

Occult hepatitis B virus infection in Egypt

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Abstract

The emerging evidence of the potentially clinical importance of occult hepatitis B virus (HBV) infection (OBI) increases the interest in this topic. OBI may impact in several clinical contexts, which include the possible transmission of the infection, the contribution to liver disease progression, the development of hepatocellular carcinoma, and the risk of reactivation. There are several articles that have published on OBI in Egyptian populations. A review of MEDLINE database was undertaken for relevant articles to clarify the epidemiology of OBI in Egypt. HBV genotype D is the only detectable genotype among Egyptian OBI patients. Higher rates of OBI reported among Egyptian chronic HCV, hemodialysis, children with malignant disorders, and cryptogenic liver disease patients. There is an evidence of OBI reactivation after treatment with chemotherapy. The available data suggested that screening for OBI must be a routine practice in these groups of patients. Further studies needed for better understand of the epidemiology of OBI among Egyptian young generations after the era of hepatitis B vaccination.

Key words: Hepatitis B virus; Occult hepatitis B virus infection; Hepatitis C virus; Egypt; Blood donors; Hemodialysis; Hepatitis B virus reactivation

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Core tip: Hepatitis B virus (HBV) genotype D is the only detectable genotype among Egyptian occult HBV infection (OBI) patients. Higher rates of OBI reported among Egyptian chronic HCV, hemodialysis, children with malignant disorders, and cryptogenic liver disease patients. There is an evidence of OBI reactivation after treatment with chemotherapy. The available data suggested that screening for OBI must be a routine practice in these groups of patients. Further studies are needed to understand the epidemiology of OBI among

Egyptian young generations after the era of hepatitis B vaccination.

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INTRODUCTION

The detection of hepatitis B virus (HBV) nucleic acid in the blood or liver of hepatitis B surface antigen (HBsAg) negative patients is called occult HBV infection (OBI). The molecular basis of OBI usually attributed to the long-term persistence viral covalently-closed-circular DNA in the nuclei of the hepatocytes^[1,2]. The majority of the OBI cases infected with replication-competent HBV showing strong suppression of replication and gene expression^[1]. The causes of this suppression had not yet clarified, although host immune response and epigenetic factors may play crucial roles. As a consequence of HBV suppression, the viral load is very low (usually below 200 IU/mL) or even undetectable in OBI cases^[1].

Patients with OBI can be either seropositive or seronegative. Seropositive OBI is characterized by positivity of anti-hepatitis B core antibody (anti-HBc) with or without the presence of anti-hepatitis B surface antibody (anti-HBs) while the seronegative OBI is characterized by the negativity of both antibodies. Sero-positive OBI constitutes the vast majority of OBI which can be quite explained by the larger proportion of resolved HBV infection^[3]. More than 20% of the occult carriers are seronegative for all HBV markers^[1,3]. Whether OBI-seronegative persons lack circulating antibodies due to the progressive antibodies disappearance in the years after acute infection resolution or it occurs from the beginning of HBV infection is unknown^[1,4]. Similarly, the difference in terms of clinical impact between OBI-seropositive and OBI-seronegative individuals is entirely obscure. What is known that OBI shows long-lasting specific T-cell immune response against HBV epitopes with a profile that is different between these two subsets of individuals? In fact, while *ex vivo* responses are similarly weak, *in vitro* T-cell expansion following specific peptide stimulation is more efficient among seropositive OBI cases than seronegative OBI cases^[1,5].

The only reliable diagnostic marker of OBI is HBV-DNA detection. No standardized assays for the detection of OBI in liver tissue are available^[1]. It is strongly recommended to utilize a highly sensitive^[1] and specific approach, for both blood and liver analysis based on "nested" or "real time" polymerase chain reaction (PCR) techniques. In addition, the use of primers specific for different HBV genomic regions and complementary to highly conserved (genotype shared) nucleotide

sequences highly suggested^[1]. Anti-HBc should be used, as a less than ideal surrogate marker if highly sensitive HBV-DNA testing is not feasible^[1,6].

