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Studies on Hepatitis B and D Viruses Co-Infection in Egyptian Hemodialysis Patients

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ABSTRACT

Hepatitis D virus (HDV) infection is exceedingly pathogenic, and it aggravates the natural viral hepatitis B (HBV) infection by progressing to cirrhosis. Therefore, we aimed to ascertain the incidence, prevalence, and features of hepatitis B and/or D virus co-infection in individuals with renal impairment. A total of 92 renal patients were enrolled in the study between October 2017 and November 2021. liver and kidney functions were assessed, and HBsAg, IgM anti-HDV, and total HDV antibodies were detected to determine HBV/HDV coinfection. We found that HBV/HDV coinfection is more common in patients with renal failure than in renal insufficiency, furthermore, 26.1% (24 of a total 92) of patients with (HBV) renal failure and 5.4% (5 of a total 92) of individuals with (HBV) renal insufficiency showed antibodies to (HDV). HBV/HDV coinfection resides in rural areas than in urban ones. Alanine transaminase (ALT) is in the normal range while aspartate transaminase (AST), total and direct bilirubin (T Bil), (D Bil), creatinine, uric acid, and urea serum levels and Prothrombin time (PT) were high, and albumin (ALB) was decreased. In addition, the death rate in renal patients infected with virus 19 out of a total of 29 (virus B infection), including 13 co-infections with the virus. It is concluded that among the examined (HBV) & (HDV) renal patients, renal impairment may significantly increase the prevalence and incidence of hepatitis infection due to the weakening of the immune system of patients. If coinfection is not treated this will result in 100% death.

KEYWORDS

Hepatitis B (HBV); Hepatitis D (HDV); Medical Biotechnology; Renal Dysfunction.

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INTRODUCTION

Acute and chronic liver infections caused by hepatitis viruses are a global health issue that can lead to cirrhosis and hepatocellular carcinoma. These conditions are also linked to a high mortality rate, with an estimated 1.3 million fatalities occurring globally each year **(Ringelhan *et al.,* 2017).** The construction, release, and transmission of the small, faulty RNA virus known as hepatitis D are all dependent upon the hepatitis B surface antigen (HBsAg) of the hepatitis B virus (HBV) **(Chang *et al.,* 2022).** Polaris Observatory Collaborators claim that between 248 and 292 million persons globally are infected with HBV **(Polaris Observatory Collaborators, 2018)**. It was originally estimated that 15 to 20 million of these patients also have HDV infection based on these estimations **(Wedemeyer *et al.,* 2019).** Additionally, Chen et al. claim that globally, 62–72 million people are co-infected with the hepatitis B and delta viruses (HBV) **Chen *et al.,* 2018)**. The most frequent cause of liver cirrhosis and hepatocellular carcinoma (HCC), hepatitis B virus (HBV), has a significant negative influence on global health **(Tyng-Yuan *et al.,* 2021)**. In research carried out in the Middle East, the prevalence of hepatitis B surface antigen (HBsAg) was reported to range from 3 to 11 percent in Egypt. The chronic carriers include adults, children, babies, pregnant women, blood donors, and healthcare professionals **(Hussein *et al.,* 2018)**. Chronic HBV/HDV infection has severe and challenging clinical manifestations **(Abbasi *et al.,* 2022).**

Additionally, dialysis patients are vulnerable to hepatitis B infection, therefore they could get HDV **(Bernieh *et al.,* 2015).** Due to the high risk of HDV/HBV transmission, the high mortality and morbidity rates of hepatitis D, the difficulty in diagnosing HDV in HD patients, the irreversible complications of its infection, and the challenging treatments, HDV infection has become a significant concern in HD patients **(Alexander *et al.,* 2020).** This study aims to find out the occurrence, dominance, and laboratory finding of hepatitis B and/or D virus co-infection in individuals with renal impairment.

MATERIALS AND METHODS

The study was carried out at the hospital of Zagazig University, Faculty of Medicine, Al-Ahrar General Hospital, and some private laboratories in Sharkia Governorate, Egypt. It was conducted from October 2017 and November 2021, the Study included **92** renal patients divided into two groups (according to medical data obtained from the place of sampling).

