

# Natural history of chronic hepatitis B infection in Eritrean patients: a laboratory-based cross-sectional study

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## Research Article

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# Abstract

**Background** Understanding the natural history of chronic hepatitis B (CHB) virus infection is important for determining optimal management and predicting prognosis in patients. The aim of this study was to determine the prevalence of different phases of CHB infection among Eritrean patients and to identify the proportion of patients eligible for treatment according to 2018 American Association for the Study of Liver Diseases (AASLD) guidelines.

**Methods** This cross-sectional study enrolled 293 CHB patients between Jan 2017 and Feb 2019 and classified them into four groups, namely, immunotolerant, immune clearance, immune control, and immune escape, based on the results of Hepatitis B virus (HBV) serological panel (HBsAg, anti-HBc total, HBeAg and anti-HBe), ALT levels, and HBV DNA viral load.

**Results** Our study cohort of 293 patients comprised 213 males and 80 females, with a mean age of 41.66 ± 13.84 years. Of these, 5 (1.7%) were at the immune tolerant phase, 46 (15.7%) at immune clearance, 217 (74.1%) at immune control, and 25 (8.5%) at immune escape phase; thus, 71 (24.2%) patients were eligible for treatment, i.e., patients in immune clearance and immune escape phases. As most subjects (93%) were HBeAg-negative, based on AASLD guidelines, only 5 (1.7%) were eligible for treatment, and these patients were part of the group of 71 patients eligible for treatment based on chronic HBV status.

**Conclusions** Our data show that CHB patients in Eritrea were predominantly in the immune control phase. Although initiating antiviral therapy is not recommended in these patients, periodic assessment of liver function and disease severity should be considered in patients older than 40 years. The immunotolerant phase had the fewest patients, most of whom were above 20 years old, attesting to the success of incorporating HBV vaccine in the national childhood immunization program since 2002. Our study shows that adopting AASLD treatment guidelines with adjustments to suit the local setting represent a suitable option in the management of Eritrean CHB patients.

## Background

Hepatitis B virus (HBV) is one of the most common causes of liver cirrhosis and hepatocellular carcinoma (HCC) [1], and chronic hepatitis B (CHB) is defined as a detectable level of HBV surface antigen (HBsAg) in serum for 6 months or more [2]. CHB currently affects approximately 240 million people globally, has an annual mortality rate of 1.5 million, and accounts for the loss of 42 million disability-adjusted life years (DALYs) [1, 3].

CHB has a dynamic and complicated clinical course characterized by a complex interaction between host, viral, and environmental factors that affect the natural history of the infection, and this virus-host immune relationship is reflected in the number of different observable clinical phases of the disease [4]. These phases show considerable variation in HBV DNA viral load, hepatitis B e antigen (HBeAg) status, and concentration of serum liver transaminases [5]. The initial stage of CHB is termed the immune tolerant phase (non-inflammatory and asymptomatic) and is characterized by normal liver histology and

alanine aminotransferase (ALT) levels, apart from detectable levels of HBeAg and very high levels of HBV DNA. After decades (10–40 years) of CHB infection, many patients progress to the second phase, namely the immune clearance phase or the immune active HBeAg-positive phase, which is categorized by observable immune-mediated liver damage and elevated ALT levels, detectable HBeAg and lower HBV DNA (viral load) compared to the immune tolerant phase. In the immune control or inactive HBV carrier phase, seroconversion from HBeAg-positive to anti-HBeAg-positive occurs in most patients, and this immune response suppresses viral replication, thereby lowering HBV DNA to undetectable levels. It also slows the progression of liver injury and normalizes ALT levels. Lastly, some patients enter the immune escape phase or the HBeAg-negative chronic hepatitis phase, which is characterized by a negative HBeAg test and reactivation of virus replication, leading to higher HBV DNA levels compared with that observed in the low replicative phase (inactive HBV carrier phase). Importantly, this phase is associated with more severe and active liver damage and elevated ALT levels [4–6].

An understanding of the natural history of CHB infection is useful for determining the phases of the disease and for choosing appropriate antiviral therapy, i.e., optimal management [7]. The management of CHB patients is complex process and requires an in-depth knowledge of the natural history of the disease [8] because not all CHB patients go through all phases or follow a specific sequence of events. Additionally, wide variation in the duration of the various phases, coupled with imperceptible transitions from one phase to another, render distinguishing between the phases clinically difficult [4]. Therefore, only patients in the immune clearance and immune escape phases of the infection are considered eligible for treatment [8–10], and guidelines of both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) also make identical recommendations [11, 12]. However, the updated 2018 AASLD guideline endorses treatment of patients who are in the immune clearance phase (HBeAg-positive with HBV DNA viral load levels  $>20,000\text{IU/ml}$  and an ALT value at twice the upper limit normal (ULN)), and in the immune escape phase (HBeAg-negative patients with HBV DNA levels  $\geq 2,000\text{IU/ml}$  and an ALT value that is twice the ULN) [2].

