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**RESEARCH ARTICLE**

# HEPATITIS C VIRUS AND LEUKEMIA PATIENTS: PREVALENCE AND RISK FACTORS ASSOCIATED WITH INFECTION AMONG LEUKEMIA PATIENTS WHO ACHIEVE LONG-TERM REMISSION AFTER CHEMOTHERAPY

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## Abstract

**Aim and objective**: Leukemia patients are at elevated risk of hepatitis C virus infections, with anti-HCV prevalence ranging from 4.3% to 70% post-chemotherapy remission. Long-term leukemia survivors' natural histories are unclear. We measured anti-HCV antibodies to investigate the frequency of HCV infections and the associated odds factors of contracting HCV among leukemia patients who achieved long-term remissions after chemotherapy.
**Methods:** This study is a cross-sectional study, comprising leukemia patients at the oncology center at Kuwait Hospital in Sana'a, Yemen. It included people with leukemia of different ages and genders. Data was collected through a standard questionnaire prepared for this study, which includes clinical symptoms, risk factors, demographic data, and the results of diagnostic tests. Antibody tests for the hepatitis C virus (HCV) were done by ELISA.
**Results:** The majority of patients with HCV are male, with a mean age of 12.8 years. The prevalence is 5.5%, with males having a higher prevalence. Most patients receive blood transfusions more than twice, with major blood banks, Al-Kuwait hospitals, and private hospitals being the primary sources. AML and ALL are the two most common leukemias. Male patients have a higher risk, and those over 15 years old have a higher risk.
**Conclusions**: This study is the first in Yemen to investigate the prevalence of HCV infections in patients with leukemia. According to our research, leukemia patients had a greater prevalence of HCV than the general population's national prevalence. However, health care workers (HCWs) and patients receiving maintenance hemodialysis (HD) patients have prevalence's of HCV that are comparable.
**Keywords**: Anti-HCV antibodies, associated odds factors, chemotherapy, HCV infections, leukemia, long-term remissions.

## INTRODUCTION

In a 2021 report, the WHO predicted that, as of 2019, 58 million people worldwide have chronic hepatitis C. An anticipated 290,000 individuals die every year from hepatitis C- associated illnesses, primarily cirrhosis and liver cancer, and an estimated 1.5 million people become infected each year[1]. In Yemen, thousands of people are affected by the serious public health issue of hepatitis virus-related liver illness. HAV, HBV, HCV, HEV, HDV, and recently discovered hepatitis viruses, for instance hepatitis G virus, combine to generate a unique combination of liver illness[2-11]. In Yemen, all of these viruses have been linked to high rates of illness and mortality[2,3]. Hepatitis virus prevalence in Yemen has been predicted to be significant[2-11], yet specific data regarding the current state of infection among cancer patients in Yemen caused by hepatitis viruses is still lacking. Despite the availability of efficient treatments to eradicate HCV infection, the majority of

afflicted persons remain unaware of their infection[12]. Patients with cancer present particular difficulties in managing and treating chronic HCV. There is no established standard of care to determine the best course of action for treating patients in this patient population, who also have a higher risk of developing occult HCV infection, developing liver disease, and experiencing viral reactivation. Studies on HCV infection in cancer patients are scarce, despite the fact that chronic HCV infection is widespread in this population. As a result, little is known about the natural course of HCV infection and the effectiveness of infection therapy in cancer patients. There is a dearth of information regarding HCV infection in cancer patients.

The incidence of HCV infection in cancer patients is predictable to be among 1.5% and 32%[13,16]. HCV antibody-based serological testing may produce false-negative results for cancer patients, especially those with hematologic malignancies. PCR testing for HCV RNA quantification in blood is necessary for the identification of patients with concealed infections in some of these critically immunocompromised individuals, as routine finding of anti-HCV antibodies may not be sufficient for diagnosis[17-20]. Furthermore, HCV reactivation may occur following chemo-therapy[21]. Hematopoietic stem cell (HSCT) recipients with the virus have a higher chance of developing early cirrhosis and a faster pace of fibrosis advancement compared to HCV-infected individuals who do not receive this transplant. For example, it was found that patients who had HSCT and had a persistent HCV infection had an estimated median period to cirrhosis development of 18 years, while patients in the control group who had the same infection but did not receive HSCT had an expected median time to development of 40 years. Therefore, regardless of the genotype of the virus, doctors should think about doing a liver biopsy before to starting conditioning therapy if they have a medical suspicion of cirrhosis or severe fibrosis brought on by a persistent viral infection, including HCV infection[18].