Group I: Included **77** (83.7%) patients with renal failure who were on dialysis,

Group II: Included 15 (16.3%) patients with renal insufficiency who were taking medication only.

Before starting their first hemodialysis session, patients had blood drawn monthly. The findings were obtained after centrifuging blood samples at 5,000 rpm for five minutes.

The serum was separated in 3 to 4 hours while being kept under strict aseptic conditions, and it was then kept at -70°C until testing. HBsAg, IgM anti-HBc, and Anti-HDV antibodies were checked in the serum samples. Using ELISA kits that are available commercially, the serological assays were conducted following the manufacturer's instructions. The viral markers (HBsAg, IgM anti-HBc, and Total anti-HDV) were identified with an ELISA kit from Diasorin, S.P.A. Italy. While liver function tests [ALT, AST, ALB, Total bilirubin (T.Bil), Direct bilirubin (D.Bil), and Prothrombin time (PT)] and renal function tests (Creatinine, Uric acid, and Urea), which were all tested with Biosystems S.A. – Spain.

STATISTICAL ANALYSIS

The statistical software SPSS was used to analyze the data (16.0 version). The mean standard devi-

ation of three distinct experiments is used to express all data. The statistical significance was established using an analysis of variance. A P-value of less than 0.05 was considered significant.

RESULTS

Comparing group I and group II according to HBV/HDV infection.

a) **HBsAg was positive** in 29 (31.5% of total 92) of renal patients, of them 24 (26.1% of total 92) of renal failure patients, and 5 (5.4% of total 92) of renal insufficiency. As regard control samples (without virus) there are 63 (68.5%) negative HBV of them 53 (57.6%) in group I (renal failure and 10 (10.9%) in group II (renal insufficiency) as represented in table (1) and fig. (1).

b) **IgM anti-HBc Ab positive** in 7 cases (indicate of acute infection), of them 6 in group I and one in group II while **IgM anti-HBc Ab** negative in 22 cases (indicate of chronic infection may develop into other liver diseases) but through ultrasound and computed tomography scan of abdomen for these cases note the following; 18 had chronic (15 in group I and 3 in group II), 3 had cirrhosis (2 in group I and 1 in group II) and 1 had HCC in group II only, as represented in table (2) and fig. (2).

c) **HDV Ab (total) was positive** in 13 (44.8% of total 29) of HBV-infected renal patients, of them 12 (41.4% of total 29) of the patients in group I, and in 1 (3.4% of total 29) of the patients in group II.

d) Of the total anti-HDV Ab, **IgM anti-HDV Ab was positive** in 5 (17.2% of a total 29), this test was done to find out more about recent infection with the virus, of them 4 cases in group I while was 1 case in group II as represented in table (3) and fig. (3).

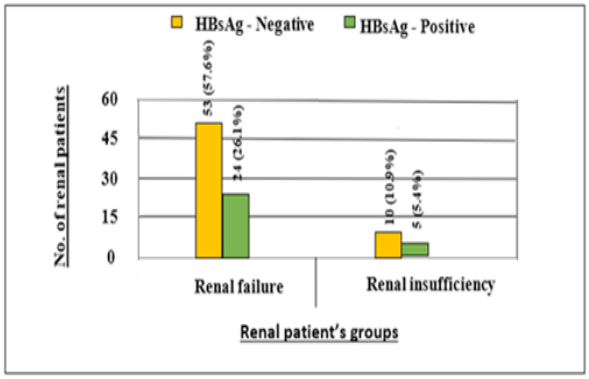

Fig. (1): Distribution of HBV infection among the studied renal patient groups.

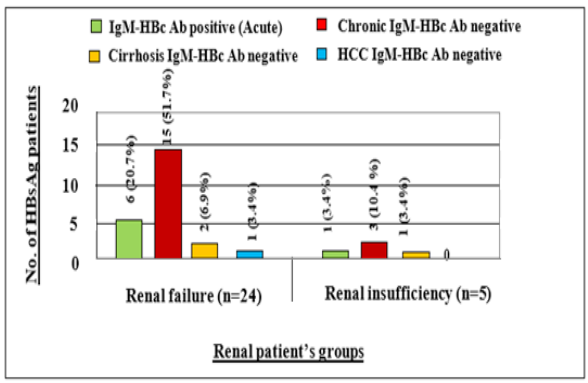

Fig. (2): Detection of IgM anti-HBc Ab related liver diseases among HBsAg – positive renal patients.

