OCCULT HBV INFECTION REACTIVATION IN NON-HODGKIN'S LYMPHOMA: AN UPDATE ON PREVALENCE AND MANAGEMENT

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Disclosure: No potential conflict of interest.
Received: 31.10.14 **Accepted:** 03.12.14
Citation: EMJ Hepatol. 2015;3[1]:70-78.

ABSTRACT

Occult hepatitis B virus infection (OBI) is characterised by the persistence of hepatitis B virus (HBV) genome in the liver, without any evidence of overt infection: without HBV surface antigen (HBsAg) and HBV DNA detectable in the serum, or fugacious spots of very low levels of viraemia. OBI, a possible phase in the natural history of chronic hepatitis B, is mainly due to the strong suppression of viral replication by host's immunity. Although every condition inducing a strong immunosuppression may cause an OBI reactivation, onco-haematological patients, particularly those affected by non-Hodgkin's lymphoma (NHL), are at the highest risk of this occurrence. This is mostly due to the primary involvement of the immune system that characterises these diseases, and the strong immunosuppressive treatments used for their cure. OBI reactivation represents a life-threatening risk, because of the possible development of an overt acute hepatitis that may lead to hepatic failure. Prophylaxis with lamivudine can prevent OBI reactivation and, when it occurs, the prompt administration of an antiviral therapy with nucleos(t)ide analogues can stop it. Currently, no valid serological tests for occult HBV detection are available, in this way every HBsAg-negative patient undergoing treatment for NHL is to be considered at risk of a 'probable OBI reactivation'. The estimation of the real extent of this occurrence in a NHL setting is a difficult challenge, mostly due to the difficulty of obtaining a definitive diagnosis (which involves the availability of a liver biopsy performed before its development) and the high variability of the literature reports on this issue. In fact, the data concerning this prevalence range from 2.3-27.7% among the different papers, according to different study designs, different diagnostic criteria, different study populations, and different geographical areas of origin of the patients. The aim of this review is to browse the available knowledge about occult HBV infection amongst NHL patients, focusing on the prevalence of OBI reactivations, their identification, and their management.

Keywords: Occult HBV infection, non-Hodgkin's lymphoma, hepatitis B virus reactivation, immunosuppression.

INTRODUCTION

Occult hepatitis B virus infection (OBI) is one of the most difficult challenges in the field of hepatology. In fact, it is difficult to diagnose, it can be present in patients that are totally seronegative for hepatitis B virus (HBV) markers, and when it occurs in a patient that needs a strong immunosuppressive treatment (i.e. for non-Hodgkin's lymphoma [NHL]), it represents a life-threatening risk of overt HBV reactivation. OBI represents a possible phase of the natural history of chronic hepatitis B,[1] and it is characterised by long-lasting persistence and low-level replication of HBV genomes in the liver, without the evidence of overt HBV infection. It is defined by the presence of HBV DNA in the liver with undetectable or occasionally detectable (with fugacious 'spots' of viraemia of very low levels)

HBV DNA in the serum, in individuals with negative testing for HBV surface antigen (HBsAg) and positive testing for HBV core antibodies (HBcAb).[2] It has been episodically reported also in 'totally negative' patients (HBsAg/HBcAb negative) and even in HBV surface antibody (HBsAb) positive patients.[3] In other cases, the presence of a HBV infection, with the undetectability of HBsAg, is caused by the so-called 'S-escape mutants' that produce a modified HBsAg not identified by the standard commercially available diagnostic kits.[4] This last entity is not to be considered an OBI. In fact, OBI is caused by viruses with no genetic mutations, their replication being strongly suppressed by the host's immuno-surveillance.[5] In immunocompetent subjects, occult infection is totally asymptomatic, without any amount of damage of the liver.[5] Nevertheless, every condition inducing a strong immunosuppression, such as immunosuppressive therapies used in post-transplant and autoimmune diseases, or chemotherapies for solid and haematologic malignancies, has been indicated to eventually cause an OBI reactivation, in the same way it can cause the reactivation of an overt HBV infection.[2] In the real practice, onco-haematological malignancies, and in particular B cell NHL and their treatments, have demonstrated to represent the highest risk of OBI reactivation.[6] The aim of this paper is to review the available data about occult HBV in patients with NHL, focusing on the prevalence of reactivations, its identification, and management.

