the African continent, it is now a world-wide disorder.[2,3] SCD is highly prevalent in Oman, with the reported incidence of sickle trait close to 6% of the population.[4-6]

The most common complications of SCD are recurrent vaso-occlusive crises, predisposition to significant anemia, acute chest syndrome and recurrent infections.[7,8] Blood transfusion therapy is one of the

established therapies commonly used in the management of SCD-related complications, including stroke, ACS, priapism, pregnancy-related complications, and symptomatic anemia.[9] Unfortunately, such transfusions increase the risk of exposure to bloodborne infections like hepatitis B virus (HBV), hepatitis C virus (HCV) and immune deficiency virus (HIV).

Chronic viral hepatitis is a major global public health problem because of its association with increased morbidity and mortality related to chronic hepatitis, cirrhosis and hepatocellular carcinoma.[10] In 2015, WHO Global hepatitis report describes the global and regional estimates of viral hepatitis with an estimated 257 million people living with chronic HBV infection and 71 million people with chronic HCV infection.[11] The report also addresses mortality due to these infections, with viral hepatitis causing 1.34 million deaths in 2015, a number comparable to deaths caused by tuberculosis, but higher than those caused by HIV. However, the number of deaths due to viral hepatitis is steadily increasing over time, while mortality due to tuberculosis and HIV is declining.[12]

SCD patients are at high risk for transfusion-associated infections such as HBV, HCV, and HIV. The prevalence of these infections in SCD has been studied worldwide. In Mexico, the prevalence of HBV, HCV, HIV in multi-transfused patients was 7%, 13.7%, and 1.7%, respectively[13]. In Turkey between 1996 to 2005, HBsAg positivity was found to be 0.79% whereas, anti-HCV antibody positivity was 4.51%, but no HIV infections were observed among multi-transfused patients.[14] In comparison, Oman is a country with an intermediate prevalence of HBV carriers (2.8–7.1%), reported by a retrospective study conducted in 2010, with a prevalence rate of 5.8% for HBV infection.[15] Further, among the entire resident population in Oman, anti-HCV antibody positivity was reported to be 0.41%.[16] The WHO classifies Oman as having a low HIV prevalence, with total of 2917 HIV/AIDS infections among Omanis that were notified until end of 2017 with 1606 patients still being alive.[17]

Thus, despite the high prevalence of SCD in Oman, there is no data on the prevalence of HBV, HCV, and HIV in these patients. We, therefore, conducted this retrospective study using electronic medical records to estimate the prevalence of these infections and study its impact on morbidity and mortality.

Material and Methods. This is a retrospective cross-sectional study performed in patients with SCD, admitted to our hospital between 2011 to 2017, and data is obtained from the electronic patients' records (EPR). Among a total of 1012 EPR records that were retrieved, twelve patients were excluded from the final analysis as their data was incomplete.

The details obtained from the EPR records included: age, diagnosis, frequency of blood transfusion, laboratory markers for hepatitis B including surface antibody (anti-HBs), hepatitis B surface antigen (HbsAg), anti-hepatitis B IgM (anti-HBc IgM), hepatitis B core total antibodies (total anti-HBc), hepatitis B polymerase chain reaction (HBV DNA), hepatitis B e-antigen (HBeAg), hepatitis B e-antibody (anti-HBe), anti-hepatitis C antibody (anti-HCV), hepatitis C polymerase chain reaction (HCV RNA), hepatitis C genotype (HCV Genotype), HIV. Radiological data included abdominal liver ultrasound study results to assess for hepatomegaly and cirrhosis of the liver. The frequency of blood transfusions was categorized into four groups; never (no blood transfusion), occasional (less than two times per year), intermittent (3-6 times per year), and regular (monthly). Information was also collected on the current status of patients to obtain mortality data.