HBV infection is considered endemic in Eritrea [13]; however, information on the prevalence of the various phases of HBV infection among CHB patients is lacking, despite such knowledge being essential for improving the management of HBV infected patients. Many international guidelines describe the management of patients with CHB based on related natural history of the disease, including prevalence of the various phases [2, 12, 14]. Therefore, this study aimed to quantify the prevalence of the various phases of CHB infection among patients based on laboratory testing criteria, namely HBeAg status, ALT and HBV DNA viral load levels, and to identify the proportion of patients eligible for treatment based on 2018 AASLD guidelines.

## Methods

### Patient population

This laboratory-based cross-sectional study recruited 293 CHB patients between Jan 2017 and Feb 2019 who were seropositive for the HBV surface antigen (HBsAg) and displayed antibodies to HBV core antigen (anti-HBc total). Patients were recruited from referrals to the Orotta National Referral and Teaching Hospital, the Halibet Hospital, the Sembel Hospital, or the Eritrean National Health Laboratory from different parts of the country. Patients with chronic HBV and patients who tested reactive for both HBsAg and anti-HBc (total) were included in the study. Patients with acute hepatitis and blood donors who tested positive for HBsAg were excluded from the study.

Patient demographic characteristics and medical report forms were completed by qualified practitioners. Written informed consent was obtained from each participant and the study protocol was approved by the ethical research committee board of the Orotta College of Medicine and Health Sciences (OCMHS) and the ethical and research committee of the Ministry of Health.

### **Laboratory methods**

Venous blood sample (5mL) was collected aseptically from each patient, transferred to a dry tube, and centrifuged at 3000 rpm for 5 min at room temperature for serum separation. Then, the serum samples were stored at  $-20^{\circ}\text{C}$  until further testing. HBsAg, anti-HBc total, HBeAg, and anti-HBe were tested using an enzyme-linked immunosorbent assay kit (Fortress Diagnostics, United Kingdom) while alanine transaminase (ALT) levels were quantified by an automatic chemistry analyzer (Roche Diagnostics, Switzerland) according to manufacturer's protocol. Quantitative HBV DNA (viral load) was measured in using the COBAS AmpliPrep/COBAS TaqMan 48HBV Test, version 2.0 (Roche Diagnostics, Switzerland) according to manufacturer's instructions for automated amplification and detection that also incorporated internal quality control. The results for HBV viral load were quantified as IU/ml, which corresponds to copies/mL (1 IU = 5.82 copies).

### **Classification of CHB patients into the various phases**

The Croagh and Lubel classification [4] was used to categorize CHB patients, as follows.

Phase 1: Immune tolerant, i.e., HBeAg-positive, HBV DNA levels  $\geq 20,000$  IU/ml, ALT-persistently normal;

Phase 2: Immune clearance, i.e., HBeAg-positive or seroconversion transitional stage with HBeAg-negative and HBeAb-negative, HBV DNA levels between 2000 and 20,000 IU/ml, ALT-persistently elevated (abnormal) or fluctuating (one abnormal and one normal result);

Phase 3: Immune control, i.e., HBeAg-negative, HBeAb-Positive, HBV DNA levels  $< 2000$  IU/ml, ALT-persistently normal; and

Phase 4: Immune escape, i.e., HBeAg-negative, HBeAb-Positive, HBV DNA levels  $\geq 2000$  IU/ml, ALT-persistently elevated (Abnormal). ALT normal range according to traditional cut-off values (40 IU/L).

### **Identification of CHB patients eligible for treatment based on 2018 AASLD guidelines**

Study participants were divided into two groups based on their HBeAg status. Patients with elevated ALT values, i.e., 2 times the upper limit normal (ULN) in healthy adults (2× ULN for ALT) were selected from HBeAg-positive and HBeAg-negative patients. HBeAg-positive patients with ALT values 2× ULN and HBV DNA levels of  $\geq 20,000$  IU/ml were considered eligible for treatment. HBeAg-negative patients with ALT values 2×ULN and HBV DNA levels  $\geq 2000$  IU/ml were also considered eligible for treatment. The ULN value in healthy adult males was defined as 35 U/L while that for females was 25 U/L [2]

## Statistical analysis

Data are described as numbers, percentages, mean, median, standard deviation (SD), and range, as applicable. Categorical comparisons between different clinical phases of CHB were based on two ALT values and were performed using the Chi-square test and the Fisher's exact test to determine significant between-group differences. All analyses were performed on SPSS software, version 25.0 (IBM; Chicago, IL, USA).