METHODS

To estimate the prevalence of OBI reactivation, we performed a computer based literature search in PubMed, Scopus, Google Scholar, and MEDLINE databases using the medical subject headings "hepatitis B" and "lymphoma". We limited the research to English language publications and excluded reviews and case reports. Eligible studies were limited to those focusing on HBsAg-negative/HBcAb positive patients receiving treatment for lymphoma. From 856 studies only 16 were selected as eligible. Despite this narrow selection, prevalence of OBI reactivation varies greatly between the selected studies.

OBI DIAGNOSIS AND VIROLOGY

The occult infection status depends on the peculiar life cycle of the HBV and the ability to convert its viral genome into a covalently closed circular DNA (cccDNA), a long lasting HBV intermediate that persists in the nucleus of the hepatocyte as a stable chromatinised episome.[7] The cccDNA is a stable and long-term persistent molecule, therefore, in a long half-life cell as the hepatocyte, this peculiar form of infection may persist for its lifetime, even in the absence of replicating HBV DNA strains in the cytoplasm.[8] The ability of HBV to develop an occult infection does not appear to be related to its genetic variability. In fact, an occult carrier may transmit HBV through blood transfusion or organ transplantation inducing a classic acute hepatitis B in the recipients,[9,10] and during OBI reactivation, the carriers may show a typical hepatitis B serological profile with titratable HBsAg and HBV DNA in the serum.[3] According to Taormina statements,[11] we can distinguish two types of OBI carriers on the basis of the HBV antibody profile: seropositive-OBI (HBcAb and/or HBsAb positive) and seronegative-OBI (HBcAb and HBsAb negative) individuals. Seronegative-OBI is reported to occur in about 20% of the cases.[5] It represents the main challenge forthe prevention of reactivation during chemosuppressive and immunosuppressive therapies due to the fact that no HBV markers are present to suspect such a condition.

OBI diagnosis: At present, no valid serological tests for occult HBV detection are available. Indeed, the gold standard for OBI diagnosis is the analysis of DNA extracts from liver tissues. It must be performed by the use of highly sensitive techniques such as nested polymerase chain reaction (PCR) or real-time PCR, conducted with specific primers for different HBV genomic regions (core, X, and S genes), complementary to highly conserved (genotype shared) nucleotide sequences, in order to find the low quantities of nuclear cccDNA.[11] To obtain the diagnosis of OBI, at least two of the three genes are to be found on the liver specimens of a HBsAg negative patient that is suspected to carry this infection. Obviously, only in a minority of cases, liver tissue specimens (collected before the reactivation) are available for this diagnostic analysis, and the liver biopsy is not always feasible in NHL patients. On account of the fluctuating profile of detectable viraemia in OBI, serially collected samples should be tested. A serological assay for HBcAb should be considered less than an ideal surrogate marker for identifying potential seropositive OBI, indeed not all HBcAb positive individuals are found to be

HBV DNA positive and this test may provide false-positive results.[11]

OBI reactivation diagnosis: By now, a precise definition of OBI reactivation has not yet found a consensus in literature. In most of the cases, it is reported as the reappearance of HBsAg or a *de novo* detection of HBV DNA in the serum, in patients where previous negativity of both of these virological markers can be demonstrated. Besides this evidence, the presence of almost two of three genes ('core', X, and S) of HBV DNA sequence in liver specimens, collected any time before the reactivation itself,[12,13] must also be demonstrated. As reported above, the availability of liver samples is limited and, moreover, these specimens must have been stored in liquid nitrogen to allow DNA extraction. For these reasons, the most common approach used by the clinicians to address this issue is to define the presence of a 'probable OBI reactivation' when an overt HBV acute reactivation occurs in a patient with previous evidences of a 'resolved HBV infection' (i.e. an HBsAg negative, HBcAb positive individual). In this way, when it is not possible to directly confirm the presence of HBV on the liver tissue prior to reactivation and/or any sign of a previous contact with HBV (i.e. in totally seronegative patients), we should consider every reactivation occurring in patients who are HBsAg negative prior to starting immunosuppressive treatments, as 'probable OBI', recalling also the possibility of a *de novo* infection.[2] In this context, it appears clear that the real prevalence of this 'elusive' infection in the general population is difficult to know, and it is not easy to estimate the probability of reactivation in the onco-haematological setting.