Worldwide, the prevalence of OBI is quite variable^[7]. This variability depends on the sensitivity of the HBV DNA detection assay, the sample size, and whether it tested in the liver or the serum^[8,9]. There is a growing evidence of a positive correlation between prevalence of OBI and the endemicity of HBV infection^[1,3]. HCV infected patients appear to be a category of individuals with a higher prevalence of occult HBV^[1,3]. In particular, HBV-DNA is detectable in about one-third of HBsAg-negative HCV carriers in the Mediterranean countries^[1,3]. In addition, it was suggested that OBI is highly prevalent in HCV-infected patients with the advanced liver disease even in areas with less HBV spread^[1]. Prevalence of OBI appears to be fairly elevated even in patients with the cryptogenic liver disease, particularly in those with cirrhosis^[1]. Among blood donors, OBI appears to be a rare occurrence in the western world. It is a frequent incident in the developing countries^[1]. OBI rate in hepatitis B (HB)-vaccinated children varies in different risk groups, according to the local incidence of HBV, and irrespective^[10] to anti-HBs sero-status.

The emerging evidence of the potentially considerable clinical importance of occult HBV infection is the main reason for increasing interest in this topic^[11]. OBI may impact in several clinical contexts. The possible transmission of the infection^[11], the contribution to liver disease progression^[11], the development of hepatocellular carcinoma (HCC)^[11], and the risk of reactivation are the most relevant contexts^[12-14].

In 2013, the Food and Drug Administration had drawn attention to the possible fatal risk of hepatitis B reactivation in patients receiving anti-CD20 drugs^[12]. HBV reactivation is known to occur with a wide variety of immune-suppressive therapies and may occur in the context of cancer treatment^[12], immunosuppressive therapy for autoimmune disease^[12] and transplantation. It is a potentially lethal condition and yet is preventable^[12].

HBV reactivation does occur in persons who have anti-HBc^[12] with and without anti-HBs and no detectable HBsAg in serum^[12]. Among 100 patients undergoing chemotherapy for non-Hodgkins lymphoma, reactivation was noted in 2 of 45 (4%) anti-HBc positive/HBsAg negative patients^[12]. In a study^[12] from the Brigham and Women's Hospital in Boston. Sixty-one patients identified with resolved HBV infection before a hematopoietic stem cell transplant (HSCT), (HBsAg negative, anti-HBc positive)^[12]. Of these, 12 (20%) developed reverse seroconversion^[12]. A recent systematic literature review identified reports of 257 patients with active or recovered HBV infection^[12] treated with anti-tumor necrosis factor^[14]. Reactivation detected in 5% of those who were HBsAg negative but anti-HBc positive^[14]. These data hint that all patients undergoing chemotherapy, immunosuppressive therapy, HSCT or solid organ transplantation should screen for prior HBV infection^[11]. The use of antiviral treatment appears to diminish the

Table 1 General, and epidemiological characteristics of included studies *n* (%)

Ref.	Study period	Studied population	Location of the study	Age group	Total number	OBI rate
Elrashidy <i>et al</i> ^[10]	2013-2014	Healthy/diabetic children	Lower Egypt	Children	170	0 (0)
Raouf <i>et al</i> ^[20]	2011-2013	HCV positive cancer	Lower Egypt	Children	50	16 (32)
Kishk <i>et al</i> ^[21]	ND	HCV	Lower Egypt	Adults	162	3 (1.85)
Elkady <i>et al</i> ^[22]	2010-2011	Hematologic malignancy	Upper Egypt	Adults	53	1 (1.88)
Said <i>et al</i> ^[34]	ND	HBD	Lower Egypt	Adults	3167	52 (1.64)
El-Ghitany <i>et al</i> ^[31]	ND	HBD and HCV-BD	Lower Egypt	Adults	504	21 (4.16)
Youssef <i>et al</i> ^[23]	ND	CLD	Lower Egypt	Children	24	7 (29.2)
Abu El Makarem <i>et al</i> ^[18]	ND	HD	Upper Egypt	Adults	145	6 (4.1)
Elgohry <i>et al</i> ^[19]	ND	HD	Lower Egypt	Adult	93	25 (26.9)
Shaker <i>et al</i> ^[27]	ND	Thalasemias	Lower Egypt	Children	80	26 (32.5)
Selim <i>et al</i> ^[30]	2008-2009	HCV	Lower Egypt	Adult	60	23 (38.3)
Hassan <i>et al</i> ^[34]	ND	HCC	Lower Egypt	Adult	40	25 (62.5)
Emara <i>et al</i> ^[32]	ND	HCV	Lower Egypt	Adult	155	6 (3.9)
Antar <i>et al</i> ^[25]	2007-2008	HBD	ND	Adult	1021	5 (0.48)
El-Sherif <i>et al</i> ^[29]	2005-2006	HCV	Lower Egypt	Adult	100	16 (16)
Youssef <i>et al</i> ^[26]	ND	CLD	Lower Egypt	Adult	204	119 (58.3)
El-Zayadi <i>et al</i> ^[33]	2005	HBD	Upper/lower Egypt	Adult	712	9 (1.26)
Said <i>et al</i> ^[28]	ND	Hematologic malignancy and disorders	Lower Egypt	Children	100	21 (21)
¹ El-Sherif <i>et al</i> ^[39]	1998-1999	HBD	Lower Egypt	Adults	150	2 (1.3)