In conclusion, the treatment decisions for cancer patients, especially those with leukemia, are made more difficult by the presence of the HCV. The lack of average of care recommendations for the management of HCV-infected cancer patients exacerbates this. Not only can HCV infection cause non-Hodgkin lymphoma and hepatocellular cancer, but it can also impact how antineoplastic chemotherapy treats cancer when HCV infection is present in cancer patients. Patients with cancer may experience worsening side effects from HCV therapy as a result of comorbidities and underlying cytopenias. Compared to the general non-cancer population, cancer patients respond to treatment less well when they are treated for HCV infection[22]. The current study aims to study the prevalence of HCV infections by measuring anti-HCV antibodies and the associated odds factors of contracting HCV among leukemia patients who completed long-term remissions after chemotherapy.

## METHODS

**Study design:** This research was a case-control study.

**Subjects and study area:** This study included individuals with acute leukemia who have achieved remission after chemotherapy at the Oncology Center in Al-Kuwait Hospital in Sana'a City, Yemen.

**Sample size:**

The population to estimate is 999–999. If the prevalence of hepatitis C among the risk group is 5%[10], with a margin of error of 2.9%, at least 217 patients would need to be within 95% confidence.

**Data collection:** Each case was given a thorough history, which was then entered into a pre-made questionnaire containing demographic, private, and medical information.

**Specimen collection:** Each patient had five milliliters of whole blood drawn aseptically via venous puncture, and the serum was separated by centrifugation following coagulation. Samples were put in an Eppendorf tube, and sera were kept until testing at -20 ºC.

**Laboratory tests:** Samples were evaluated using a commercially available kit (abia HCV Ab) in a closed-system Enzyme-Linked Immunosorbent Assay (ELISA). The "sandwich" form of direct immunoenzymatic approach, known as bio-ELISA anti-IgG immunoglobulin, involves incubating the samples to be evaluated in microplate wells covered with highly pure IgG antigens.

**Ethical approval:** The Institutional Ethical Committee of the Sana'a University Faculty of Medicine and Health Sciences approved the current study. Written informed permission was obtained from each subject prior to recruitment and research initiation.

**Statistical analysis:** The statistical program's software was used to do the statistical analyses, which were then shown as percentages, tabulations, or graphical representations. Risks' odds ratio and significance as determined by logistic regression, geometric means, 95% confidence interval, and chi-square test calculations. If there were significant differences, the *p*-value was less than 0.05. The Statistical Package for Epi-Info version 7 was used for all statistical analyses.

## RESULTS

The age and sex distribution of 218 leukemia patients who had HCV testing is displayed in Table 1. There are 44.9% females and 55.1% males. In terms of ages, 12.8 ±12.3 years was the mean. The age range of the majority of patients was 6-10 years (32.1%), then 1-5 years (24.8%), 11-15 years (22.9%), and older than 15 years (20.2%). Table 2 displays the frequency of HCV in 218 leukemia patients by age and sex. The crude prevalence of HCV was 5.5%, with a 6.7% greater prevalence in males than in females (4.1%). When it came to age groups, the group older than 15 had the highest percentage (13.6%). The frequency of residency, blood transfusion frequency, and blood source information for leukemia patients tested for HCV is displayed in Table 3. The majority of patients (64.2%) live in cities, while 35.8% do so in rural areas.

**Table 1: Sex and age distribution of 218 leukemia patients tested for HCV.**

| Characters | N (%) |
|---|---|
| **Sex** | |
| Male | 120 (55.1) |
| Female | 98 (44.9) |
| **Age in Years** | |
| 1-5 | 54 (24.8) |
| 6-10 | 70 (32.1) |
| 11-15 | 50 (22.9) |
| >15 | 44 (20.2) |
| Mean | 12.8 years |
| SD | 12.3 years |
| Median | 10 years |
| Mode | 5 years |
| Min to Max | 1-57 years |