All blood samples were tested for HIV (anti-HIV 1/2), HBV HBsAg (if HBsAg was positive, full markers were performed including HBeAg, and anti-HBe, and total core IgM) and HCV. In case of HCV (anti-HCV) serological markers were screened by Architect HCV Ag Test (Architect HCV Ag Test, Abbot, Germany), and if positive were confirmed by second confirmatory method, the electrochemiluminescence immunoassay on Cobas e 411 immunoassay analyzer. Samples that were initially reactive by ELISA were retested in duplicate, and results were interpreted according to manufacturers' instructions.

HCV antigen was tested by third-generation assays (RIBA HCV 3, Chiron and HCV Blot, Genelab Diagnostics, Singapore). Sera, reactive in ELISA, were tested by RIBA according to manufacturers' recommendations. In these assays specimens were considered positive if they demonstrated reactivity to two or more antigen bands at an intensity higher than or equal to the weak positive control.

HCV ribonucleic acid (RNA) was tested on samples using the RT-PCR kit COBAS® AMPLICOR HCV Test, Version 2.0 (Roche Molecular Systems Inc., Pleasanton, California, USA). Since 2009, HCV RNA was tested using quantitative COBAS® TaqMan® analyzers (Roche Molecular Systems Inc.) with a linear quantification range between <15 and 100×10^6 IU/mL and a lower limit of detection of 12.6 IU/mL.

HBV infection was ascertained by assaying for HBeAg and HBsAg using enzyme-linked immunosorbent assay (Axsym, Abbott Laboratories). The assay cut-off for HBeAg was ≥1 unit/ml and the assay cut-off for HBsAg was ≥0.17–0.6 ng/ml; however, the assay cut-off varied according to the lot number of the kit. HBV DNA level was assessed using plasma with the platform of Roche COBAS® TaqMan® HBV Test, V1.0, with a linear quantification range between <20 and 170×10^6 IU/mL.

HIV (anti-HIV 1/2) was ascertained by an immunometric bridging technique using the VITROS ECi/ECiQ Immunodiagnostic System. Any positive serology would be confirmed by Western-Blot assay or HIV DNA PCR assay using the Cobas AmpliPrep/Cobas TaqMan HIV-1 v2.0, with a linear quantification range between <20 and 10×10^6 IU/mL.

Statistical Analysis. The statistical package for social science (IBM SPSS, USA ver.23) was used to analyze the collected data. Normally distributed data were characterized as mean with standard deviation, whereas data for continuous variable and percentage and frequency for categorical variables. The prevalence was reported as counts and percentages as appropriate.

Results. Table 1 shows the data from 1000 SCD patients (491 males and 509 females) with a mean age of 29.48 ± 10.40 years (range 1-82). 197 (19.7%) never received blood transfusions, whereas, 607 (60.7%) had occasional transfusions, 148 (14.8%) had intermittent transfusions and 48 (4.8%) were receiving regular transfusion.

In this study cohort, twenty-three (2.3%) were positive by serology for HBsAg, with sixteen (1.6%) being HBV DNA positive as well. Total anti-HBc, anti-HBe, and HBeAg were positive in 10.3%,1.8%, and 0.1%, respectively. 74.4% of these SCD patients showed anti-HBs positivity, indicating adequate immunity against hepatitis B. 126 (12.6%) had serologically positive anti-HCV antibodies (anti-HCV), with fifty-two (5.2%) showing HCV RNA positivity. The prevalence of anti-HCV in SCD patients with regular, intermittent, occasional and those with no transfusion was 16.7%,19.6%,14.5% and 0.5% respectively. A total of thirty-six patients 63.23%) had genotype 1; two patients (3.86%) had genotype 2, seven patients (13.46) each had genotype 3, and 4 (**Figure 1**). Furthermore, none of the SCD patients in this cohort had positive serology for HIV.

Abdominal liver ultrasound showed a normal liver in 78.8% (788) patients, whereas 20.8% (208) had hepatomegaly and only four patients had liver cirrhosis (0.4%). A total of thirty-six patients (3.6%) in this study cohort had died; however, in only two patients, death was due to cirrhosis of liver.