## Results

Our cohort of 293 CHB patients had a mean age  $41.66 \pm 13.84$  years (range 16-78 years), and comprised 213 (72.7%) males and 80 (27.3%) females. The mean age of males was  $42.30 \pm 14.1$  years while that of females was  $39.07 \pm 13.01$  years. Age and gender distribution data are presented in Figure 1. Table 1 summarizes the results obtained from ALT and viral load tests.

**Table 1. Summary of ALT and HBV Viral load tests results**

| Test parameters         |               | Males<br>n = 213    | Females<br>n = 80 | Total<br>n = 293   |
|-------------------------|---------------|---------------------|-------------------|--------------------|
| ALT (U/L)               | Mean $\pm$ SD | 31.5.50 $\pm$ 21.20 | 31.94 $\pm$ 22.87 | 31.625 $\pm$ 21.63 |
|                         | Median        | 27.0                | 25.25             | 26.0               |
|                         | Minimum       | 5.0                 | 10.5              | 5.0                |
|                         | Maximum       | 238.3               | 150.6             | 238.0              |
| HBV Viral load (Log IU) | Mean $\pm$ SD | 3.48 $\pm$ 1.08     | 3.45 $\pm$ 1.42   | 3.74 $\pm$ 1.17    |
|                         | Median        | 3.49                | 3.28              | 3.47               |
|                         | Minimum       | 1.30                | 1.30              | 1.30               |
|                         | Maximum       | 6.68                | 7.95              | 7.95               |

Patients with elevated ALT had a significantly higher mean viral load (log IU) compared to patients with normal ALT ( $p = 0.028$ ) (Table 2). HBV viral load <2000 IU/ml was recorded in 226 patients, 40 patients had HBV viral load between 2000 and 20,000 IU/ml, while 27 patients had values >20,000 IU/ml. A significantly higher proportion of patients with elevated ALT also had viral loads between 2000–20,000 or >20,000IU/ml (P-value = 0.044) compared to the proportion of patients with normal ALT and identical viral load ranges (Table 3).

**Table 2. HBV viral load (log IU) across gender and ALT**

| Patient demographics |          | n   | Mean HBV viral load (Log IU) comparison |                |                  |              |
|----------------------|----------|-----|---|----------------|------------------|--------------|
|                      |          |     | Mean ± SD                               | Standard error | 95% CI*          | P-value      |
| Gender               | Males    | 213 | 3.48 ± 1.08                             | 0.241          | -.443 to 0.510   | <b>0.890</b> |
|                      | Females  | 80  | 3.45 ± 1.42                             |                |                  |              |
| ALT                  | Normal   | 249 | 3.36 ± 1.11                             | 0.268          | -1.129 to -0.066 | <b>0.028</b> |
|                      | Elevated | 44  | 3.95 ± 1.35                             |                |                  |              |

\*CI: Confidence interval

**Table 3. Categorization of HBV viral load by gender, age, and ALT**

| Patient demographic |          | HBV DNA levels (IU/ml)  |            |             |              |   |            |           |              |
|---------------------|----------|---|------------|-------------|--------------|---|------------|-----------|--------------|
|                     |          | Comparison between cases with <2000IU/ml and 2000–20,000IU/ml |            |             |              | Comparison between cases with <2000IU/ml and >20,000IU/ml |            |           |              |
| Characteristics     |          | n   | <2000      | 2000–20,000 | P-value      | n   | <2000      | >20,000   | P-value      |
| Gender n (%)        | Male     | 195   | 162(83.1)  | 33 (16.9)   | <b>0.178</b> | 180   | 162 (90.0) | 18 (10.0) | <b>0.654</b> |
|                     | Female   | 71  | 64 (90.1)  | 7 (9.9)     |              | 73  | 64 (87.7)  | 9 (12.3)  |              |
| Age                 | <40      | 130   | 104 (80.0) | 26 (20.0)   | <b>0.039</b> | 119   | 104 (87.4) | 15 (12.6) | <b>0.416</b> |
|                     | >40      | 136   | 122 (89.7) | 14 (10.3)   |              | 134   | 122 (91.0) | 12 (9.0)  |              |
| ALT n (%)           | Normal   | 229   | 199 (86.9) | 30 (13.1)   | <b>0.044</b> | 219   | 119 (90.0) | 20 (9.1)  | <b>0.044</b> |
|                     | Elevated | 37  | 27 (73.0)  | 10 (27.0)   |              | 34  | 27 (79.7)  | 7 (20.6)  |              |

When CHB patients were classified into the four different phases, 5 (1.7%) were in the immune tolerant phase, 46 (15.7%) were in the immune clearance phase, 217 (74.1%) were in the immune control phase, and 25 (8.5%) were in the immune escape phase (Fig. 2). Table 4 summarizes the distribution of CHB phase based on age group and gender. Only 71 (24.2%) of the patients fulfilled eligibility criteria for treatment, i.e., they were either in the immune clearance phase or the immune escape phase. Figure 3 shows grouping of patients in the various CHB phases according to age as  $\leq 40$  years and  $>40$  years.

