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Incidence of hepatitis B and C in children with cancer: a single institution experience in Iraq.

1. Dr. Usama Al-Jumaily
M.B.Ch.B.
F.I.B.M.S. (**Pediatrics**)
A.B.M.S. (**Pediatrics**)
J.B.M.S. (**Pediatric Hemato-Oncology**)
Ministry of Higher Education and Scientific Research, University of Kerbala, Medical College, Karbala, Iraq.
usama.a@uokerbala.edu.iq
2. Dr. Ali Emaduldeen Abdulmunem
M.B.Ch.B. \ C.A.B.P. \ (**Pediatrics**)
Iraqi Ministry of Health, Al_Rusafa Health Directorate, Ibn Al-Balady Hospital for Children and Maternity, Baghdad, Iraq.
alialdargazly@gmail.com
3. Dr. Oday Abdullhussein Abbood
M.B.Ch.B. \ F.I.B.M.S. \ (**Pediatrics**)
Iraqi Ministry of Health, Karbala Health Directorate, Karbala Teaching Hospital for Children, Karbala, Iraq.
forestforest7000@gmail.com

Abstract
Background: Hepatitis viruses, including B and C, are present in a large number of cancer cases, such as leukemia, and they are responsible for most of hepatitis. **Objective:** To determine the incidence of hepatitis virus infection among children being treated for cancer and to evaluate the factors that may increase the risk of infection. **Methods:** A cross-sectional study was conducted at Al-Imam Al-Hussain Oncology Center in Kerbala during a period of seven months, from the 13th of June 2019 till the 13th of January 2020. One hundred fifty-one patients were included in this study; their ages were < 18 years. They were diagnosed with cancer for at least six months before. They were either on current treatment or finished treatment and were attending for follow-up. A two ml of blood was drawn from all patients to test for liver function test, hepatitis B surface antigen (HBs Ag), and anti-hepatitis C antibody (anti-HCV). **Results:** In this study, the incidence of hepatitis C was 4%, and the incidence of hepatitis B was 1.3%. The highest prevalence of hepatitis infection was significantly seen in patients who received platelets transfusion more than ten times, in leukemia patients, in patients who received packed RBC transfusion 1-10 times, in patients who had elevated liver function tests, and in patients who received the last transfusion outside Kerbala. **Conclusion:** Incidence of blood born hepatitis is comparable with other published studies, higher with more frequent blood product transfusion, and higher with hematological malignancies rather than solid malignancies.

Keywords: Hepatitis B, hepatitis C, malignancy, children, Iraq.

Introduction

Hepatitis is a worldwide health problem resulting in liver malfunction. Although the primary cause of hepatitis is viral infections, other non-viral causes, such as toxins, drugs, autoimmune diseases, infections with bacteria, as well as parasites, can also lead to hepatitis. Hepatitis B is an infectious disease caused by the hepatitis B virus (HBV) that affects the liver. HBV is one of the public health issues worldwide. It is a partially double-stranded DNA virus that belongs to the Hepadnaviridae family ***[1,2]*** in the Orthohepadnavirus genus. It is the causative agent of hepatitis B infection, resulting in both acute and chronic hepatitis infections. Chronic HBV infection can progress to hepatocellular carcinoma and liver cirrhosis and subsequently leads to death, and therefore, it is considered a life-threatening virus worldwide, leading to significant rates of mortality. Approximately one million people die each year from HBV-related chronic liver disease, including liver cirrhosis and hepatocellular carcinoma. The prevalence is varying

