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HBsAg Status, Molecular Detection and Therapy Evaluation of Hepatitis B Patient

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Abstract
The management of chronic hepatitis B involves various therapeutic approaches, including nucleotide analogs (NUCs) and pegylated-interferon alpha (peg-IFN), either in isolation or in combination. Reverse transcriptase enzyme is competitively inhibited by NUCs, which effectively suppresses HBV replication and lowers viral load. Concerning their cost-effectiveness, high response rates, low side effects, and oral administration, NUCs are recommended. Prolonged use, particularly of NUCs with a low genetic barrier or as monotherapy, can, however, lead to resistance, long-term safety issues, and the need for ongoing treatment. Physicians and other healthcare professionals are extremely concerned about the emergence of resistance and possible safety concerns related to the long-term use of NUCs. Moreover, the requirement for continuous therapy presents notable obstacles concerning patient adherence, distribution of healthcare resources, and overall economic viability. To clarify these problems and direct the creation of more potent and long-lasting treatment plans for chronic hepatitis B, urgent research is required. Hepatitis B surface antigen (HBsAg) detection is frequently accomplished via the use of the Chemiluminescent Microparticle Immunoassay (CMIA), which is a crucial early serologic marker for screening and diagnosis. Polymerase chain reaction (PCR) molecular testing is employed to confirm the presence of HBsAg. Polymerase Chain Reaction (PCR) was the technique we utilized to verify the outcomes. Twenty-eight of the HBsAg-positive patients at W.Z. Johannes Kupang Hospital had positive PCR results, highlighting the significance of molecular confirmation. The results of this study emphasize the value of precise HBsAg testing and the supplementary function of molecular confirmation in the treatment of patients with chronic hepatitis B. Furthermore, it clarifies the current therapeutic approaches applied to this patient population, highlighting the necessity of customized therapeutic approaches based on each patient's unique profile and potential complications.

Keywords: Hepatitis B Virus, HBsAg, PCR, Treatment.

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1. INTRODUCTION

Chronic hepatitis B, stemming from the hepatitis B virus (HBV) infection, stands as a pressing global health concern, notably in developing nations (World Health Organization, 2016a; World Health Organization, 2016b). Muljono, (2017) estimated that 257 million people worldwide suffer from chronic HBV infection. With a population of more than 250 million, Indonesia changed HBsAg prevalence from 9.4% in 2007 (based on data from Basic Health Research) to 7.1% in 2013, indicating a change from a high-endemic to a moderate-endemic nation (Kementerian Kesehatan Republik Indonesia, 2018; Wijayadi et al., 2018). Notably, Kambuno et al., (2017) discovered that among blood donors in East Nusa Tenggara, Indonesia, the prevalence of hepatitis B and hepatitis C was 3.5% and 0.5%, respectively.

Recently, the management of chronic hepatitis B hinges on nucleoside(s) analogs (NUCs) and pegylated-interferon alpha (peg-IFN), which can be administered independently or in combination (Jefferies, et al., 2018; Kim & Kim, 2018; Khairani, 2022). According to Hindarto, Rostinawati, and Retnoningrum, (2011), NUCs effectively suppress HBV replication and lower the amount of the virus in the host's system by acting as competitive inhibitors of the reverse transcriptase enzyme. Treatment regimens have incorporated a variety of NUCs, such as emtricitabine, telbivudine (LdT), entecavir monohydrate (ETV), adefovir dipivoxil (ADV), lamivudine (LAM), and tenofovir disoproxil fumarate (TDF) (Wibowo et al., 2020). With ETV or TDF achieving undetectable HBV DNA levels in 94-98% of cases and HBeAg seroconversion in 40-41% of HBeAg-positive patients, long-term NUC administration has demonstrated the ability to suppress HBV DNA, achieve HBeAg seroconversion, induce HBsAg loss, and reduce ALT levels (Fahira & Hasan, 2020).