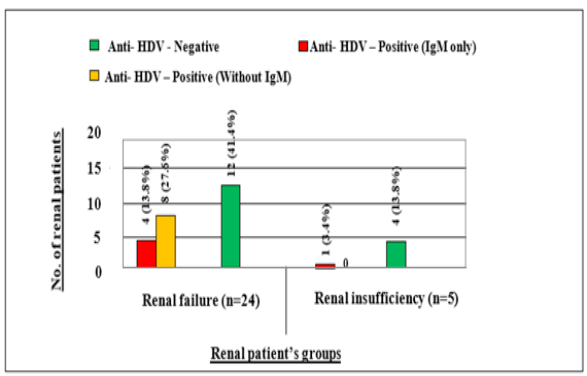

Fig. (3): Distribution of HDV infection among the studied HBV-infected renal patients..

Table (1) : *Distribution of HBV infection among the studied renal patient groups.*

Renal patients groups (n=92)		HBsAg	
		Positive (n=29)	Negative (n=63)
Renal failure (n=77)	Count	**24**	**53**
	%	26.1	57.6
Renal insufficiency (n=15)	Count	**5**	**10**
	%	5.4	10.9

Table (2) : *Detection of IgM anti-HBc Ab related liver diseases among HBsAg – positive renal patients.*

HBsAg – positive renal patients (n=29)		IgM anti-HBc Ab / related liver diseases			
		Positive (n=7) (Acute)	Negative (n=22) through ultrasound and CT scan		
			chronic	cirrhosis	HCC
Renal failure (n=24)	Count	**6**	**15**	**2**	**1**
	%	20.7	51.7	6.9	3.4
Renal insufficiency (n=5)	Count	**1**	**3**	**1**	**0**
	%	3.4	10.3	3.4	0.0

Table (3) : *Distribution of HDV infection among the studied HBV-infected renal patients.*

HBV-infected renal patients (n=29)		Total anti-HDV		
		Positive (n=13)		Negative(n=16)
		IgM only	Without IgM	
HBV - Renal failure (n =24)	Count	**4**	**8**	12
	%	13.8	27.6	41.4
HBV – Renal insufficiency (n= 5)	Count	**1**	**0**	4
	%	3.4	0.0	13.8

Regarding liver disease and its relationship to HDV infection

a) HDV Ab (total) was positive in 5 (17.2% of total 29) patients were acute, 6 (20.7%) patients had chronic, 1 (3.4%) patient had cirrhotic and 1 (3.4%) patient had hepatocellular carcinoma as represented in table (4) and fig. (4).

Table (4) : *Distribution of HBV/ HDV co-infection among liver diseases.*

Liver diseases (n=29)		Total Anti-HDV Ab	
		Positive (n=13)	Negative (n=16)
Acute (n = 7)	Count	**5**	**2**
	%	17.2	6.9
Chronic (n = 18)	Count	**6**	**12**
	%	20.7	41.4
Cirrhoses (n = 3)	Count	**1**	**2**
	%	3.4	6.9
HCC (n = 1)	Count	**1**	**0**
	%	3.4	0.0

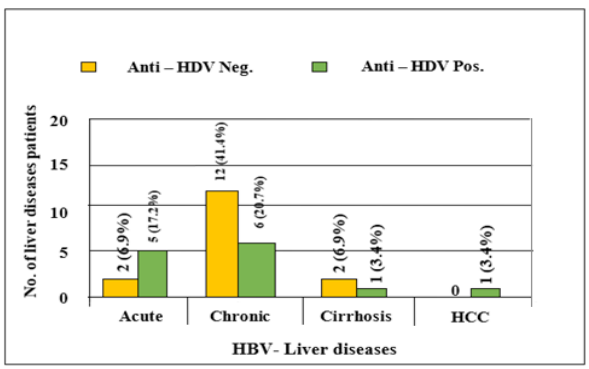

Fig. (4): Distribution of HBV/ HDV co-infection among liver diseases.