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among geographic regions, from 1-20%. ***[3,4]*** Hence, it is expected that the prevalence of HBV in migrants from these countries would be high, considering the ethnic diversity of the population. Indeed, studies conducted in the Arabian Gulf region reported HBV seroprevalence to be between 2–7%. ***[5,6]*** The lifetime risk of HBV infection is less than 20% in low-prevalence areas, and sexual transmission and percutaneous transmission during adulthood are the main modes through which it spreads. About 12% of HBV-infected individuals live in low-prevalence areas, ***[7,8]*** which include the United States, Canada, western Europe, Australia, and New Zealand. Sexual and percutaneous transmission and transmission during delivery are the major transmission routes in areas of intermediate prevalence (rate of 3-5%), ***[9,10]*** including Eastern and Northern Europe, Japan, the Mediterranean basin, the Middle East, Latin, and South America, and Central Asia. ***[11]*** This rate is higher in human immunodeficiency virus (HIV) infected patients and lower in women and children. With HCV worldwide. ***[12]*** Rates have increased substantially in the 20th century due to a combination of intravenous drug abuse and reused but poorly sterilized medical equipment. ***[13]*** These are then cleaved by both host proteases and virally encoded proteases known as NS3-4a serine proteases. ***[14]*** These mature peptides then go on to reside on the endoplasmic reticulum, forming a replication complex which contains an important enzyme, the NS5B RNA-dependent RNA polymerase. Acute symptoms develop in some 20-30% of those infected. This study aims to determine the incidence of hepatitis viruses (B and C) infection among children being treated for cancer and to evaluate the factors that may increase the risk of infection. ***[15]***

Patients and Method

Plasma was screened by standard enzyme-linked immune-sorbent assay (ELISA) techniques. The test was done by HBs Ag Hepatitis B Surface Antigen Rapid Test Device, which is a qualitative, solid phase, two-site sandwich immunoassay for the detection of HBs Ag in whole blood, serum, or plasma. The membrane is pre-coated with anti-HBs Ag antibodies on the test line region of the Device. During testing, the whole blood, serum, or plasma specimen reacts with anti-HBs Ag antibodies conjugated particles. The mixture migrates upward on the membrane chromatographically by capillary action to react with anti- HBs Ag antibodies on the membrane and generate a colored line. The presence of this colored line in the test region indicates a positive result, while its absence indicates a negative result. To serve as a procedural control, a colored line will always appear in the control line region, indicating that the proper volume of specimen has been added and membrane wicking has occurred. This test was done by HCV kit, which is an enzyme-linked immunosorbent assay for the qualitative detection of antibodies to the hepatitis C virus in human serum or plasma. His kit employs a solid phase, indirect ELISA method for the detection of antibodies to HCV in a two-step incubation procedure. Polystyrene microwell strips are pre-coated with recombinant, highly immunoreactive antigens corresponding to the core and the non-structural regions of HCV (Fourth generation HCV ELISA). During the first incubation step, anti-HCV-specific antibodies, if present, will be bound to the solid phase pre-coated HCV antigens. The wells are washed to remove unbound serum proteins, and rabbit anti-human IgG antibodies (anti-IgG) conjugated to horseradish peroxidase (HRP Conjugate) are added. During the second incubation step, these HRP-conjugated antibodies will be bound to any antigen-antibody (IgG) complexes previously formed, and the unbound HRP conjugate is then removed by washing.

Chromogen solutions containing Tetramethylbenzidine (TMB) and urea peroxide are added to the wells, and in presence of the antigen-antibody-anti-IgG (HRP) immunocomplex, the colorless chromogens are hydrolyzed by the bound HRP conjugate to a blue-colored product. The blue color turns yellow after stopping the reaction with sulfuric acid. The amount of color intensity can be measured and is proportional to the amount of antibody captured in the wells and to the sample, respectively. Wells containing samples negative for anti-HCV remain colorless. The data was analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data is presented as mean, standard deviation, and ranges—categorical data presented by frequencies and percentages. The Chi-square test was used to assess the association between the results of the hepatitis screen and certain information. A level of P-value less than 0.05 was considered significant.