The attractiveness of NUCs lies in their oral administration, minimal side effects, high response rates, and cost-effectiveness (Bedre, 2016). Extended use, however, particularly with low-genotypic barrier NUCs or as monotherapy, may lead to drug resistance, long-term safety issues, and an ongoing need for treatment to maintain suppression of viral replication. Combination therapy using nucleoside and nucleotide analogs is advised to combat drug resistance. Treatment for NUC is complicated by genetic variations, particularly in the polymerase gene's reverse transcriptase domain (Nugraha et al., 2022).

Remarkably, genetic mutation patterns of hepatitis B patients receiving NUC treatment at Prof. Dr. W. Z. Johannes Kupang Hospital have never been studied before. Obtaining data on mutation patterns has substantial clinical significance, enabling medical professionals to make more knowledgeable treatment choices. Consequently, there may be a decrease in the viral load and an interruption to the progression of the disease (Trisnaningtyas, Sari, & Setyaningrum, 2017).

Due to these considerations, this study undertakes an exploration of the mutation patterns among hepatitis B patients undergoing NUC treatment, intending to provide invaluable insights to enhance treatment precision and ultimately contribute to more effective disease management.

2. RESEARCH METHOD

This study is a descriptive observational study with a cross-sectional design, which received ethical clearance from the Health Research Ethics Committee of Poltekkes Kemenkes Kupang, under the reference number LB.02.03/1/0112/2022. The study encompassed a cohort of 28 outpatients receiving therapy at Prof. W. Z. Johannes Hospital who had all previously undergone PCR testing to confirm that they were positive for the hepatitis B surface antigen (HBsAg). Using particular primers, the P and S genes of the Hepatitis B Virus (HBV) were generated for the PCR analysis.

In this study, we utilized advanced diagnostic techniques to comprehensively assess the presence and characteristics of Hepatitis B surface antigen (HBsAg) (Winata, 2017). Our evaluation employed the Abbott Architect HBsAg Qualitative II reagent, a highly sensitive automated assay designed for the detection of HBsAg in human serum or plasma. With the Chemiflex protocol, the diagnostic technique known as Chemiluminescent Microparticle Immunoassay (CMIA) demonstrated exceptional sensitivity and 100% accuracy in identifying positive samples. This assay's analytical sensitivity ranged from 0.017 to 0.022 IU/ml, guaranteeing accurate and consistent results (Yulia, 2020).

Furthermore, the Molecular Biology Laboratory in the Hematology-Oncology Division of the Department of Internal Medicine at Cipto Mangunkusumo Hospital managed the molecular examination portion of our study. In this phase, we utilized the QIAamp DNA Mini Kit from QIAGEN (CA, USA) to carefully extract VHB DNA from serum samples that were obtained from each research subject. The DNA that had been extracted was then dissolved in a 60 µL solution. To investigate further the genetic aspects of the virus, we used particular primers following the protocol that Hindarto, Rostinawati, & Retnoningrum, (2011) established. In particular, we employed the Polymerase Chain Reaction (PCR) technique to amplify the polymerase gene (P gene) and the S gene, which encode the envelope proteins of the VHB, including HBsAg and two other essential proteins.

The research encompassed a two-phase approach. Firstly, a qualitative serological examination for HBsAg was conducted at the Clinical Pathology Laboratory of Prof. Dr. W. Z. Johannes Kupang Hospital. The P and S genes on the HBV were then identified by molecular PCR analysis at the Molecular Biology Laboratory of the Hematology-Oncology Division at RS. Cipto Mangunkusumo Jakarta. Patient-related data, including demographic data like age and gender, were gathered retrospectively from the medical records of outpatients at Prof. Dr. W. Z. Johannes Hospital who had previously received a hepatitis B diagnosis. The medical records offered valuable insights into treatment data, involving information on prescribed medications, including type, dosage, and duration, as well as details regarding any coexisting conditions the patients may have had. Antiviral therapy and supportive therapy were both included in the treatment profile data. The Indonesian Liver Research Association (PPHI) Guidelines' criteria were utilized to evaluate treatment compliance.