Discussion. The survival rate of SCD patients has recently increased with improved patient care, including blood transfusions, vaccinations and use of antibiotics. However, repeated blood transfusions are still necessary for many patients with SCD. Thus,

Table 1. Demographic, clinical, laboratory and radiological parameters in the SCD patient cohort (n=1000)

Parameters	Value
Age, years	
Mean ± SD	29.5±10.4
Range , Years	1-82
Gender,	
Males n, (%)	491(49.1)
Females n, (%)	509(50.9)
Frequency of Blood Transfusions	
None n, (%)	197(19.7)
Occasional n, (%)	607(60.7)
Intermittent n, (%)	148(14.8)
Regular n, (%)	48(4.8)
Prevalence of anti-HCV antibodies (as per transfusion frequency)	
None n, (%)	1(0.5)
Occasional n, (%)	88(14.5)
Intermittent n, (%)	29(19.6)
Regular n, (%)	8(16.7)
Total n, (%)	126(12.6)
Prevalence of Hepatitis B markers	
HBsAg n, (%)	23(2.3)
HBeAg n, (%)	1(0.1)
anti-HBe n, (%)	18(1.8)
total anti-HBc n, (%)	103(10.3)
HBV DNA	16(1.6)
Anti-HBs n, (%)	744(74.4)
Liver function Studies	
AST (U/L) Mean, [Range]	71, 13-372
ALT (U/L) Mean, [Range]	76, 7-768
Total S. Bilirubin (umol/L) Mean, [Range]	61, 4-825
S. Albumin (g/L) Mean, [Range]	39, 22-51
Liver Abdominal ultrasound	
Normal n, (%)	788(78.8)
Hepatomegaly n, (%)	208(20.8)
Cirrhosis of Liver n, (%)	4(0.4)

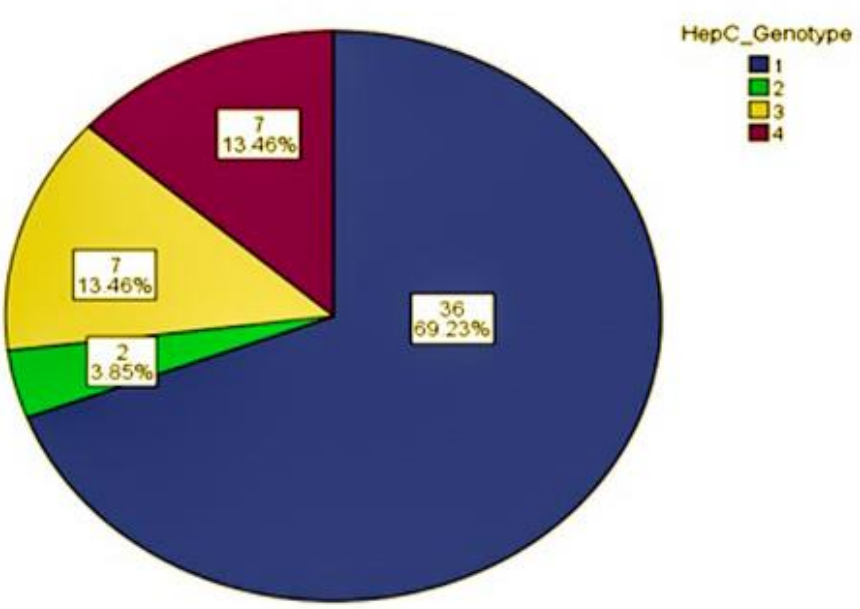

Figure 1. HCV genotypes in SCD patients (n=1000).

multiply transfused patients with SCD are at an increased risk of transfusion-associated infections such as HBV, HCV, and HIV.

The screening for HBsAg became available in the late 1960s and had been implemented widely since 1970s.[18] Despite regular HBV screening and national neonatal vaccination programs since early nineties, HBV infection is still present. In Oman, the prevalence of HBV infection was 5.8% in healthy adult population.[15] In another study, Al Awaidy, S. et al.[19] reported that the prevalence of HBV among pregnant Omani women in 2006 was found to be 7.1%, with 0.5% being HBeAg positive. However, there is no data related to HBV in SCD population from Oman.