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Result

Figure 3.1- *Distribution of patients group by age*

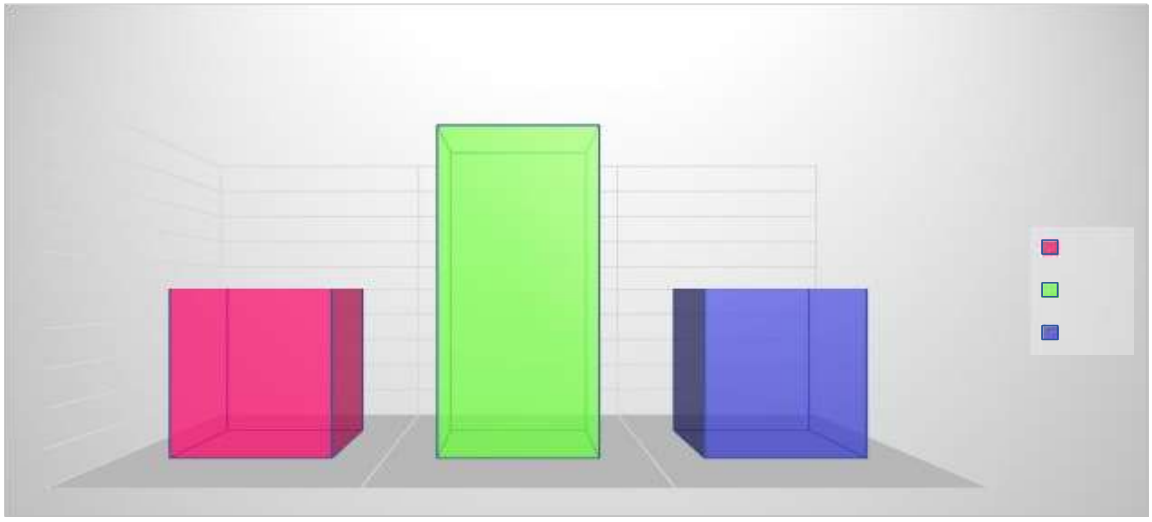

Figure 3.2- *Distribution of study groups by gender*

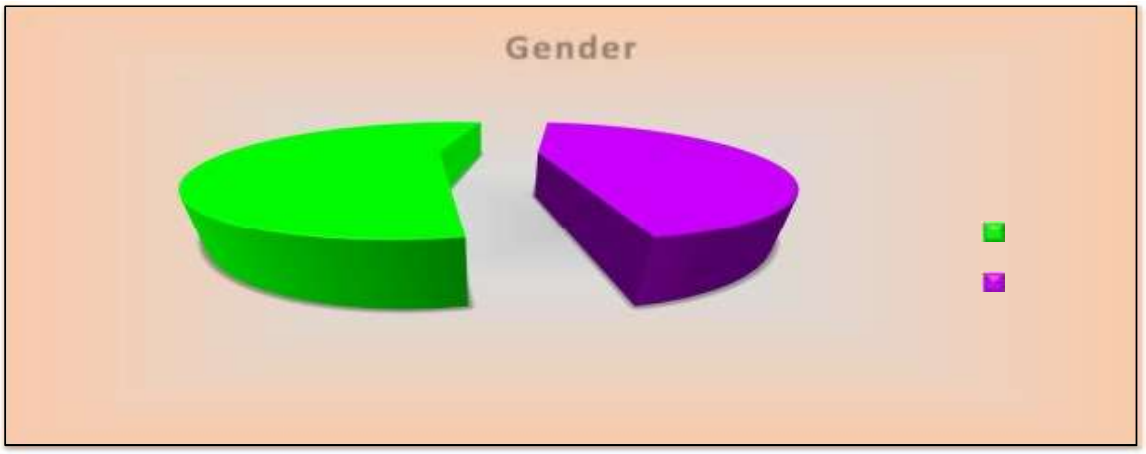

Table 3.1- Distribution of study patients by type of malignancy.

Type of Malignancy	No. (n= 151)	Percentage (%)
Leukemia	70	46.4
Lymphoma	24	15.9
Solid Tumor	50	33.1
Brain Tumor	7	4.6

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Table 3.2- *Distribution of study patients by blood product transfusion.*

Blood Product Transfusion	No. (n= 151)	Percentage (%)
Number of Platelets Transfusion		
No Transfusion	84	55.6
1 - 10	54	35.8
> 10	13	8.6
Number of Packed RBC Transfusion		
No Transfusion	33	21.9
1 - 10	110	72.8
> 10	8	5.3
Last place of transfusion	**n= 119**	
Karbala	99	83.2
Outside Karbala	20	16.8