3. RESULTS AND DISCUSSION

To validate the outcomes of our molecular examination, we introduced a positive control sample of VHB DNA, sourced from a hepatitis B patient through the Eijkman laboratory. If the VHB sample from a research subject produced the same product size (249 bp) as the previously mentioned positive control, it was considered positive. Through PCR molecular analysis, our thorough investigation produced an 82.1% confirmation rate for positive serology results. Of the 28 samples that were analyzed, 23 demonstrated evidence of VHB, as indicated by the presence of the P gene or both ORFs, the P gene and the S gene, which developed an electrophoresis product that regularly measured 249 bp, which was consistent with the positive control (refer to Figure 1).

The VHB PCR examination involved the targeted amplification of both the P gene and the S gene, representing two of the four overlapping open reading frame (ORF) regions that collectively constitute the compact genome and protein structure of the virus. The hepatitis B surface antigen (HBsAg) is encoded by the Surface gene (Gen S), and the largest ORF is the Polymerase gene (Gen P), which is located between nucleotides 2357 and 1621 (Winata, 2017; Tiollais, Pourcel, & Dejean, 1985). Particularly, there is some overlap between the Gen P and Gen S sequences, as well as some between Gen C and Gen X. Gene alterations in Gen S, C, or X, can significantly affect the polymerase's ability to function. It should be understood that

mutations resulting in drug resistance frequently occur in the polymerase gene. Genetic variations in this gene, specifically in the reverse transcriptase domain, can present a significant obstacle to the administration of Nucleos(t)ide analogues (NUCs).

The Surface gene (Gen S) encodes a polypeptide which constructs the virus's outer envelope. It is situated in an ORF between nucleotides 2848 and 833, as described by Hindarto, Rostinawati, and Retnoningrum, (2011). 226 amino acids constituents of the fundamental protein of the virus envelope, which is produced when transcription begins at the Gen S region. The determinant, which is the principal antigen of HBsAg and is located between amino acids 124 and 149, remains a crucial component. This determinant is universally present in all VHB variants and is consistently present in the three protein types (large, medium, and small) synthesized by Gen S. Importantly, any alterations in the amino acids within the determinant region hold the potential to induce changes in the double loop conformation, thereby resulting in modifications to the antigenicity of HBsAg. According to Zampino (2015), these changes prevent antibodies produced after vaccination or infection from attaching to this antigen. Our investigation encompassed a thorough analysis of HBsAg using molecular and serological tests. These findings possess significant ramifications for how treatment plans are developed and how the illness is managed.