**Table 4. CHB phase distribution based on age group and gender**

| Phases of CHB    | Total<br>n (%) | Gender |        | Age group |       |       |       |             |
|------------------|----------------|--------|--------|-----------|-------|-------|-------|-------------|
|                  |                | Male   | Female | >20       | 21–30 | 31–40 | 41–50 | 51 or above |
| Immune tolerance | 5 (1.7)        | 5      | 0      | 2         | 2     | 0     | 1     | 0           |
| Immune clearance | 46 (15.7)      | 35     | 11     | 5         | 13    | 11    | 11    | 6           |
| Immune control   | 217 (74.1)     | 154    | 63     | 4         | 45    | 56    | 55    | 57          |
| Immune escape    | 25 (8.5)       | 19     | 6      | 1         | 4     | 2     | 12    | 6           |

Based on the 2018 AASLD guidelines, 5 (1.7%) of the 293 patients were eligible for treatment (Fig. 4); these patients were part of the 71 cases eligible for treatment as they were either in the immune clearance or immune escape phases.

## Discussion

Data from this study provide essential insight into the natural history of CHB infection among HBV infected patients in Eritrea, and to the best of our knowledge, this is the first such major study. In the last decade, Eritrea had been classified as having low-intermediate prevalence of HBV infection and the main route of HBV transmission was determined to be perinatal acquisition [13, 15].

In our cohort, the proportion of males was higher in all age groups, and this is congruent with data from other studies [16, 17]. Most of our patients were aged 41–50 years (26.9%), followed by 51 years or above, and then 31–40 years (23.5%). A similar study from Iran has also shown higher prevalence of chronic HBV infection in middle aged individuals and elders, compared to children, teenagers, or youth [18].

As 1.7% of participants were in the immune tolerant phase, which is the first phase in perinatally-acquired disease, and most of the patients were over 20 years old, it is very likely that they acquired HBV infection before implementation of the neonates vaccination program. Further, the low rate of patients in the immune tolerant phase indicates the effectiveness of the neonate vaccination program introduced in Eritrea since 2002 [13]. Such patients usually remain in this phase for years and this chronic course increases risk of developing liver complications. Therefore, in such patients, HBeAg and liver function must be monitored every 3–6 months to detect any rise in ALT levels [5, 9, 19].

Most of the 293 participants in this study (74%) were in the immune control phase (inactive carrier phase), and this phase may last a lifetime without reactivation of HBV infection or HBsAg

seroconversion, implying that this huge proportion of patients in our study area were HBeAg-negative, have very low viral loads, and that they may not require antiviral treatment as they probably have minimal or no liver injury. Nonetheless, liver function tests and biopsy should be considered in patients above 40 years of age [9, 19]. Other studies have similarly documented a high percentage of patients in the immune control phase [8, 20]; however, this may not always be true as discrepancies exist among the reported studies with respect to classification of patients in this phase [8, 20] due to controversies regarding the HBV DNA cut-off point to be used. While we considered HBV DNA levels of <2000IU/ml in this study and thus obtained a high percentage (74%), differences in settings or populations among the studies can affect prevalence data.

The rate of HBeAg-negative CHB patients was higher than that of HBeAg-positive CHB patients, which is similar to data from recent studies from Europe, Asia, and the United States that have shown an increase in the prevalence of HBeAg-negative CHB patients and a decrease in the prevalence of HBeAg-positive CHB patients. This shift, which has strongly affected treatment strategies, can be explained by a reduction in new HBV infection rates [21–23].

The classification of CHB patients into four different phases (immune tolerance, immune clearance, immune control and immune escape phases) can be used as a guide for determining treatment necessity [2]. However, the challenge for the clinician is to determine the phase of the infection and anticipate its natural course in each patient so that antiviral treatment can be directed to those most likely to benefit. Identifying CHB infected patients who need treatment is challenging and requires a series of expensive tests that are not commonly available in resource-limited settings, such as in Eritrea. Notably, such tests must also be done periodically and interpreted by a specialist for a definitive determination.