In our study, we found that the prevalence of HBV infection among SCD was 2.3% with 16 (1.6%) HBV DNA positive, and 0.1% HBeAg positive. Significantly, the prevalence is considerably lower than the earlier studies in the general Omani population.[15,19] A possible explanation for this lower prevalence is the higher prevalence of anti-Hbs (74.4%) in our SCD patient cohort. This high prevalence of anti-HBs positivity reflects the success of prophylactic hepatitis B vaccinations that are judiciously pursued by our physicians, as well as the introduction of hepatitis B vaccination in this relatively young patient population. The isolated total anti-HBc pattern (anti-HBs negative/anti-HBc positive) found in 8.7% in our study may reflect previous hepatitis B exposure and ability of human body to eliminate the virus in some cases after infection.

Although the burden of chronic HBV viral infection was low (1.6%) in this study, it reflects the potential for chronic liver disease and hepatocellular carcinoma. Treatment of chronic HBV infection can control viral replication in most patients and reduces the risks for progression and may even reverse liver fibrosis. Nevertheless, in this study cohort, liver cirrhosis was only documented in 0.4% of patients with 0.2% deaths related to liver disease.

There has been a significant drop in transfusion-associated viral hepatitis since the implementation of testing for HCV in the early 1990s.[20] In 1993, Al Dhahry, S.H et al[21] reported the prevalence of antibodies to HCV among Omani patients with renal disease. They observed anti-HCV antibodies in 26.5% patients undergoing hemodialysis, 13.4% kidney transplant patients and 1% non-dialyzed non-transplanted patients with various renal diseases.[21] In another study, Al Dhahry, S.H et al.[22] reported the prevalence of HCV among Omani blood donors between 1991 to 2001 using a third-generation enzyme-linked immunosorbent assay (ELISA) and recombinant immunoblot assay (RIBA) to confirm positive ELISA tests.[22] Out of 30,012 samples from blood donors that were screened for anti-HCV, 272 (0.91%) were positive. However, among those, almost half (127) were confirmed positive by RIBA.[22] Al-Naamani, K et al,[23] in a retrospective study of 200 thalassemic patients from Oman, reported that the prevalence of anti-HCV antibodies in thalassemia patients was 41%.[23] However, no previous data related to HCV in SCD population in Oman is available.

The prevalence of anti-HCV positivity (12.6%) in

this study was higher than that observed in SCD patients from the United States (5.4%),[24] France (7.5%),[25] but lower than that reported from Egyptian SCD children (23%).[26] Further, there is a 12-fold increase in the prevalence of HCV in SCD patients in this study, as compared to that reported earlier by Al Dahry et al.[22] from Oman, which was essentially a population-based study. HCV is a major problem in SCD patients, and this might be because we still do not have a specific HCV vaccine as opposed to Hepatitis B vaccine. SCD patients are at great risk since they are often multi-transfused, especially in those patients with a severe disease background. The frequency of transfusion was identified as a major risk factor for HCV infection, according to study conducted in 1995 in Bahrain[27] and another in Siria reporting a cohort of frequently transfused hemoglobinopathy patients,[28] However, although the risk of infection increased with increasing frequency of transfusions, the prevalence of HCV in the current study is much lower than reported in thalassemic patients from Oman (41%).[23] Though there are several factors responsible for this high prevalence, frequency of transfusions is indeed the most significant factor for the high HCV prevalence in the thalassemia population from Oman.[23] Further, although we did not study any close family contacts, lack of transmission of HCV in very close family contacts of patients undergoing multi-transfusions for thalassemia has been reported, emphasizing that the nature of HCV transmission is predominantly by the parenteral route.[29]