OBI Reactivation in NHL

As mentioned above, it is well known that the presence of OBI can represent a life-threatening risk in patients who undergo cytotoxic chemotherapies. This is due to the fact that an overt HBV reactivation (with titratable HBsAg and HBV DNA levels) may occur for the loss of the host's immnosurveillance. Even if this occurrence is less frequent in individuals with OBI than in HBsAg positive patients,[14] it represents a non-neglectable risk. Rarely, it presents itself as a fibrosing cholestatic hepatitis that can occur at any time from the beginning of immunosuppression, and it is characterised by a direct cell damage produced by an intense intrahepatic production of viral antigens.[3] However, in the majority of cases the hepatic damage is related to T cell immune reaction against the viral replication, which starts at the end of chemotherapy, when the immune competence is restored. This can lead to the development of an acute hepatitis that may range from a simple lobular hepatitis with mild alanine transaminase (ALT) elevation and only minimal lesions to a fulminant liver failure (LF).[15] Compared to the other cancer patients, onco-haematological patients, and particularly those affected by NHL, have the highest risk of HBV reactivation.[6] This is caused by the primary involvement of the immune system peculiar to this group of lymphoproliferative diseases[16] and also by the strongly immunosuppressive treatment regimens.[2] For example, the majority of treatment regimens contain high doses of corticosteroids that are administered for long periods. This type of administration (high-dose-long-time) as well as establishing an immunosuppressive state, may directly stimulate HBV replication through the glucocorticoid responsive element, a transcriptional enhancer element present in HBV viral genome.[17] Nevertheless, the drug that has attracted more attention in this field is certainly rituximab. Rituximab is a chimeric mouse-human monoclonal antibody (mAb) that has been introduced in CD20-positive NHL therapy since 1997, in addition to conventional chemotherapy. This drug radically changed the natural history of NHL, giving a great improvement of patient outcomes in both indolent and aggressive NHL, becoming the major part of the standard of care for these diseases.[18,19] It is also to be noted that the use of rituximab is not limited to haematological malignancies but its use is also spreading in a wide range of diseases in which there is an autoimmune involvement of B lymphocytes (i.e. rheumatoid arthritis, inflammatory bowel diseases, etc.).[20]

After a few hours of infusion, rituximab induces a strong depletion of B lymphocytes and this condition persists for 6-8 months, in which the patient remains immunosuppressed.[20] It is very interesting that this drug, a strong inhibitor of B lymphocytes, is considered the most potent inductor of the HBV reactivation, even if the host immune control on HBV has been historically considered to be exerted by T lymphocytes. Probably, B lymphocytes intervene in the control of HBV replication by enhancing the cytotoxic response of CD8 T lymphocytes through their activity as antigen-presenting cells.[21] The

combination of rituximab with cyclophosphamide, hydroxydaunorubicin, oncovin, and predniso(lo)ne (R-CHOP protocol) provide the highest risk of reactivation both in patients with overt infection and those with occult infection.[22] In support of these hypotheses, before the introduction of rituximab in the standard of care for lymphoproliferative disease, OBI reactivation was a rare and anecdotal event and was mostly widespread among patients undergoing haematopoietic stem cell transplantation.[16,23-25]

Ofatumumab, used for treatment of onco-haematological diseases, is another anti-CD20 mAb considered a potential factor responsible for reactivation of OBI.[26] OBI reactivation has also been occasionally observed in patients with rheumatologic diseases, undergoing treatments with 'biologic' drugs (anti-CD20 and/or anti-tumour necrosis factor-alpha) or high doses of corticosteroids.[27,28] Moreover, besides NHL and rheumatologic patients, other high-risk categories of OBI reactivation consist of subjects undergoing haematopoietic stem cell transplantation (in which itwas described that HBsAg inverse-seroconversion often occurs, although often without a clinically typical acute hepatitis[29,30]), and liver or kidney transplantation from HBcAb positive donors.[31,32] There are also few data about the real risk of OBI reactivation in patients undergoing chemotherapy for solid tumours[33] and transarterial chemoembolisation for hepatocarcinoma.[2] In this review our attention has been focused on OBI reactivation in NHL patients.