When it came to blood transfusions, 89.9% of the patients received them more than twice, while 3.7% received them just once. The major blood bank (15.6%), Al-Kuwait hospital (15.6%), Al-Thorah hospital (7.3%), Al-Sabian hospital (32.6%), Al-Jumhori hospital (11.9%), and private hospital (33.5%) were the sources of the blood. The kind of leukemia among leukemia patients with HCV testing is displayed in Table 4. Acute myelogenous leukemia (AML or myeloblastic) counts 2.8%, acute lymphoblastic leukemia (ALL) counts 78.9%, chronic lymphocytic leukemia (CLL) counts 14.3%, chronic myelogenous leukemia (CML) counts 4.1%. When examining the related factors of HCV, a male patient's associated odds ratio of 1.7 was found, compared to a female patient's OR of 0.6. However, the results were not statistically significant ($p$=0.4). When age groups were taken into account, the age >15 years showed a high associated odds ratio of 4.4, with a confidence interval ranging from 1.4 to 14.5 and a significant $p$-value of 0.008. Al-Jumhori Hospital exhibited a high associated odds ratio of 9.3, with a confidence interval ranging from 2.7 to 31, and a significant $p$-value of less than 0.0001, when blood sources were taken into account as a risk factor for HCV infection. A family history of HBV linked odds ratio of 25.3 with a confidence range spanning from 5.4 to 119 and a significant $p$-value of <0.0001 was found when looking at the related factors of HCV.

**Table 2: Prevalence of HCV among different Sex and age of 218 leukemia patients.**

| Characters | N (%) |
|---|---|
| **Sex** | |
| Male (n=120) | 8 (6.7) |
| Female (n=98) | 4 (4.1) |
| Total n=218) | 12 (5.5) |
| **Age in Years** | |
| 1-5 (n=54) | 2 (3.7) |
| 6-10 (n=70) | 4 (5.7) |
| 11-15 (n=50) | 0 (0) |
| >15 (n=44) | 6 (13.6) |
| Mean | 23.8 |
| SD | 22.9 |
| Median | 13 |
| Mode | 7 |
| Min to Max | 5-57 |

**Table 3: Frequency of residence, blood transfusion, sources of the blood among leukemia patients tested for HCV.**

| Characters | N (%) |
|---|---|
| **Residency** | |
| Urban | 140 (64.2) |
| Rural | 78 (35.8) |
| **Blood transfusion** | |
| Once | 8 (3.7) |
| Twice | 14 (6.4) |
| More than 2 | 196 (89.9) |
| **Source of the blood** | |
| Main Blood bank | 34 (15.6) |
| Al-Kuwait Hospital | 34 (15.6) |
| Al-Thorah Hospital | 16 (7.3) |
| Al-Sabian Hospital | 71 (32.6) |
| Al-Jumhori Hospital | 26 (11.9) |
| Private hospital | 73 (33.5) |

Additionally, a significant $p$-value of less than 0.0001 was found for the related odds ratio of 19.6 with a confidence range spanning from 5.2 to 71.7 and a family history of jaundice as a risk factor for HCV infection. Additionally, the history of dental visits was found to be a risk factor for HCV infection; the related odds ratio for this factor was 4.9, with a significant $p$-value of 0.0008 and a confidence interval that ranged from 1.4 to 17.8. The risk factors for HCV linked with each form of leukemia are listed in Table 7. A linked risk factor for HCV infection was discovered to be Chronic Lymphocytic Leukemia (CLL); the related odds ratio for this factor was 3.3, with a significant $p$-value of 0.05 and a confidence interval spanning from 1.1 to 11.7.

## DISCUSSION

The chronic HCV infection prevalence in the Sana'a, Yemen, among leukemia survivors was 5.5%, approximately 10 times greater than the 0.5% national prevalence[23,24]. Additionally, past international studies have documented a noteworthy prevalence of HCV infection acquired through transfusion in children who have survived cancer[25,28]. The geography, time period, and cancers included in the study all affect the prevalence. The incidence of 5.5% chronic HCV infection was found in the HCV tested cohort of leukemia survivors in Sana'a city, which is equivalent to HCV risk groups such as dental workers 5.5%[7,10], albeit being lower than the 11.5% of public health center workers in Yemen[10]. The greater than anticipated percentage of HCV infections among leukemia patients, given that nearly all of them need blood transfusions while undergoing therapy[29,30].

The higher incidence of HCV in environments with insufficient resources is recognized to be caused by several variables. Among these problems are under diagnosis, inadequate preventive measures, contact tracking, and inadequate treatment for those who are affected. Low community awareness of infection and transmission, treatment accessibility and cost concerns, and occasionally healthcare providers' ignorance of current treatment guidelines are further contributing factors.