¹Data taken by direct contact with authors. ND: Not determined; OBI: Occult HBV; HBD: Healthy blood donors; HCV-BD: Blood donors positive for HCV; CLD: Cryptogenic liver disease; HD: Hemodialysis; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus.

risk of severe or fatal reactivation of HB infection^[12].

Egypt had a high prevalence of HCV (17.5%)^[15,16] and intermediate endemicity for HBV infection^[16]. The rising prevalence of OBI in Egypt is not surprising. Several reports published on OBI in Egyptian populations. We find that it will prudent to enumerate those studies, and review them to clarify the overall prevalence of OBI and determine the size of that problem in Egypt.

GEOGRAPHIC DISTRIBUTION OF OBI IN EGYPT

Lehman *et al*^[17] were unable to compare the HBV prevalence between Upper and Lower Egypt due to the inadequate number of HBV prevalence studies in Upper Egypt. Similarly, only two studies^[18,19] addressed OBI prevalence in Upper Egypt (Table 1). Lower OBI rate (4.1%)^[18] reported among Upper Egypt hemodialysis (HD) patients compared with HD patients in Lower Egypt (26.9%)^[19]. HCV prevalence was significantly higher in patients from Lower Egypt according to Lehman *et al*^[17], which in turn confirms the positive correlation between HCV and OBI frequencies.

OBI GENOTYPES AMONG EGYPTIANS

The genetic background of OBI studied by Raouf *et al*^[20]. The researchers recruited only children with cancer and the results pointed out that the incidence of OBI in those patients was 32% (Table 1). All infections were with genotype D, and 5 out of 16 OBI patients showed some mutation in the HBV sequence. Two patients had a mutation in the surface gene, and a third one had mutation with a significant shift from the wild-type genetic sequence and those three mutations

were presumed to be the cause of OBI. The remaining two mutations were considered silent and not the cause of OBI. In addition Kishk *et al*^[21] concluded that HBV genotype D was the only detectable genotype in Egyptian OBI patients with chronic HCV^[21]. Among 53 HBsAg negative patients with hematologic malignancies, 5 of them (9.4%) experienced HBV reactivation. OBI was confirmed in one of them (1.88%) (Table 1), and all five patients had Genotype D1^[22]. HBV-DNA detected in 7/24 HBsAg-negative children with symptomatic hepatic dysfunction. The G1896A mutation found in 3/7 (43%) HBsAg-negative children and all classified as genotype D^[23]. Classically it had been concluded that HBV genotype D is more common in the Mediterranean area, the Middle East and India^[24]. The similarity of OBI genotype and the reported HBV genotype in Egypt could support the assumption that OBI infection is part of the natural history of HBV rather than a distinct entity of infection.

OBI DISTRIBUTION AMONG DIFFERENT AGE GROUPS

HBV prevalence is decreasing in Egyptian young generations^[10], which may attributed to universal HBV vaccination. The average prevalence of HBV in Egyptian adults is 8% while the average prevalence in children is 1.6%^[10]. OBI prevalence among Egyptian adults ranges from 0.48%^[25] to 58.3%^[26], with lower prevalence among blood donors and higher prevalence among chronic liver disease patients (Table 1). Unexpectedly the prevalence of OBI in children was high according to available data. OBI detected in 32%^[20], 32.5%^[27], 21%^[28] of HCV-positive cancer children, thalassemic and children with hematologic malignancy and disorders

respectively (Table 1). These high OBI rates could be attributed to the fact that; these studies assessed OBI in children with multiple risks for HBV transmission, includes poly-transfusion and immunosuppression. In addition, many children in these studies were HCV co-infected, which may explain the higher OBI prevalence among tested children. Going with our notion Elrashidy *et al.*^[10], were unable to detect OBI among HB-vaccinated healthy children ($n = 107$).