Regarding the place of residence in our study

a) Out of the 92 renal patients investigated, 59 (64.1%) patients were living in rural and 33 (35.9%) patients were living in urban.

b) In renal failure cases, 49 (53.3%) were living in rural and 28 (30.4%) were living in urban, while in renal insufficiency cases, 10 (10.9%) were living in rural and 5 (5.4%) were living in urban.

c) Of the 29 (31.5% of the total 92) were HBsAg positive, of them 17 cases (18.5%) were living in rural and 12 cases (13.0%) were living in urban as represented in Table (5) and fig. (5).

d) Of the 13 cases (44.8% of a total 29) which were positive total anti-HDV, of them 9 cases (31.0%) were living in rural and 4 cases (13.8%) were living in urban as represented in table (6), and fig. (6).

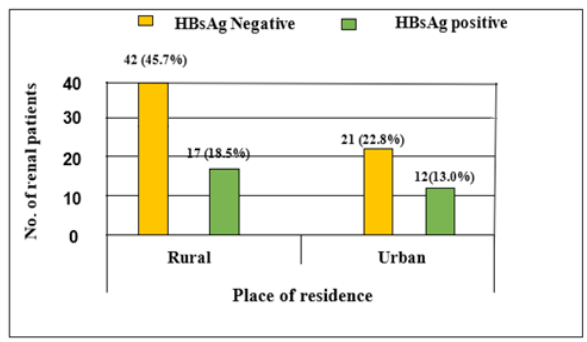

Fig. (5): HBsAg concerning place of residence.

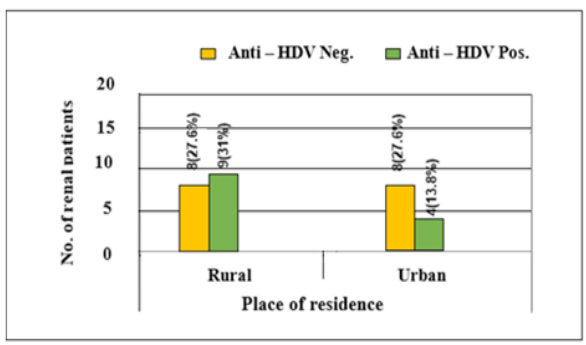

Fig. (6): Total anti-HDVAb concerning the place of residence.

Table (5) : *HBsAg concerning place of residence.*

Place of residence (n=92)		HBsAg	
		Positive	Negative
Rural (n = 59)	count	17	42
	%	18.5	45.7
Urban (n = 33)	count	12	21
	%	13.0	22.8

Table (6) : *Total anti-HDVAb concerning the place of residence.*

Place of residence (n+29)		Total anti-HDV	
		Positive	Negative
Rural (n = 17)	count	9	8
	%	31.0	27.6
Urban (n = 12)	count	4	8
	%	13.8	27.6

Regarding liver and renal function tests.

a) Regarding control, it was on patients without viral infection and it is as follows in liver function tests where alanine aminotransferase level was 35.2±7, aspartate aminotransferase was 41.3±5, albumin was 3.4±1.6, total bilirubin was 0.97±0.33, direct bilirubin was 0.25±0.1 and prothrombin time was 73.4±9.1. on the other hand, in renal function tests, creatinine level was 7.2±1.8, uric acid was 6.8±2.7 and urea was 152.3±17.7.

b) In our study, especially in renal patients with viral co-infection, AVH markedly increases AST, and bilirubin serum levels while decrease in albumin levels. on the other hand in chronic cases, it also appears to increase in AST serum level and also decrease in albumin. While cirrhosis is characterized decrease in ALB, and PT content and an increase in AST level. Also, HCC was characterized by markedly elevated AST, T Bil, and decreased ALB, and PT content as represented in Table (7) and fig. (7,8,9).

c) Renal function tests it is noticeable and clear that the level of kidney function is much higher than normal in all patients, especially those who suffer from liver disease and are undergoing dialysis in HDV coinfection, as represented in Table (8) and fig. (10,11)