**Table 4: Type of leukemia among leukemia patients tested for HCV.**

| Types of leukemia | N (%) |
|---|---|
| Chronic lymphocytic leukemia (CLL) | 31 (14.3) |
| Chronic myelogenous leukemia (CML) | 9 (4.1) |
| Acute myelogenous leukemia (AML or myeloblastic) | 6 (2.8) |
| Acute lymphoblastic leukemia (ALL) | 172 (78.9) |
| Total | 218 (100) |

**Table 5: Associated risk factors of HCV among leukemia patients.**

| Factors | Positive HCV (n=12) No (%) | *OR* | *95% CI* | $X^2$ | *p* |
|---|---|---|---|---|---|
| **Sex** | | | | | |
| Male (n=120) | 8 (6.7) | 1.7 | 0.5-5.7 | 0.69 | 0.4 |
| Female (n=98) | 4 (4.1) | 0.5 | 0.17-2 | 0.6 | 0.4 |
| **Age groups in years** | | | | | |
| 1-5 (n=54) | 2 (3.7) | 0.59 | 0.12-2.8 | 0.4 | 0.5 |
| 6-10 (n=70) | 4 (5.7) | 1.1 | 0.3-3.6 | 0.08 | 0.92 |
| 11-15 (n=50) | 0 (0.0) | 0 | Undefined | 3.7 | 0.05 |
| >15 (n=44) | 6 (13.6) | 4.4 | 1.4-14.5 | 7 | 0.008 |
| **Blood transfusion** | | | | | |
| Once (n=8) | 0 (0.0) | 0 | Undefined | 0.48 | 0.48 |
| Twice (n=14) | 0 (0.0) | 0 | Undefined | 0.8 | 0.35 |
| More than 2 (n=196) | 12 (6.1) | Undefined | | 1.4 | 0.23 |
| **Source of the blood** | | | | | |
| Main Blood bank (n=34) | 2 (5.9) | 1.1 | 0.2-5.1 | 0.01 | 0.91 |
| Al-Kuwait Hospital (n=34) | 0 (0.0) | 0.0 | Undefined | 2.3 | 0.12 |
| Al-Thorah Hospital (n=16) | 0 (0.0) | 0.0 | Undefined | 1.0 | 0.3 |
| Al-Sabian Hospital (n=71) | 2(2.8) | 0.4 | 0.08-1.8 | 1.4 | 0.22 |
| Al-Jumhori Hospital (n=26) | 6 (23.1) | 9.3 | 2.7-31 | 17.5 | <0.0001 |
| Private hospitals (n=73) | 2 (2.7) | 0.3 | 0.08-1.7 | 1.6 | 0.2 |

Rising rates of both internal and external migration, administrative and organizational issues that obstruct the national health organization's commitment to resource mobilization, inadequate coordination with international partners or their departure from Yemen due to the conflict, and a lack of sense of duty on the part of some state employees towards the community members' health are other factors that contribute to the spread of this disease[31,36]. The most frequent cancer in the group of HCV-positive was ALL, as virtually all of these patients needed blood transfusions while undergoing therapy[37,38].

Current study found that the HCV sero-prevalence in men was 5.5% and higher (6.7%), but the HCV rate in the age group under 15 was 13.6%. These results are in line with the general reports of HCV seropositive rates in African nations[39,42]. Patients with CLL, where the prevalence of HCV was 12.9%, showed variations in HCV prevalence. This stands in contrast to studies that discovered higher HCV virus prevalence among AML patients in Korea[43,44]. This could be connected to differences in the onset age of HCV infection and leukemia[43,44]. According to previous reports, people with leukemia are more likely to get transfusion-associated hepatitis C virus (HCV) infections.

**Table 6: Associated confessional risk factors of HCV among leukemia patients.**

| Factors | Positive HCV (n=12) No (%) | *OR* | *95% CI* | $X^2$ | *p* |
|---|---|---|---|---|---|
| Blood products transfusion (n=181) | 10 (5.5) | 1.02 | 0.2-4.8 | 0.008 | 0.97 |
| Family history of HCV (n=4) | 0 (0.0) | 0.0 | Undefined | 0.23 | 0.62 |
| Family history of HBV (n=8) | 4 (50) | 25.3 | 5.4-119 | 31.6 | <0.0001 |
| Family history of Jaundice (n=16) | 6 (37.5) | 19.6 | 5.2-71.7 | 33.9 | <0.0001 |
| Mother suffering HCV (n=1) | 0 (0.0) | 0.0 | Undefined | 0.05 | 0.8 |
| Mother suffering HBV (n=4) | 0 (0.0) | 0.0 | Undefined | 0.23 | 0.6 |
| Mother suffering Jaundice (n=15) | 2 (13.3) | 3 | 0.5-14 | 1.8 | 0.16 |
| History of operation (n=7) | 0 (0.00) | 0 | Undefined | 0.42 | 0.51 |
| History of dental visit (n=23) | 4 (37.4) | 4.9 | 1.4-17.8 | 6.9 | 0.008 |