OBI Reactivation Prevalence in NHL Setting

Approximately 350 million people worldwide are chronically infected with HBV, but many of them do not develop a chronic active hepatitis and remain asymptomatic. Moreover, in high endemic areas it is estimated that the prevalence of isolated HBcAb positivity is higher than 60% and, therefore, it is estimated that almost 40% of the world population has been in contact with or is a carrier of HBV.[34-36] As mentioned above, OBI reactivation can occur in patients with evidences of a 'previously resolved' HBV infection. With 'previously resolved infection' we refer to various clinical situations ranging from the complete immunity (HBsAb positivity), the isolated HBcAb positivity, and the total seronegativity for HBV markers. Considering this scenario, to estimate the prevalence of OBI reactivation is a difficult challenge. The reports in the literature, in fact, seem to confirm this statement, showing a high variability in the prevalence among various patient cohorts, also analysing only the NHL setting.

This variability can be, in part, accounted for by the different designs of the studies, but also to the patient characteristics themselves. The studies differ mainly in the characteristics of the population on which it is estimated the prevalence of reactivation: in some cases it is calculated on the general HBsAg negative population, obtaining lower prevalence rates, in other cases it is evaluated exclusively among HBsAb negative/HBcAb positive patients, thus resulting in higher prevalence rates. Although in recent years the research has been focused on anticore positive patients, in whom the reactivation is more frequent, it must be stressed that >20% of occult carriers are negative for all serum markers of HBV[5] and the risk of reactivation between these patients is not negligible. Therefore, in our view, the reports that analyse all HBsAg negative patients may be considered more reliable on assessing this issue. The methods to diagnose HBV reactivation varied widely across the different studies and thus also the definition of OBI reactivation. In the majority of the studies, especially those in a small population, a 'pre-clinical HBV reactivation' is considered, that is defined as the reappearance of detectable HBV DNA in the serum, even without an abnormal ALT level. On the contrary, large population studies very often use a 'clinical reactivation' definition, usually described as the derangement of ALT/aspartate transaminase (at least 2/3 times upper normal values), with HBsAg and HBV DNA detectable in the serum. Finally, among the reviewed studies, only a few papers reported that an analysis of DNA extracts from liver tissues was performed, thus assessing the 'true prevalence of OBI'.[37] As previously said, after the OBI reactivation, the patient can develop an acute hepatitis that can range from simple lobular hepatitis with minimal lesions to fulminant LF, or have non-clinical complication. As will be widely discussed in the section of the management, currently the treatment should be started in the preclinical phase of reactivation to ensure the best results.

Undoubtedly, the most talked about risk factor for the OBI reactivation is the treatment that patients receive. As said previously, many evidences in the literature identify as the main risk factor for the OBI reactivation therapy with anti CD20 mAb (rituximab). In 2006, Hui et al.[13] performed a study on 244 HBsAg-negative

NHL patients receiving systematic chemotherapy with or without rituximab. Among the 8 (3.3%) who developed HBV reactivation, 7 were treated with rituximab, and multivariate analysis demonstrated that rituximab was a risk factor for HBV reactivation in HBsAg negative patients.[13]

Table 1: Reported prevalence of occult hepatitis B virus (HBV) reactivation in non-Hodgkin's lymphoma patients.