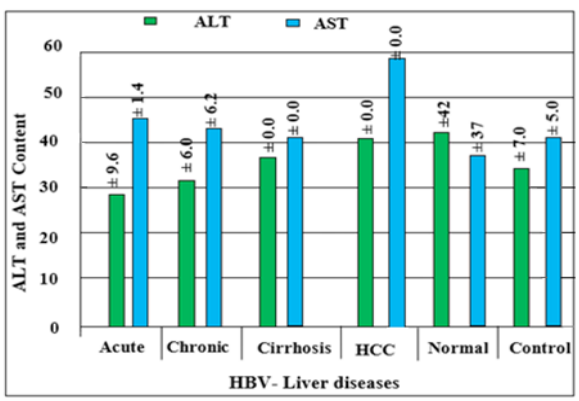

Fig. (7): ALT and AST level in liver disease with virus co-infection.

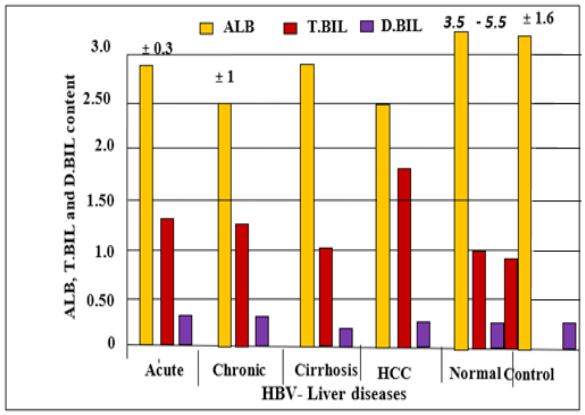

Fig. (8): Albumin, T. bilirubin, and D. bilirubin content in liver disease with virus co-infection.

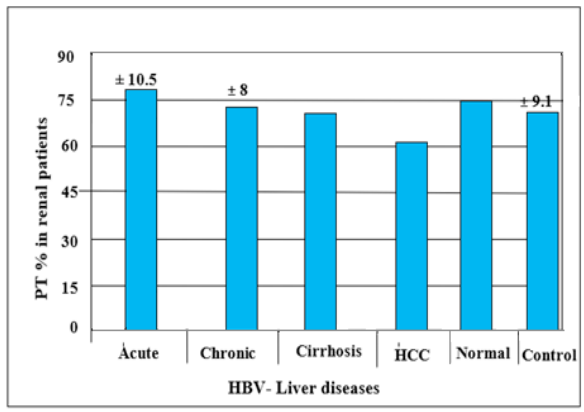

Fig. (9): Prothrombin time level in liver disease with virus co-infection.

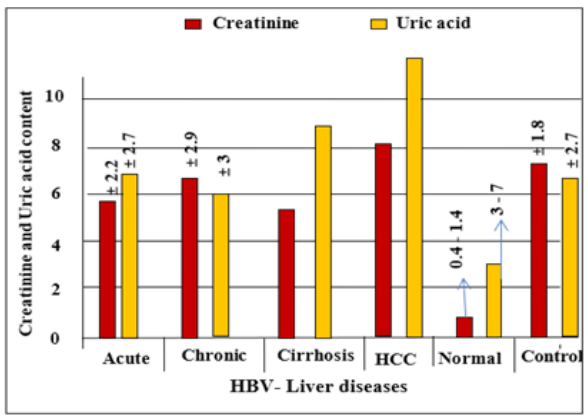

Fig. (10): Creatinin and Uric acid level in liver disease with virus co-infection.

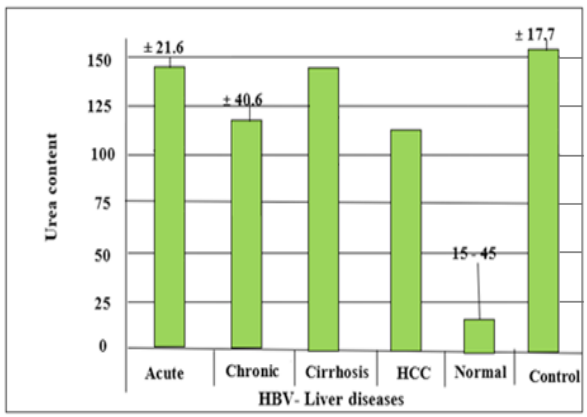

Fig. (11): Urea level in liver disease with virus co-infection.