**Table 7: Associated risk factors of HCV with type of leukemia.**

| Factors | Positive HCV (n=12) No (%) | *OR* | *95% CI* | $X^2$ | *p* |
|---|---|---|---|---|---|
| Chronic lymphocytic leukemia (CLL) (n=31) | 4 (12.9) | 3.3 | 1.1-11.7 | 3.8 | 0.05 |
| Chronic myelogenous leukemia (CML) (n=9) | 0 (0.0) | 0.0 | Undefined | 0.5 | 0.45 |
| Acute myelogenous leukemia (AML or myeloblastic) (n=6) | 0 (0.0) | 0.0 | Undefined | 0.35 | 0.54 |
| Acute lymphoblastic leukemia (ALL) n=172 | 8 (4.7) | 0.51 | 0.14-1.7 | 1.14 | 0.28 |

The current investigation found that the frequency of HCV in leukemia patients in Yemen was higher than that of the community population in general[45]. The prevalence of anti-HCV in matures with acute leukemia who are in remission following treatment ranges from 4.3 to 70%[46-48]. Similarly, the anti-HCV prevalence in recipients of bone marrow transplants (BMT) ranges from 3.3 to 70%[49-51]. Studies limited to children with leukemia have found a somewhat lower frequency of 1 to 49%[52-54]. Since the induction of subsequent generation assessment in 1992 and anti-HCV screening for blood donors in 1990, the rate of infection has declined[46]. There is a paucity of information on how immunosuppression affects the severity of liver disease and viral load in long-term anti-HCV positive leukemia survivors. Nonetheless, a number of researchers have noted that people who are co-infected with HIV and anti-HCV positive have far greater viral levels than people who are anti-HIV negative[55]. According to certain findings[55,56], HCV RNA levels rise as the immune deficit worsens, but not according to other reports[57,58]. Additionally, it has been demonstrated that co-infection with HIV raises the risk of liver failure and cirrhosis[59-61]. Similar outcomes have been reported in patients with primary hypogammaglobulinemia[62]. In contrast, leukemia patients who achieved remission following chemotherapy had only a little increase in liver disease-related mortality, according to long-term follow-up of immunocompetent individuals[63].

**Limitation of the study**

The current study has some limitations that should be discussed. First, there was a lack of information about prior antiviral therapies for HCV. If leukemia patients had received effective treatment for HCV infections, however, this would not have had a substantial effect on the identification of antibodies linked to the virus. Secondly, results of imaging studies of the hepatobiliary system or tests for abnormalities of liver enzymes were not included in the patient database. Fourth, the detection tests had a number of limitations that could have led to an overestimation or underestimation of the frequency of occult HCV in this population. Finally, the lack of liver tissue makes it impossible to draw firm conclusions on the incidence of occult HCV infections in leukemia patients, given that HCV infection can exist even in cases where tests on sera and peripheral blood lymphocytes come out negative. Furthermore, we cannot be positive that the prevalence of viral infections is the same as it is in the general population because we did not include a control population of non-leukemic patients; nonetheless, these findings are in line with earlier systematic reviews of numerous population-based studies conducted globally.

## CONCLUSIONS

This study is the first in Yemen to investigate the prevalence of viral infections in patients with leukemia. According to current research, leukemia patients had a greater prevalence of HCV than the general population's national prevalence. However, HCWs and patients receiving maintenance (HD patients) have a prevalence of HCV that is comparable. Screening patients for HCV infections is strongly encouraged by clinicians, as these individuals are susceptible to complications connected to chemotherapy.

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## AUTHOR'S CONTRIBUTIONS

The author of the original draft, method, and investigation is Monya Abdullah Yahya El-Zine. Formal analysis, data organizing, and visualization by Yusra Ahmed Saleh Dawood. Khaled Abdul-Karim Al-Moyed: technique; writing, reviewing, and editing. Formal analysis, data organization, and visualization were handled by Hassan Abdel-Wahab Al-Shamahy, while the remaining authors reviewed and edited the piece.

## DATA AVAILABILITY

Anyone can seek access to the data by contacting the respective author.

## CONFLICT OF INTEREST

There is no conflict of interest around this work.

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