OBI IN HCV EGYPTIAN PATIENTS

As HBV and HCV share many risk factors and the same transmission routes, OBI detection in HCV patients is not surprising. Indeed, El-Sherif *et al.*^[29] showed that; among HBsAg-negative patients, the number of patients with parenteral antischistosomal therapy (PAT) is significantly higher in anti-HBc-positive HCV-positive patients, compared with anti-HBc-negative HCV-positive patients^[29]. They concluded that PAT transmitted both HCV and HBV in many Egyptians. OBI prevalence in Egyptian HCV-positive patients is 1.85% to 38.3% according to the available data^[21,30] (Table 1). This wide range of OBI may be related to different study designs as well as different HBV-DNA detection methods. Moreover, it may related to the liver disease severity and the immunity of the studied patients.

Occult HBV prevalence correlated with the severity of liver disease in HCV patient^[1], and it inflicted an adverse impact on HCV outcome^[29]. Selim *et al.*^[30] found that OBI prevalence was higher among patients with alanine aminotransferase (ALT) flare (63.3%) in contrast with normal ALT patients (13.3%). One hundred chronic HCV patients negative for HBsAg subdivided into two groups according to anti-HBc seroreactivity and tested for OBI by El-Sherif *et al.*^[29]. Group A included 71 patients positive for anti-HBc and group B included 29 patients negative for anti-HBc. HCV- patients positive for anti-HBc have more severe liver disease compared with anti-HBc negative patients^[29]. Although HBV-DNA in the serum detected in 22.5% of anti-HBc-positive chronic HCV patients, it was not detected in any of anti-HBc-negative patients^[29]. There was no significant difference in the clinical and laboratory parameters tested, between anti-HBc-positive patients with and without HBV-DNA in the serum^[29]. Kishk *et al.*^[21] examined the difference between HCV-infected and HCV/OBI dually infected patients in terms of proinflammatory markers, and histopathological picture. Although they used small sample size (3 patients) their results highlighted that OBI associated with higher Necro inflammatory markers and worse histopathological picture. A clear example came from El-Ghitany *et al.*^[31] who compared OBI prevalence between two groups of apparently healthy blood donors, they found no significant difference between OBI prevalence among both HCV-positive (3.2%) and HCV-negative (5.1%) cohorts.

One cannot perform firm conclusion about the OBI impact on response to HCV antiviral therapy from

the available literature data. Two studies, with a small number of OBI patients (6 patients), addressed the impact of OBI on the response of HCV patients to antiviral therapy. Emara *et al.*^[32] concluded that; detection of OBI in chronic HCV-positive patients ($n = 3$) has no impact on response to combined pegylated interferon/ribavirin therapy. Similarly, Kishk *et al.*^[21]. 2014 reported OBI patients ($n = 3$) were responsive to combine pegylated interferon/ribavirin therapy after 12 wk.

OBI IN EGYPTIAN BLOOD DONORS

Occult HBV infection extensively explored in blood donors^[1] where it appears to occur quite rarely in the western world and more frequently in developing countries^[1]. According to available data, OBI was detected in 1.26%^[33] to 4.16%^[31] of Egyptian blood donors (Table 1). The detection rate of OBI in Egyptian HBsAg-negative blood donors, without known anti-HBc serostatus, is relatively low (4.16%)^[31]. This rate markedly increased when OBI tested in anti-HBc positive donors (14.3%)^[34]. This high rate of OBI among anti-HBc-positive donors is not consistent with the findings of many published studies^[35-38], which ranged from 0%-6%. This high prevalence may attributed to the high sensitivity of used assay. Out of five studies, three^[25,33,39] used nested PCR. The fourth one^[34] used a real time PCR with very low detection limit (3.8 IU/mL) (Table 2), increasing the sensitivity of OBI detection.

Little data are available about the infectivity of OBI after a blood transfusion, although the overall OBI transmission rate is 28% according to a recent European study^[40]. A lower rate detected in a Taiwanese study^[41] (18.2%). The lower transmission rate detected among Japanese (3%) may related to exclusion of patients with detectable levels of HBV-DNA in mini pool nucleic acid test and those with high titer anti-HBc, and many recipients were immune^[42]. The infectivity of OBI assessed in a small number of Egyptian blood recipients^[34], where 11/34 recipients received anti-HBc positive blood, two of them were HBV-DNA positive, and none developed post-transfusion hepatitis. Like other lookback studies; this study reported several difficulties and limitations in addition to the small sample.