Further, the current study found active HCV infection, confirmed by positive HCV RNA using RT-PCR, in 5.2% of the anti-HCV positive patients. This datum reflects a significant burden for chronic liver disease as these patients are at risk of developing liver cirrhosis and progressing to end-stage liver disease and liver cancer.[30] In 2016 the World Health Organization (WHO) released their first global health sector strategy with an ambitious plan to reduce the incidence of global chronic hepatitis infections from the current 6–10 million cases of chronic infection to 0.9 million cases worldwide, and to reduce the annual deaths from chronic hepatitis from 1.4 million to less than 0.5 million by 2030.[31] It is now feasible to aim for these objectives as the treatment for HCV has improved dramatically with the addition of direct-acting antivirals, which are easy to take, being an oral regimen that is highly effective, has minimal side effects, and achieves cure rates of over 90%.[32,33]

This study showed that HCV-genotype 1 was the most common genotype seen (69.2%), which is similar to the most common HCV genotype reported in thalassemic patients from Oman.[23] Although, the genotype is not related to the mode of virus transmitted or with histologic findings at presentation, patients with HCV genotype 1 tend to develop more severe liver disease with lower rates of response to interferon-based therapy than did patients with other HCV genotypes.[34]

HIV continues to be a major global public health issue. In 2016, an estimated 36.7 million people were living with HIV.[35] Some studies reported a low prevalence of HIV among SCD patients, with the prevalence in USA being 0.87%.[24] In the current study, we did not identify any case with seropositivity for HIV in this cohort, and no other cases have been identified with SCD and HIV in our institution. Exposure to blood and blood products is also common to two other diseases, i.e., hemophilia and thalassemia. However, comparatively speaking, in our observation, although we had seen respectively 3 and 4 HIV patients before 1990, currently, among our 112 hemophilia and 200 thalassemia patients,[23] we do not have any patient with positive serology for HIV-1 & 2. The reason for the lower risk of HIV comorbidity with SCD is unclear. Although the general population prevalence of HIV in Oman is low,[17] SCD may have a unique effect in altering the risk of HIV infection or progression, raising the possibility of SCD protective effect against HIV infection.[36] Investigation of how the hemolytic and immunological changes of SCD influence HIV might lead to a new therapeutic or preventive approaches.[37]

Liver involvement in patients with SCD includes a wide range of alterations, from mild liver function test abnormalities to cirrhosis and acute liver failure. Liver cirrhosis is a major public health problem and a significant source of morbidity and mortality that is preventable and underestimated. In HBV infection, it is estimated that 10% to 33% of those who develop persistent infection end up with chronic hepatitis of which 20% to 50% may develop liver cirrhosis.[38]

Studies in patients who had acquired hepatitis C by blood transfusion for 15–25 years, revealed that 20% to 30% developed cirrhosis.[39] In our current study we found that the proportion of liver cirrhosis among HCV, HBV infected SCD patients was significantly low (0.4%), and only two patients (0.2%) died due to liver cirrhosis.

SCD and homozygous β-thalassemia are common hemoglobinopathies in Oman,[5] with financial consequences for national healthcare services. It is thus prudent to follow the recommendations for blood banks and transfusion services in Oman. The transfusions of such patients take place in many hospitals throughout the country. Indications for blood transfusions require local recommendations and guidelines to ensure standardized levels of care.[40] Furthermore, not all patients with positive results received blood transfusions. This apparent discrepancy is mainly due to the fact that these patients also receive blood transfusions at other health care facilities in the Sultanate.

Conclusions. The study documents the prevalence of HBV, HCV, and HIV infections among SCD patients from Oman for the first time. Compared to the not affected Omani population, the prevalence of HBV was significantly low (anti-HBs), but that of HCV infection was significantly high (anti-HCV). Persistence of viral infections was found to be 5.2% and 1.6% based on HCV PCR and HBV DNA respectively, indicating an ongoing risk for chronic liver disease, cirrhosis, and liver cancer. Importantly, no case with HIV was observed. Although the overall mortality was 3.6%, liver cirrhosis was seen in only 0.2% of cases.

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