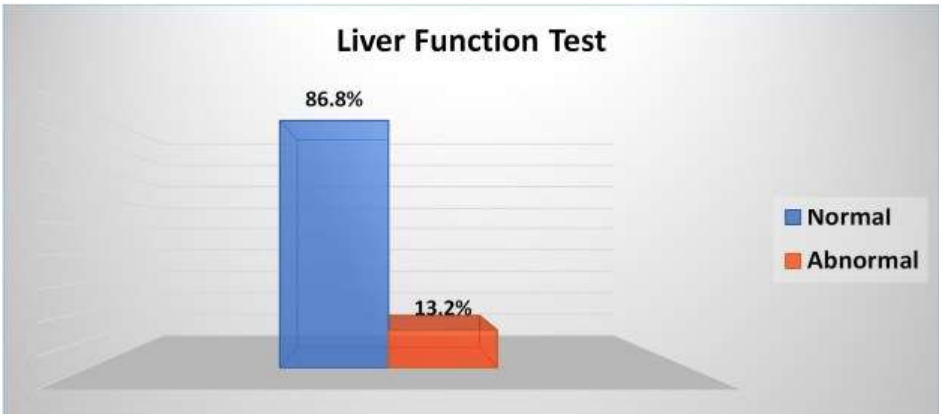

Figure 3.3- *Distribution of study groups by liver function test.*

Table 3.3- *Distribution of study patients by type of hepatitis infection.*

Type of hepatitis infection	No. (n= 151)	Percentage (%)
Hepatitis B		
Negative	149	98.7
Positive	2	1.3
Hepatitis C		
Negative	145	96.0
Positive	6	4.0

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Table 3.4- *Association between hepatitis infection with age and gender*

Variable	Hepatitis Infection		Total (%) n= 151	P - Value
	Positive (%) n= 8	Negative (%) n= 143		
Age (Year)				
< 5	3 (7.9)	35 (92.1)	38 (25.2)	**0.358**
5 - 9	2 (2.7)	73 (97.3)	75 (49.6)	
≥ 10	3 (7.9)	35 (92.1)	38 (25.2)	
Gender				
Male	6 (7.1)	78 (92.9)	84 (55.6)	**0.257**
Female	2 (3.0)	65 (97.0)	67 (44.4)	

Table 3.5- *Association between hepatitis infection and types of malignancy*

Type of malignancy	Hepatitis Infection		Total (%) n= 151	P - Value
	Positive (%) n= 8	Negative (%) n= 143		
Leukemia				
Yes	7 (10.0)	63 (90.0)	70 (46.4)	**0.016**
No	1 (1.2)	80 (98.8)	81 (53.6)	
Lymphoma				
Yes	1 (2.0)	23 (92.0)	24 (15.9)	**0.509**
No	7 (7.0)	120 (95.2)	127 (84.1)	
Solid Tumor				
Yes	0 (0)	50 (98.0)	50 (33.1)	**0.191**
No	8 (5.6)	93 (93.0)	101 (66.8)	
Brain Tumor				
Yes	0 (0)	7 (92.9)	7 (4.6)	**0.522**
No	8 (5.6)	136 (94.4)	144 (95.4)	

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Table 3.6- Association between hepatitis infection and different blood product transfusion

Variable	Hepatitis Infection		Total (%) n= 151	P - Value
	Positive (%) n= 8	Negative (%) n= 143		
Number of Platelets Transfusion				
No Transfusion	1 (1.2)	83 (98.8)	84 (55.6)	**0.001**
1 - 10	3 (5.6)	51 (94.4)	54 (35.8)	
> 10	4 (30.8)	9 (69.2)	13 (8.6)	
Number of Packed RBC Transfusion				
No Transfusion	0 (0)	33 (100.0)	33 (21.9)	**0.018**
1 - 10	6 (5.5)	104 (94.5)	110 (72.8)	
> 10	2 (25.0)	6 (75.0)	8 (5.3)	
Last Place Transfusion				
Karbala	4 (4.0)	95 (96.0)	99 (83.2)	**0.027**
Outside Karbala	4 (20.0)	16 (80.0)	20 (16.8)	

Table 3.7- Association between hepatitis infection and liver function test

Liver Function Test	Hepatitis Infection		Total (%) n= 151	P - Value
	Positive (%) n= 8	Negative (%) n= 143		
Normal	1 (0.8)	130 (99.2)	131 (86.8)	**0.001**
Elevated	7 (35.0)	13 (65.0)	20 (13.2)	

Table 3.8- Characteristics of patients who were diagnosed with hepatitis infection