These data indicated that screening Egyptian blood donors for HBsAg only is not safe and the need for additional blood safety measures to reduce post-transfusion HBV transmission. Anti-HBc screening of Egyptian blood donors (in addition to HBsAg) is not practical. It could result in discarding a significant amount of blood, where HBV-DNA not detected in 82.8%^[25], 88%^[33], 90%^[39], 93.7%^[34] of HBsAg-negative/anti-HBc-positive blood donors according to available data. On the other hand missing anti-HBc/HBV-DNA-definite units may have serious implication if used in blood transfusion^[39]. Based on the high OBI rate among blood donors, we believe that HBV-DNA testing should introduce in Egypt's blood banks. Whether to test HBV-DNA in a mini pool, in all blood donors or in anti-HBc-positive donors only is

Table 2 Methods of hepatitis B virus DNA detection in included studies

Ref.	HBV DNA detected in	PCR method	DNA limit of detection
Elrashidy <i>et al</i> ^[10]	Serum	Nested	ND
Raouf <i>et al</i> ^[20]	Serum	Real-time and Nested	ND
Kishk <i>et al</i> ^[21]	Serum	Real-time and Nested	ND
Elkady <i>et al</i> ^[22]	Serum	Real-time	20 IU/mL
Said <i>et al</i> ^[34]	Serum	Real-time	3.8 IU/mL
El-Ghitany <i>et al</i> ^[31]	Serum	Semi-nested	45 copies/mL
Youssef <i>et al</i> ^[23]	Serum	Real-time	10 copies/mL
Abu El Makarem <i>et al</i> ^[18]	Serum	Nested and Real-time for HBV-DNA-positive by nested PCR	6 IU/mL for real-time PCR
Elgohry <i>et al</i> ^[19]	Serum	Real-time	ND
Shaker <i>et al</i> ^[27]	Serum	Real-time	ND
Selim <i>et al</i> ^[30]	Serum	Semi-nested	45 copies/mL
Hassan <i>et al</i> ^[54]	Liver tissue	Nested	ND
Emara <i>et al</i> ^[32]	Serum	Real-time	12 IU/mL
Antar <i>et al</i> ^[25]	Serum	Real-time	ND
El-Sherif <i>et al</i> ^[29]	Serum	Real-time	35 copies/mL
Youssef <i>et al</i> ^[26]	Serum	Nested	ND
El-Zayadi <i>et al</i> ^[33]	Serum	Nested	ND
Said <i>et al</i> ^[28]	Serum	Nested	ND
¹ El-Sherif <i>et al</i> ^[39]	Serum	Nested	ND

¹Data taken by direct contact with authors. ND: Not determined; PCR: Polymerase chain reaction; HBV: Hepatitis B virus.

debatable and attractive area for research. Similarly, the relatively high OBI rate among Egyptian blood donors justifies further lookback and traceback extensive study of OBI infectivity among blood recipients.

OBI IN EGYPTIAN THALASSEMIC

Populations at high risk of parenterally transmitted infection have widely investigated for OBI. Thalassaemic, are at increased risk of infectious disease transmission. The prevalence of OBI among Egyptian thalassaemic children was found to be 32.5% (26/80)^[27] (Table 1). The prevalence of OBI was 0% and 31.4% among Iranian^[43] and Indian^[44] thalassaemic respectively. This variation may mostly related to small samples size.

OBI IN EGYPTIAN HEMODIALYSIS PATIENTS

The OBI prevalence in Egyptian hemodialysis (HD)-patients range from 4.1% to 26.9%^[18,19] (Table 1). Studies on HD-patients have provided widely divergent results. The highest OBI prevalence (58%) in HD-patients reported from Spain^[45]. The results reported from Turkey varied from 0% to 27.5%^[46,47]. Lower prevalence (3.8%) was reported by American investigators^[48]. Studies from Greece showed that 0.9%-20.4% of HD-patients suffered from OBI^[49,50]. The prevalence of OBI among HD-patients seems to be multi-factorial and could not be explained by one factor. It is not region specific, where different studies reported contradictory results from the same county. The difference in methods sensitivity and specificity in the various studies could be the main cause responsible for the discrepant findings.