Study	Country of origin	No. of patients HBsAg negative	No. of patients HBcAb positive	Prevalence of OBI reactivation No. (%)a	Type of therapy during reactivation	Definition of reactivation	Study limitations
Hui et al.[13]	China	244	152	8/244 (3.27%)	7 +rituximab 1 -rituximab	Clinical[b]	Retrospective
Persico et al.[37]	Italy	52	18	5/18 (27.7%)	Not reported	Preclinical[c] and histological[d]	Small numbers
Hanbali et al.[41e]	USA	26		7/26 (26.9%)	7 +rituximab	Clinical	Retrospective, small numbers, only rituximab
Targhetta et al.[38]	Italy	638	74 (+rituximab) 245 (-rituximab)	2/245 (0.6%) 2/74 (2.7%)	2 +rituximab 2 -rituximab	Clinical	Retrospective
Pei et al.[42e]	Taiwan	95		4/95 (4.2%)	4 +rituximab	Clinical	Retrospective, only rituximab[e]
Yeo et al.[12]	China	80	46	5/80 (6.2%)	5 +rituximab	Clinical	
Fukushima et al.[43]	Japan	127	48	2/48 (4.1%)	1 +rituximab 1 -rituximab	Clinical and Preclinical	Retrospective
Francisci et al.[44]	Italy	56	13	3/13 (23%)	Not reported	Preclinical	Type of therapy not reported, small numbers
Ji et al.[39]	China	368	45 (-rituximab) 43 (+rituximab)	1/43 (2.3%)	1 +rituximab	Clinical	Retrospective
Méndez-Navarro et al.[45]	USA		25	0/25 (0%)		Clinical	Retrospective, small numbers
Koo et al.[46e]	Singapore		62	2/62 (3.2%)		Clinical	Only rituximab
Watanabe et al.[47]	Japan		45 (24 + rituximab)	5/24 (20.8%)	5 +rituximab	Preclinical	Retrospective
Oh et al.[48e]	Korea		67	2/67 (3%)	+rituximab	Preclinical	Retrospective, only rituximab
Huang et al.[50e]	Taiwan		39	7/39 (17.9%)	+rituximab	Preclinical	Only rituximab
Masarone et al.[40]	Italy	460		10/460 (2.2%)	5 +rituximab 5 -rituximab	Clinical	Retrospective
Hsu et al.[49e]	Taiwan		150	17/150 (11.3%)	17 rituximab	Clinical	Only rituximab

a. Prevalence as it has been reported by the study.
b. Increase in alanine transaminase (ALT) at least 3-times upper normal values with HBV DNA and/or HBsAg detectable in the serum.
c. HBV DNA detectable in the serum even without an abnormal ALT level.
d. HBV DNA detectable with polymerase chain reaction on the liver specimen.
e. Study performed only on patients undergoing rituximab treatment.
HBsAg: HBV surface antigen; HBcAb: HBV core antibodies; OBI: occult HBV infection.

Similarly in 2009, Yeo et al.[12] reported a study in 80 HBsAg-negative patients with diffuse large B cell lymphoma receiving treatment with R-CHOP or CHOP regimen, between these HBV reactivation occurred in 5 (6.2%) of the patients who received rituximab treatment. In 2008, Targhetta et al.[38] retrospectively analysed 311 HBsAg negative-HBcAb positive lymphoma patients, of which 241 received chemotherapy and 74 had immunochemotherapy with anti-CD20 mAb. Reactivation occurred in 4 patients, 2 (0.8%) in the standard chemotherapy group, and 2 (2.7%) in the rituximab group, confirming a greater incidence of HBV reactivation under anti-CD20 antibody treatment.[38] On the contrary in 2010, Ji et al.[39] performed a retrospective study on 88 HBcAb positive NHL patients during chemotherapy. Among them, 43 received R-CHOP regimen and only one of these (2.3%) had hepatitis associated with HBV reactivation. Therefore probably due to the small numbers, no statistically significant risk factors were identified.[39] Recently, our group reported a study in 460 HBsAg negative patients undergoing anti-neoplastic treatment protocols that included rituximab or high immunosuppressive drugs. We found HBV reactivation in 10 (2.2%) patients, 5 treated with rituximab and 5 without, so we concluded that the risk of HBV reactivation was not exclusively associated to rituximab.[40] This result is in contrast with recent reports of a slightly higher prevalence of OBI reactivation in rituximab-treated patients. We concluded that this surprising finding was mostly due to the retrospective nature of the study, which included a large cohort of patients treated in the past 10 years, an era in which rituximab was less widely included in chemotherapy protocols. For this reason the prevalence of OBI reactivation in non-rituximab therapies was higher. We found also that OBI reactivation in non-rituximab treatment occurred exclusively in patients treated with highly immunosuppressive ('dose-dense') regimens, enlightening the fact that the risk of reactivation may not strictly be correlated with rituximab, but rather with the strong immunosuppression, regardless of the type of treatment used. However, the prevalence of occult HBV infection, reported by the studies examined for this review, range from 2.3% to 27.7%.[12,13,37-50] The data are reported in detail in Table 1.[12,13,37-50]