Table (7) : *Liver function level in liver disease associated with virus co-infection.*

Liver function tests	Liver diseases/coinfection (n = 13)				Control (without virus n = 63)	Normal range
	Acute (n = 5)	Chronic (n = 6)	Cirrhosis (n = 1)	HCC (n = 1)		
ALT (1U/L)	29.4 ± 9.6	31 ± 6	37 ± 0	41 ± 0	35.2 ± 7	Up to 42
AST (1U/L)	45.8 ± 1.4	44.8 ± 6.2	41 ± 0	59 ± 0	41.3 ± 5	Up to 37
Albumin (g/dl)	2.9 ± 0.3	٢,٥ ± 1	٢,٩ ± 0	2.5 ± 0	3.4 ± 1.6	3.5 - 5.5
T.bilirubin (mg/dl)	1.3 ± 1.2	1.25 ± 0.7	0.97 ± 0	1.8 ± 0	0.97 ± 0.33	Up to 1.0
D. bilirubin (mg/dl)	0.32 ± 0.2	0.26 ± 0.09	0.19 ± 0	0.25 ± 0	0.25 ± 0.1	Up to 0.25
PT %	77 ± 10.5	74.5 ± 8	72.5 ± 0	62.5 ± 0	73.4 ± 9.1	75%

Table (8) : *Renal function level in liver disease associated with virus co-infection.*

Renal function tests	Liver diseases/coinfection (n = 13)				Control (without virus n = 63)	Normal range
	Acute (n = 5)	Chronic (n = 6)	Cirrhosis (n = 1)	HCC (n = 1)		
Creatinine (mg/dl)	5.8 ± 2.2	6.6 ±2.9	5.6 ± 0	8.2 ± 0	7.2 ± 1.8	0.4 - 1.4
Uric acid (mg/dl)	6.9 ± 2.7	6 ± 3	9 ± 0	7 ± 0	6.8 ± 2.7	Male (3-7) Female (2-6)
Urea (mg/dl)	140.1±21.6	115.3 ± 40.6	142 ± 0	116 ± 0	152.3±17.7	15 - 45

Regarding the Mortality rate in the patients of our study (n=19)

a) Significantly, death appeared in all renal patients with HDV – coinfection (n=13) as well as 6 other cases with HBV only, as represented in table (9) and fig. (12).

Table (9) : *Mortality rate among renal patients in liver diseases with hepatitis viruses.*

The mortality rate. among renal patient groups (n = 19)		liver diseases							
		Acute		Chronic		Cirrhosis		HCC	
The mortality rate of renal failure (n = 16)	HBV only (n=4)	0	0.0%	3	15.8%	1	5.3%	0	0.0%
	Co-infection (n=12)	4	21.1%	6	31.6%	1	5.3%	1	5.3%
The mortality rate of renal insufficiency (n = 3)	HBV only (n=2)	0	0.0%	1	5.3%	1	5.3%	0	0.0%
	Co-infection (n=1)	1	5.3%	0	0.0%	0	0.0%	0	0.0%

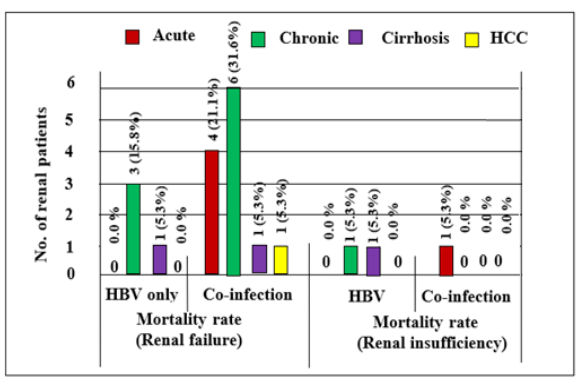

Fig. (12): Mortality rate among renal patients in liver diseases with hepatitis viruses.