Our study identified 46 (15.7%) patients in immune clearance phase and 25 (8.5%) patients in immune escape phase, resulting in a total of 71 (24.2%) patients who may be considered for treatment. However, based on the 2018 AASLD guidelines, only 5 (1.7%) patients were eligible for treatment and they were either in the immune escape or the immune clearance phase of the infection. This implies that AASLD guidelines can be useful and relevant during decision making in settings such as those seen in Eritrea as other treatment guidelines would most likely recommend treatment for these patients as well. Conversely, this may not necessarily be the case for all patients because the decision to treat some patients may require the expertise of a health specialist and some complex considerations such as age of the patient, family history of hepatocellular carcinoma, risk of transmission, and extrahepatic manifestations, among others.

## **Limitations**

To the best of our knowledge, this is the first study in an Eritrea population that addresses the natural history of CHB in HBV patients. However, some limitations do exist. This was a cross-sectional study based on laboratory data; therefore, some relevant clinical details of the patients may have been missed. The cross-sectional nature of the study also limits the results to a single HBV viral load result (at baseline), rather than a series of viral load tests conducted by following patients for a longer duration. To

address these shortcomings, therefore, in the future, designing and conducting a cohort study that includes laboratory tests and non-invasive assessment of liver fibrosis is essential [24]. Apart from follow-up of patients for both HBV viral load and liver aminotransferases over a period of 6 months or more is usually considered when classifying chronic HBV infected patients into the various phases [2].

## Conclusions

Our study documents the natural history of CHB in Eritrean patients for the first time. A majority of HBV infected patients are in the immune control phase (inactive carrier phase) and do not require antiviral therapy; rather they need regular follow-up by a trained specialist for establishing disease severity. This is especially important in those older than 40 years of age as the disease progression or phase change may be imminent. We recommend that responsible bodies in the healthcare system of the country utilize this data to establish appropriate treatment strategies and thereby improve both control and management of this disease among the citizens.

## List Of Abbreviations

AASLD, American Association for the Study of Liver Diseases;

ALT, Alanine aminotransferase;

AST, Aspartate aminotransferase;

CHB, Chronic HBV infection;

DNA, Deoxyribonucleic acid.

HBcAb (anti-HBc), Hepatitis B core antibody;

HBeAg, Hepatitis B e antigen;

HBsAg, Hepatitis B surface antigen;

HBV, Hepatitis B virus;

SPSS, Statistical Package for Social Sciences;

ULN, upper limit normal

## Declarations

**Ethics approval and consent to participate**

This study was approved by the ethics committee of the Orotta College of Medicine and Health Sciences and the health facility management division of the Ministry of Health. All patients provided written informed consent to participate in this study.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

All dataset used for this study are available from corresponding author on reasonable request.

### **Competing interests**

The authors declare no competing interests.

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### **Authors' contributions**

MEH, SMR, YS, IME, and FT conceived and designed the study. MEH, SMR, and FT analyzed the data and revised the paper. MEH and SMR wrote the manuscript. All authors read and approved the final manuscript.