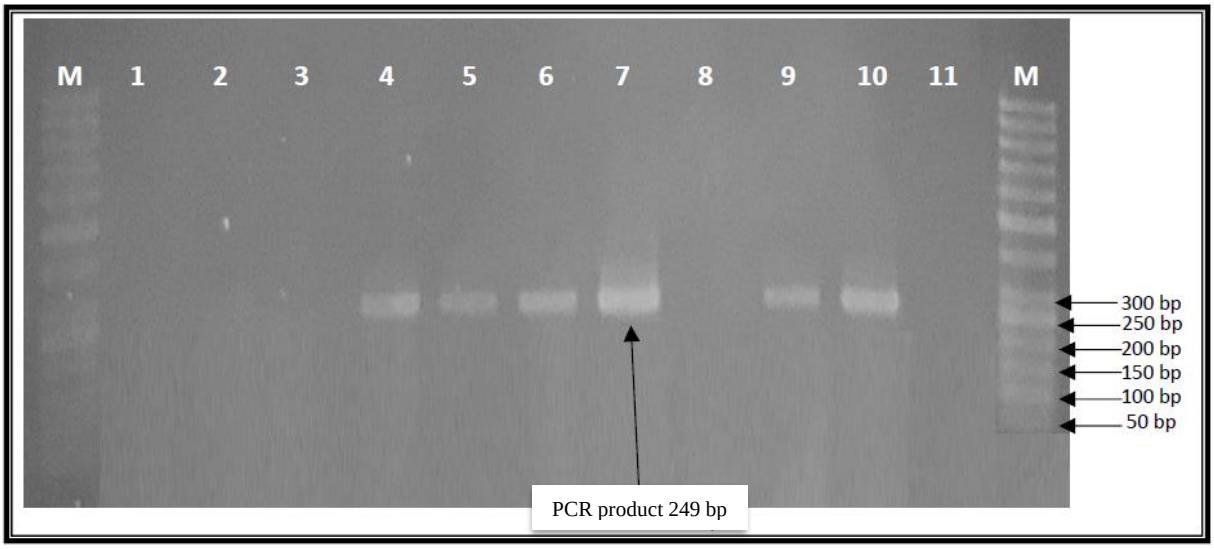

Figure 1. The result of electrophoresis of patient samples with positive HBsAg.

M= DNA Marker at 50 bp	6=sample	32	(positive)
1= sample 27	7=sample	33	(positive)
2= sample 28	8=sample	34	
3= sample 29	9=sample	14	(positive)
4= sample 30 (positive)	10=positive		control
5=sample 31 (positive)	11=NTC		

Figure 1 demonstrates that 5 samples was found to be a positive match with number 10, which was positive control.

Description of Hepatitis B Patient Therapy. Antiviral therapy in hepatitis B patients is applied after confirming positive HBsAg for morethan 6 months (chronic hepatitis B).

Therapy aims to enhance liver function and clinical status while impeding the progression of cirrhosis and hepatocellular carcinoma (Borgia et al., 2012). The disease phase must be introduced to carry out the management of hepatitis B. According to the Indonesian Liver

Research Association's (PPHI) guidelines, serum HBV DNA, HBeAg status, ALT, and liver histology parameters are required to determine when to begin treatment. Antiviral resistance is one of the crucial factors to take into consideration when delivering therapy; the prevalence of resistance will increase if therapy is administered at the incorrect time, type, or dose (Trisnaningtyas & Setyaningrum, 2017).

Initially, lamivudine, an oral nucleotide analog (NA), was the new class of treatment for hepatitis B. Interferon was the first therapy used to treat the disease. Adefovir, entecavir, Peg-IFN, telbivudine, and tenofovir were approved for use as Hepatitis B therapies as a result of later developments (Zoulim & Perrillo, 2008). It is widely acknowledged that the presence of covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes means that hepatitis B treatment cannot eradicate the hepatitis B virus (Nurainy & Muljono, 2018; Robinson, Wong, & Gish, 2023; Seto, 2019). The two types of medications employed for chronic hepatitis B therapy up to this point are nucleoside/nucleotide analogs and pegylated interferon (PEG-IFN).

To the best of our knowledge, entecavir and tenofovir are the recommended therapies due to their high barrier resistance and good efficacy. Almost every region in Indonesia encounters challenges associated with drug availability, particularly concerning the categories of drugs covered by the BPJS. Second-line treatments like lamivudine, adefovir, and telbivudine can be utilized in situations where tenofovir and entecavir are not available. However, prolonged use of the medication can lead to the issue of high resistance. As a result, the patient began taking tenofovir as a government program medication (Borgia et al, 2012).

Sulaiman et al., (2020) reported a cohort study at RSCM presenting that the use of NA in hepatitis patientswas proven to enhance hepatitis B infection in liver disease, the degree of liver stiffness also decreasedsignificantly. Furthermore, following NA administration, there was a significant decrease in alanine aminotransferase (ALT) levels. The fact that HBV DNA had been identified in 34% of the study participants, however, demonstrated that NA was unable to provide a "hepatitis B cure". Nevertheless, administering NA still markedly enhances liver function, lowers the incidence of liver cancer, delays the development of liver cirrhosis, and lengthens the life expectancy of hepatitis B patients (. The 2017 EASL guidelines define lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (TBV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) as nucleoside/nucleotide analogs for chronic hepatitis B therapy (World Health Organization, 2016; Conners et al., 2023; Jackson, Locarnini, & Gish, 2018). Clinical trials have displayed nucleoside/nucleotide analogs to have superior viral efficacy and better tolerance than PEG- IFN.

Table 1. Profile of antiviral therapy used by Hepatitis B patients.