	Hepatitis	Age	Gender	Malignancy	Platelet Trans	Packed RBC Trans	LFT
Pa ent 1	C	10	Male	Leukemia	3	4	Elevated
Pa ent 2	C	5	Male	Leukemia	25	8	Elevated
Pa ent 3	C	6	Male	Leukemia	40	28	Normal
Pa ent 4	C	3	Female	Leukemia	2	1	Elevated
Pa ent 5	B	13	Male	Leukemia	38	56	Elevated
Pa ent 6	B	16	Male	Lymphoma	0	1	Elevated
Pa ent 7	C	4	Female	Leukemia	3	4	Elevated
Pa ent 8	C	4	Male	Leukemia	30	5	Elevated

Discussion

HCV positive, also found that among cancer patients of, 50 (32%) were HBV positive. Who were HCV positive, 16 A different results were observed in the Sharaf-Eldeen et al. study in 2007, in which reported that Hbs Ag was present in 9% (5% HbsAg alone + 4% co-infected with HCV) of patients? Finally, the best results observed in the Kebudi et al. study in 2018 as found that None of the 100 patients enrolled in their study were seropositive for HBsAg, anti-HCV, and anti-HIV, either at diagnosis or at the end of treatment.

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The difference can be explained also by the fact that the global prevalence of HBV varies widely from low <2% as in Western Europe, North America, and Japan to high >8% as in Africa, Southeast Asia, and China. In the present study, ***[16]*** 10% of leukemia patients had positive results of hepatitis with a significant association between hepatitis infection and leukemia (P= 0.016), while no significant associations with all other types of malignancy (P ≥ 0.05). In contrary to the current results, Sharaf-Eldeen et al. study in 2007 reported that the type of malignancy, whether hematological or solid, and hepatitis markers were not significantly related (P>0.05). ***[17]*** In this study, no significant associations with both of age and gender (P ≥ 0.05). Similarly, Al Jadiry and colleagues in 2013 found no association exists between hepatitis infection with age and gender (P>0.05). In this study, patients who received platelet transfusion more than ten times (30.8%) had the highest prevalence of hepatitis infection, with a significant association with the number of platelet transfusions (P= 0.001). Similarly, ***[18]*** Sharaf-Eldeen and other researchers in an Egyptian study in 2007 found a positive association between the mean number of platelet transfusions and the presence of HbsAg (P <0.05). Children living in intermediate and high-endemicity areas for HBV are at risk of getting the infection, especially those with cancer who are obliged to receive intensive cytotoxic chemotherapy, which requires multiple blood transfusions and causes immunodeficiency. ***[19]*** HBV vaccination of seronegative patients at diagnosis may be recommended. In comparison to other studies, younger children were enrolled in the Al Jadiry et al. study in 2013, as noticed that the median age of the children enrolled was five years and five months (range, three months to 15 years and five months); also, male patients were outnumbered female as 65.6% were boys (male: female ratio, 1.9:1). Study in 2019 observed different results; when enrolled one hundred children with cancer who received multiple transfusions and were investigated for hepatitis B surface antigen (HBsAg), anti-HBs, and anti-HCV, they found that the mean age of participants was 4.09±2.45 years (range between 4 months – 11) years, with a nearly an equal gender distribution, as female constituted 51% of them with female to male ratio was 1.04:1. Finally, of the 289 pediatric cancer patients enrolled in Raouf et al. study in 2014, a male predominance was observed as constituted 66.7% of study patients with a male to female ratio was 2.01:1. The mean age within the cancer group was 7.8 ± 4.7 years. ***[20]***

Conclusion

Incidence of hepatitis is higher with more frequent blood product transfusions. Incidence of hepatitis is higher with hematological malignancies rather than solid malignancies. There is no gender prediction for infection with hepatitis in children with cancer. This study is recommended to Establishing cancer center transfusion guidelines to reduce unnecessary blood products transfusion, thereby lessening the incidence of blood born viral infection. Emphasizing on screening methods of blood products by the blood bank to detect donors with hepatitis in the window period. Hepatitis screening test for medical staff working in the oncology unit. Recommended hepatitis B vaccine schedule for a patient with hematological malignancies and for medical staff working in the oncology unit.

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