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## Figures

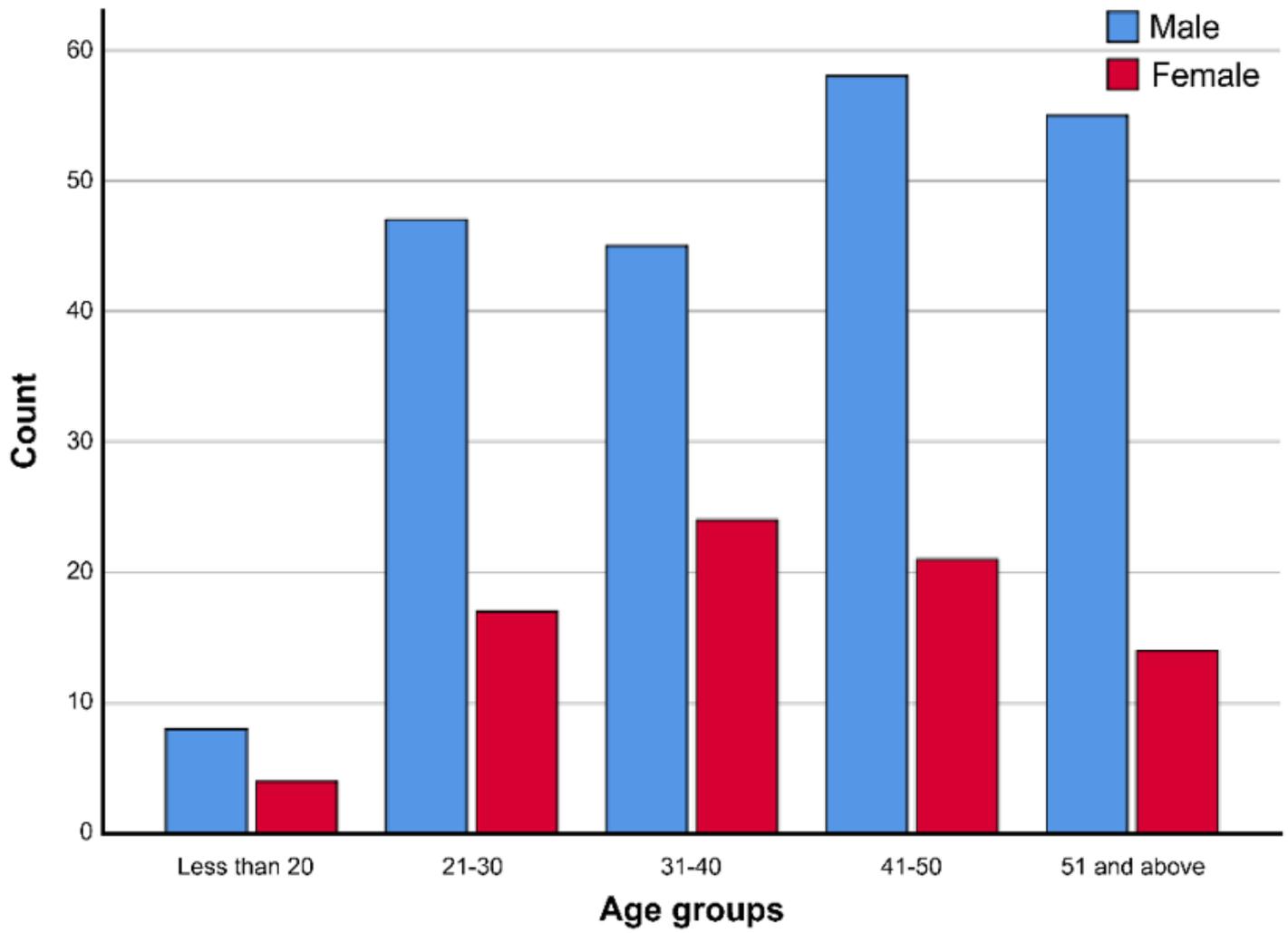
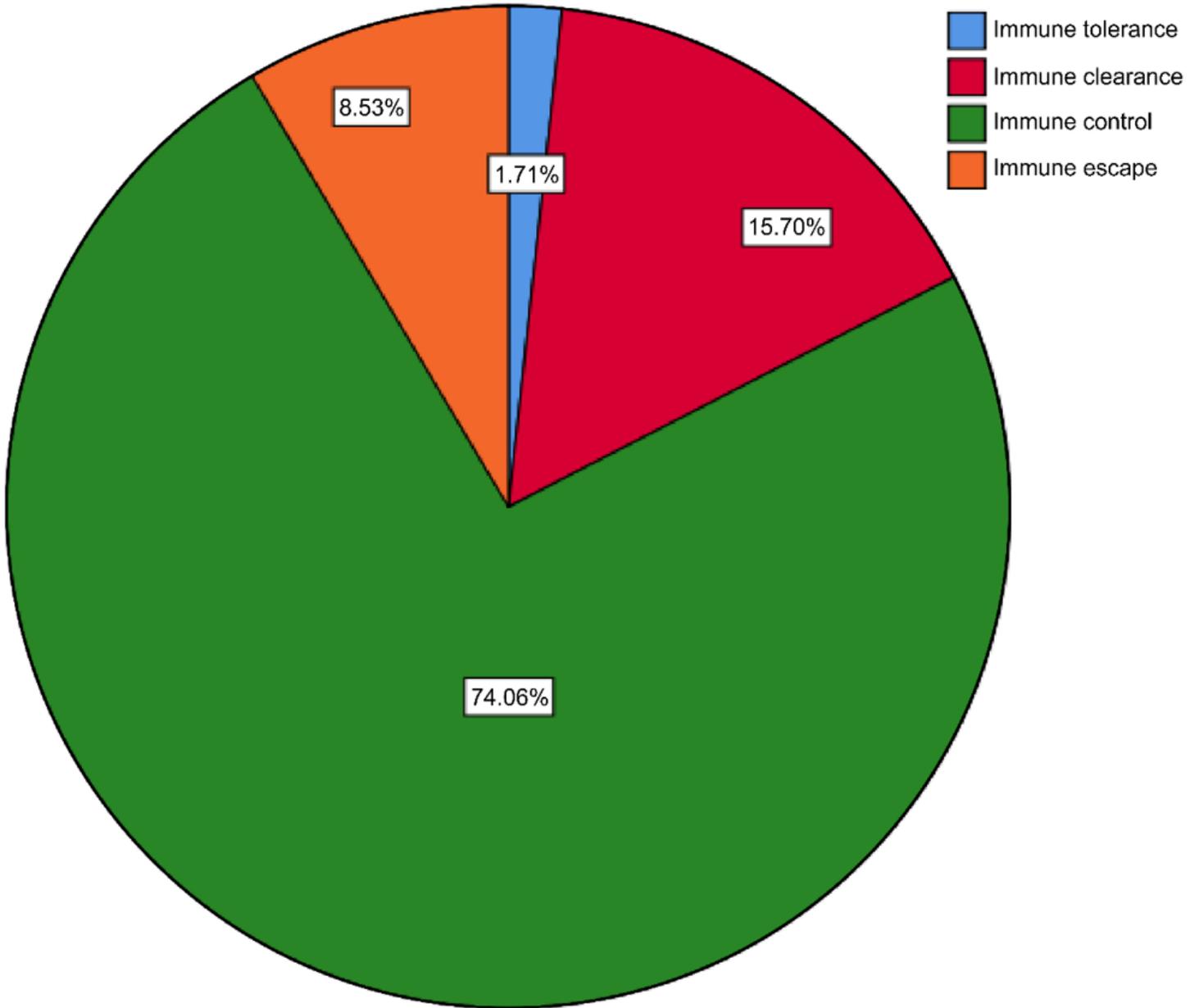