Antiviral	**Amount**	**%**
Tenofovir	5	18,0
Lamivudine	4	14,0
Total	9	32, %

In Indonesia, tenofovir and lamivudine therapy is the most frequently used treatment. These two drug types are more widely accessible, less expensive, less likely to cause side effects, and safe for a wide age range (Fadrian, 2016). Likewise, at Prof. Dr. W.Z. Johannes. No additional drug classes, including entecavir (ETV), telbivudine (TBV), tenofovir disoproxil fumarate (TDF), adefovir dipivoxil (ADV), and tenofovir alafenamide (TAF), were discovered. The scarcity of the aforementioned medications is additionally connected to hospital stock levels, which restricts doctors' options for treatment (Abdul Basit, et al., 2017; Agarwal, et al., 2015).

Furthermore, not all hepatitis B patients have the results of the serum HBV DNA examination, HBeAg status, ALT, and liver histology, which should be available to select the appropriate therapy (Sulaiman et al., 2021). This limits the comprehensiveness of the examination of patients with hepatitis B. The treatment of hepatitis B patients at Prof. Dr. W.Z. Johannes provides more supportive therapy, as indicated in the table, due to the restricted availability of medications.

Table 2. Overview of Supportive Therapy in Hepatitis B patients.

Medicine	**Amount**	**%**
Livron B Plex	14	50
Curcuma	11	39
Ranitidine	1	4
Simvastatin	3	11
Atorvastatin	1	4
Folic acid	1	4
Metformin	1	1
Glibenclamide	2	7
Vitamin D	1	4
Dexamethasone zalf	1	4
Allopurinol	1	4
Cetirizine	1	4
Amlodipine	1	4
Sulfas Ferrous	1	4
Vitamin C	1	4
Aspilets	2	7
Cefixime	1	4
Aspar K	2	7
Omeprazole	1	4
Retaphyl	1	4
Lansoprazole	1	4
Meloxicam	1	4
Domperidone	1	4
Paracetamol	1	4
	52	100,0

We discovered that only 32 percent of the patients in our study received antiviral therapy. There are various reasons for the restricted application of antiviral therapy. Initially, it supports the results of a different study by Bedre et al. from 2016, which demonstrated a comparable pattern of low antiviral therapy utilization among patients with hepatitis B. The studies' consistent treatment patterns highlight a prevalent clinical strategy that favors supportive therapies for the management of hepatitis B, such as Curcuma and Livron B Plex.

There are probably several contributing factors to this comparatively low rate of antiviral therapy initiation. The clinical circumstances of the patients, such as their SGPT levels and HBeAg status, were critical in deciding the course of treatment. According to clinical guidelines for the management of hepatitis B, patients with positive HBeAg and elevated SGPT levels were primarily treated with antiviral therapy. On the other hand, patients with distinct clinical profiles frequently received supportive treatments like Livron B Plex and Curcuma, which enhance appetite and liver function without specifically addressing viral replication.

We discovered that 11 patients in our study cohort received Curcuma plus Livron as a combination therapy, and 3 patients received Livron as a supportive therapy. The range of patient management techniques among the participants in our study is demonstrated by these differences in treatment modalities.

Recognizing the limitations of our research is crucial. The presence of additional treatments, differences in treatment approaches, and the relatively low rate of antiviral therapy utilization introduce potential confounding factors that need to be taken into consideration when interpreting our findings. Furthermore, the reality that patients' treatment regimens vary from one another may affect how generalizable our findings are, underscoring the need for more investigation into the efficacy of various therapeutic modalities in the management of hepatitis B.

4. CONCLUSION

Based on the information we gathered, we advise the W.Z. Johannes Hospital administration to finish the examination criteria for hepatitis B patients before enforcing therapy to achieve the best possible therapeutic outcomes. Therapy selection cannot be made solely based on HBsAg and HBeAg status; liver histology, serum HBV DNA, and ALT/AST status must all be taken into consideration. Second, we recommend the completeness of line 1 and line 2 hepatitis drugs as standard treatment to obtain maximum therapeutic results and reduce antiviral resistance.

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