MANAGEMENT OF OBI AND PREVENTION OF THE REACTIVATION

While HBV reactivation in patients with overt infection (HBsAg positive) is a well-recognised clinical entity on which international guidelines give highly defined recommendations for its management, the best strategy for the prevention of OBI reactivation is less clear. In fact, even if pre-emptive antiviral therapy with nucleoside/nucleotide analogues (NUCs) has demonstrated to be efficacious in preventing HBV reactivation in NHL settings,[37,51-55] OBI is not easy to diagnose and, in this way, any HBcAb positive/HBsAg negative patient could be a possible occult infection carrier. The core of the problem is that not all HBcAb positive patients have an occult infection, that there are also OBI carriers that are HBcAb negative, and, finally, that not all OBI carriers who experiment an immuno suppression have a HBV reactivation. To these statements it must be added that no reliable serum markers to predict OBI reactivation are available at the moment. Moreover, even if we consider only HBsAg negative/HBcAb positive patients (in whom there is the higher probability to find an OBI), the prevalence of this type of patient is too high to suggest a universal prophylaxis strategy with NUCs in all immunosuppressive therapy. For this particular issue, international guidelines gave their recommendations: American Association for the Study of the Liver Disease suggests a periodical monitoring of serum HBsAg and HBV DNA and commence antiviral therapy at the first sign of HBV reactivation.[56] Likewise European Association for Study of the Liver[1] recommends ALT monitoring and eventually HBV DNA assays every 2-3 months. The Italian Association for the Study of the Liver[57] proposes two different strategies for patients undergoing chemotherapy: for mild haematological therapies (standard protocol without mAbs) HBsAg monitoring is advised, whereas in intense immunosuppression therapy (i.e. protocol including mAbs and/or strongly immunosuppressive therapies, i.e. 'dose-dense' regimen) recommends universal pre-emptive therapy (universal prophylaxis). Nevertheless, it has to be noted that the strength of these recommendations is low and further studies to address this issue are encouraged. In the already mentioned above paper, our group retrospectively evaluated 498 NHL patients, comparing these two strategies, and performed a cost-effectiveness analysis by calculating the costs of universal prophylaxis

versus strict monitoring (which was the method used in the study patients), in a time interval of a standard rituximab-containing chemotherapy protocol (about 12 months). From this analysis, the 'monitoring' approach resulted in being significantly more cost-effective in respect to universal prophylaxis.[40] Considering that very often NHL patients need more than one therapy cycle to obtain NHL remission, or undergo long-term 'maintenance' therapies with rituximab, the universal prophylaxis may be less justifiable. Nonetheless, the principal limitation to the 'monitoring' approach is the possible failure of rescue antiviral therapy that has been reported in other papers in literature.[12,42,58-60]

Lamivudine, the first-generation nucleoside analogue, is the drug that is generally used as the 'first approach' for the prophylaxis of OBI. Even if it has a 'low genetic barrier' (namely a high rate of resistance development to it by the emergence of HBV mutant species that are also able to replicate in the presence of the drug), this choice is justified by the low price, the low toxicity, and the low risk of the occurrence of resistance in such patients that carry very low HBV DNA levels. The use of a potent NUC with a 'high genetic barrier' (a scarce or null tendency to develop resistance), i.e. entecavir or tenofovir, does not seem to have significant advantages in preventing OBI reactivation[61] and therefore should not be used during the prophylaxis. Nevertheless, in the unfortunate case of a reactivation occurrence, the treatment with entecavir or tenofovir should be preferred, especially if there is an ALT rise. In fact, some reports show the capacity of these NUCs to avoid the fulminant course in case of acute hepatitis.[2] In this sense, since in OBI NUCs are generally commenced after reactivation, the most potent NUCs, such as entecavir or tenofovir, may be considered as first-line treatment. However, the possibility of an occult infection with lamivudine-resistant viral strains able to determine viral reactivation even under lamivudine prophylaxis cannot be excluded, so it is recommended to continue careful HBV DNA monitoring during antiviral treatment with lamivudine, in order to switch to tenofovir if HBV DNA becomes detectable.[62] If, during treatment with lamivudine, HBV DNA becomes detectable or it increases, it is advisable to switch to tenofovir, which has proven effective in suppressing lamivudine resistant mutants.

CONCLUSION

From this brief review we can conclude that OBI reactivation in NHL patients undergoing strong immunosuppressive therapies, and, in particular, rituximab containing protocols, represents a unique challenge for the hepatologist who is called to not only make a difficult diagnosis but also to make quick decisions on a management that is not widely acknowledged. Further studies are desirable to address the various issues that are still open in this particular field of hepatology.

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