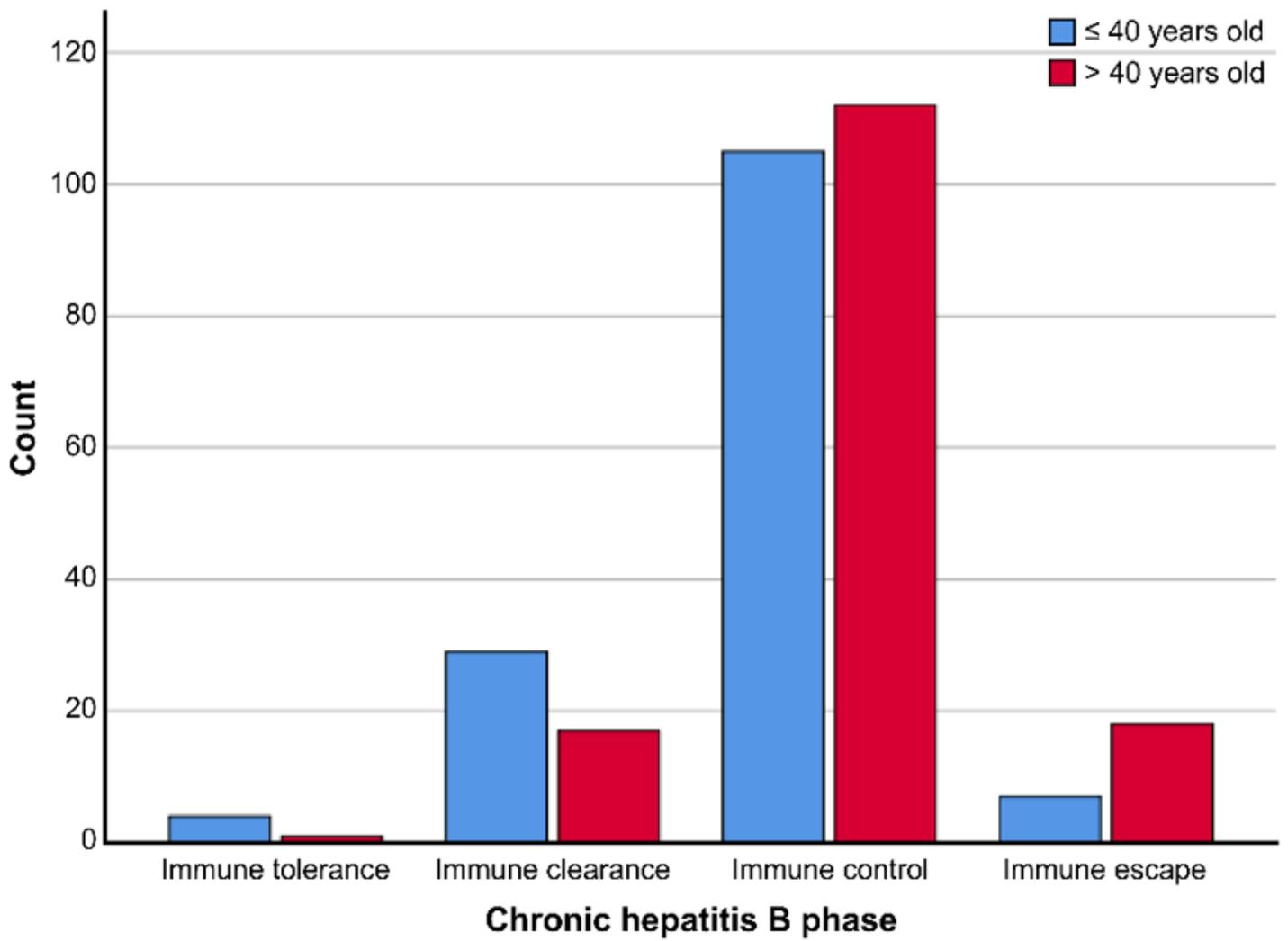
Figure 1

Age and gender distribution



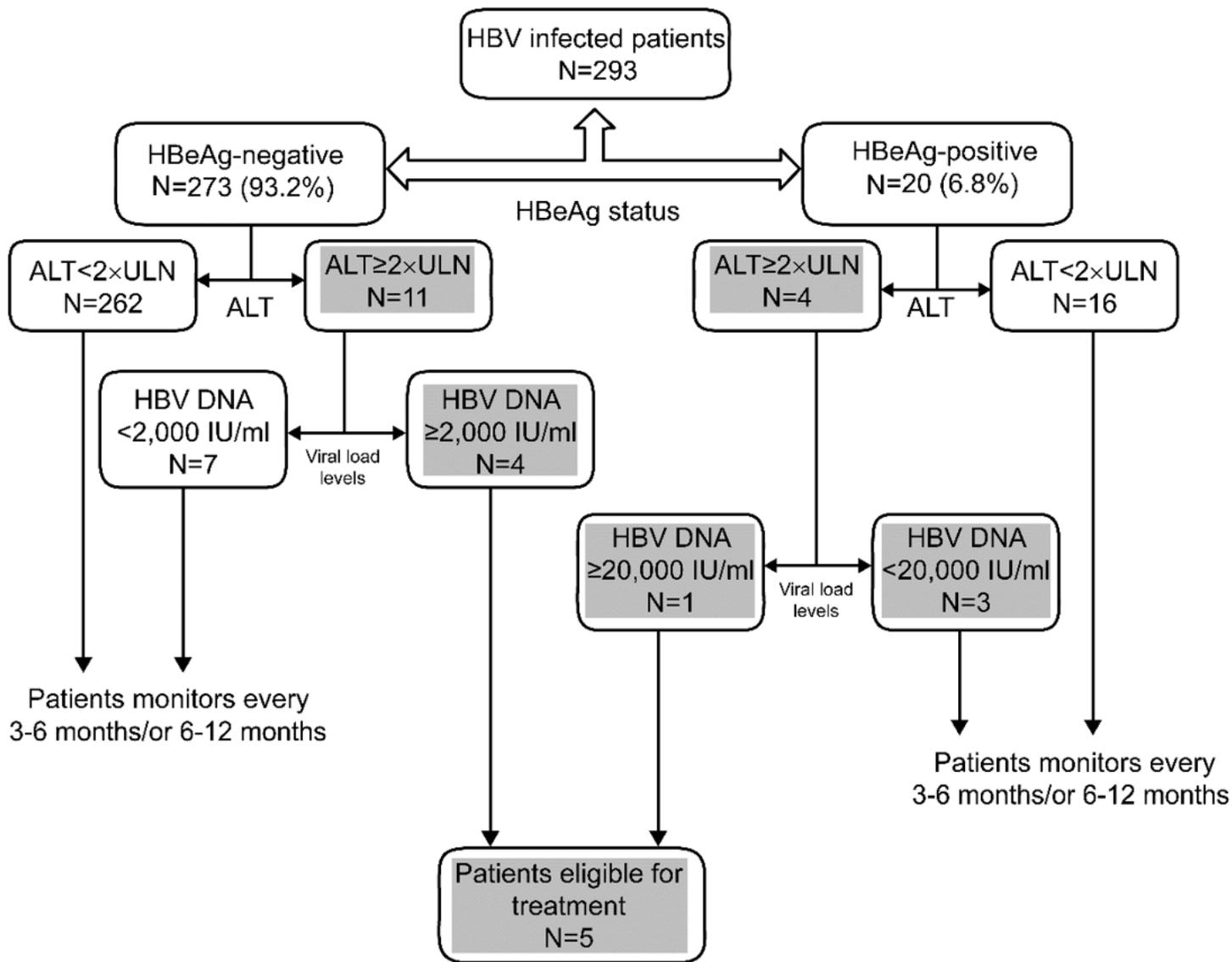
**Figure 2**

Categorization of patients in the four CHB phases



**Figure 3**

Age distribution among the four CHB phases



\*Upper limit normal (ULN) for ALT in healthy adults for males (35 U/L) and females (25 U/L).

**Figure 4**

Patients eligible for treatment based on 2018 AASLD guidelines