DISCUSSION

Viral hepatitis is a major public health concern in underdeveloped countries, particularly for people with kidney disease. Early detection in dialysis facilities now enables us to better manage and stop the spread of hepatitis **(Almeida *et al.*, 2021).**

Our results regarding phases of hepatitis B virus infection which detected within 29 renal patients (HBsAg positive) while the prevalence of anti-HDV in HBV-related liver disorders has been reported at 44.8% (13/29) which is considerably high when it is

compared with another study in Egypt where it has been reported to be 32.2% **(Mousa *et al.*, 2014)** and also considerably high when it is compared with other studies Iran and India where it has been reported to be 11.5% and 10.6% respectively **(Roshandel *et al.*, 2008)** compared with other studies from India and Iran where it has been reported to be 15.2 % (7/46) and 65.9 % (29/44) respectively **(Bakhshipour *et al.*, 2013).**

In the present study, the anti-HDV positivity in chronic hepatitis B patients was 33.3 % (6/18) which is considerably similar results or slightly higher results when it is compared with another study in Egypt where it has been reported to be 32.1% (17/53) **(Mousa *et al.*, 2014),** but considerably high when it is compared with other studies from east of Iran and India where it has been reported to be 3.1 % (13/413) and 8.1% (3/37) respectively while the anti - HDV positivity in liver cirrhosis of patients was 66.7% (2/3) in our results was considerably high when it is compared with another study in Egypt where it has been reported to be 42.8% (6/14) **(Mousa *et al.*, 2014)** and also considerably high when it is compared with other studies from India and Iran where it has been reported to be 15.2 % (7/46) and 65.9 % (29/44) respectively **(Bakhshipour *et al.*, 2013).**

In our results on the analysis of the relation of HBV/HDV - coinfected related to the place residence of patients it was found that there is a significantly higher prevalence in patients of rural areas where it has been reported to be 69.0% (9/13)where the chance of infection is higher due to low socioeconomic condition and bad hygienic measure which is considerably similar results with another study in Egypt 52% (15/29) **(Mousa *et al.*, 2014).** In our results, the biochemical analysis showed in coinfected patients where level contents of ALT, AST, T.B, D.B, creatinine, uric acid, and urea were particularly high while PT% and albumin both fell, while in another study of Egypt where AST and ALT were higher than our study **(Mousa *et al.*, 2014)**.

Furthermore, we concur with Fabrizi *et al.,* (2008) who discovered that the rate prevalence of HBV infection is currently fairly low in dialysis centers across several nations (chronic HBsAg seropositive status ranging from 0 percent to 10 percent in patients on regular dialysis) **(Fabrizi *et al.*, 2008).**

Moreover, we corroborate those of Sheng et al. (2007) who discovered that 22.2 percent of HIV-positive patients with persistent HBV coinfection tested positive for anti-HDV, putting them at a greater chance of risk of getting sick than the general HBs-positive population **(Sheng *et al.* 2007).**

Studies by Martin and Eberhand (2022) focus on the detection and treatment of hepatic consequences of HBV infection in dialysis patients. Additionally, it covers how dialysis patients with chronic HBV infection should prepare for kidney transplantation **(Martin and Eberhand 2022).**

Also, a World Health Organization global report in 2015, cirrhotic disease and hepatocellular carcinoma were the chief causes of the estimated 887 000 deaths brought on by hepatitis B. (i.e., primary liver cancer). A person's risk of developing cirrhosis (60–70%) or fulminant hepatitis increases if they also have chronic hepatitis D and the death rate for HDV is thought to range from 2% to 20% of the population **(WHO. 2015)**.

The risk of HDV/HBV transmission in hemodialysis patients, the high mortality and morbidity rate of hepatitis D, the problems of diagnosis of HDV in hemodialysis patients, the irreversible complication of it is infection and difficult and controversial treatment have made HDV infection a major concern in hemodialysis patients **(Moghaddam *et al.*, 2009).**

CONCLUSION

It is concluded that among the examined (HBV) & (HDV) renal patients, renal impairment may sig-

nificantly increase the prevalence and incidence of hepatitis infection due to the weakening of the immune system of patients. If co-infection is not treated, this will result in 100% death.

ACKNOWLEDGMENT

The assistance of Dr. Amal M. Soliman and Dr. Ahmed M. Elsayed, members of the faculty of medicine at Ain Shams University, is gratefully appreciated.

ETHICAL STANDARDS

All human studies have been approved by the appropriate ethics committee and have therefore been performed following the ethical standards laid down in 1964 The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

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