Age, sex, history of hepatitis, blood transfusion,

schistosomal antibodies, liver enzymes, and serum albumin level not associated with OBI in Egyptian hemodialysis patients. In addition, no significant differences in the age, duration of hemodialysis, biochemical parameters, and serological markers of HBV, or HBV-DNA between patients with and without HCV infection. In contrast, the presence of HBV-DNA significantly associated with anti-HBc ($P = 0.003$)^[18]. These data support the role of anti-HBc as a useful surrogate marker for OBI in HD-patients whenever HBV-DNA testing is not available.

OBI IN EGYPTIAN CHILDREN WITH HEMATOLOGIC MALIGNANCIES

Raouf *et al*^[20] and Said *et al*^[28] tested OBI in children with hematologic malignancies, and the results pointed out that the incidence of OBI in those patients was 21%-32%, respectively (Table 1). The majority of OBI patients were seronegative to anti-HBc which point that anti-HBc is not sufficient to exclude OBI at least in patients with hematologic malignancies. It believed that hematological malignancies associated with an immune deficiency that could preclude the synthesis of anti-HBs and anti-HBc. Another interesting finding is the higher OBI prevalence in HCV-infected patients.

OBI IN CRYPTOGENIC LIVER DISEASE PATIENTS

Occult HBV infection is becoming an important disease entity as a cause of liver disease in HBsAg negative patients. OBI diagnosed in 58.3%^[26] of Egyptian patients with symptomatic hepatitis (Table 1). Lower OBI

frequency (30%) reported by Chemin *et al.*^[51] among patients with chronic non-A non-E hepatitis in France. This difference may be related to the difference of HBV prevalence in general populations of both countries.

OBV IN EGYPTIAN HCC PATIENTS

Occult HBV infection may play a direct oncogenic role through both its integration into the host genome and the maintained transcriptional activity. The prevalence of OBV in HBsAg-negative and anti-HBc-negative HCC patients varies among the different population. It ranges from 16% in the United States, which has a low prevalence of chronic hepatitis B, to 70% in endemic areas like China^[52,53]. A high rate of OBV was found among Egyptian HCC patients 62.55% (25/40)^[54] (Table 1). This high frequency of OBV in Egyptian patients with HCC cannot explain the level of HBV endemicity in Egypt. The small sample size in addition to combined OBV and HCV infection may partially explain the higher OBV frequency among studied HCC patients.

REACTIVATION OF OBV AFTER CHEMOTHERAPY

Among 53 patients with hematological malignancies^[22], negative for HBsAg before the start of and throughout the chemotherapy course. Thirty-five (66%) were anti-HBc-negative, and the remaining 18 (34%) patients were anti-HBc-positive. Five of the 53 (9.4%) patients with hematologic malignancies experienced HBV reactivation^[22], one of them (1.88%) developed reactivation from an occult HBV infection (Table 1).

ROLE OF HEPATITIS B-VACCINE IN PROTECTION AGAINST OBV

Because of immune incompetence in diabetic patients compared with healthy control, OBV detected in 11% of diabetic patients vs 3% of healthy controls^[55]. Elrashidy *et al.*^[10] tested the incidence of OBV in HB-vaccinated healthy ($n = 107$) and diabetic ($n = 63$) children. None of the tested children had evidence of OBV or remote HBV infection (anti-HBc) which indicate that HB vaccination had been protective against OBV^[10] (Table 1).

CONCLUSION

Like HCV and HBV; nationwide epidemiological study providing exact data regarding OBV situation in Egypt is lacking. Our review represented a trial to synthesize the published OBV results in Egypt. The current report highlights the increase in OBV prevalence in Egyptian HCV-positive patients parallel to the progression of liver disease. Screening for OBV in HCV-positive patients may detect those vulnerable to more progression of their liver disease. Further testing of the impact of OBV on HCV antiviral therapy and transplanted patients is needed. In

addition screening for OBV must be a routine practice in blood donors and poly transfused as well as cryptogenic liver disease patients. A definitive assessment of OBV among Egyptian blood donors needed for testing all HBsAg-negative blood donors, instead of only testing anti-HBc-positive patients. Further evaluation of the OBV epidemiology among Egyptian young generations after the era of HBV vaccination is needed. As well, studies of OBV in Upper Egypt should be encouraged.

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