

Hepatitis B Virus Antibody as Potential Biomarker to Predict the Effect of Rituximab in Diffuse Large B-cell Lymphoma Patients

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Abstract

Background: Diffuse large B-cell lymphoma (DLBCL) has been correlated with virus infection and immunity status. Hepatitis B virus (HBV) infection is a significant public health problem around the world, especially in China. Previous research regarding the association of non-Hodgkin lymphoma (NHL) and HBV mostly focused on HBV antigen and HBV DNA. This study aimed to evaluate the relationship between HBV antibody and clinical prognosis in DLBCL.

Methods: We retrospectively investigated the clinical characteristics of 190 newly diagnosed and untreated DLBCL patients and did a follow-up study.

Results: Compared with HBeAb⁻ patients, HBeAb⁺ patients displayed unique clinical features, such as more advanced disease stage ($p=0.031$) and higher International Prognostic Index (IPI) score ($p=0.015$). HBV antibody-negative patients had better therapeutic efficiency than positive patients ($p<0.05$). The media progression-free survival (PFS) and overall survival (OS) of HBV antibody-positive group were shorter than the negative group, respectively ($p<0.05$). Furthermore, we found positive association between CD21 and HBsAb ($p=0.06$) and their synergistic effect for prognostic predication. Interestingly, the effect of Rituximab in prognostic improvement was more significant in HBV antibody-positive group than negative group. Univariate analysis showed that HBV antibody status was independent risk factor for prognosis of DLBCL patients.

Conclusions: Taken together, our investigations identified for the first time the close association between HBV antibody and clinical prognosis and Rituximab responses in DLBCL patients. These findings indicate the novel association between HBV infection and DLBCL prognosis, provide potential biomarker to predict the effect of Rituximab, and offer novel insights into the role of immune response to HBV infection in DLBCL progression.

Background

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), which accounts for about 30–40% of newly diagnosed cases (1). Although its pathogenesis exhibits high heterogeneity, it has been reported to be strongly correlated with virus infection and host immunity status (2, 3). To date, several viruses have been involved in the tumorigenesis and progression of DLBCL, such as Epstein-Barr virus and hepatitis C virus (HCV). Epstein-Barr virus was found to repress transcription of pro-apoptotic genes and induce continuous proliferation of primary B cells (4, 5). Besides, it's found that HCV-positive individuals had a pooled relative risk of 2.5 (95% CI 2.1–3.1) of developing NHL (6), suggesting that HCV might participant in the development of NHL. Meantime, several other virus, including human immunodeficiency virus (HIV) (7, 8), human T-cell lymphotropic virus (9) and human herpesvirus-8 (10), have also been reported to be involved in lymphoma development.

To date, Hepatitis B virus (HBV) infection remains a severe global public health problem, as nearly 2 billion people are currently suffering from it and 360 million people are living with chronic HBV infection

(11, 12). Especially, China is a highly endemic area with the HBsAg-positive rate of 7.18% and about 93 million individuals have chronic HBV infection (13). As a strong etiological factor in liver carcinoma (14), HBV has also been found to be epidemiologically associated with NHL in numerous studies (15–17). A recent meta-analysis, including 53714 NHL cases, showed that HBV-infected individuals had notably higher risk of NHL (OR = 2.50, 95% CI 2.20–2.83) in comparison with control population (16). In addition, it's found in cohort study that HBV infection increased the risk of developing NHL with risk ratio (RR) of 4.14 and HBV vaccination largely reduced the incidence of NHL (18).

Recently, HBsAg has been reported to be associated with clinical feature and prognosis in DLBCL patients. For example, HBsAg⁺ patients were diagnosed at a younger age with more advanced disease stage (19) in comparison with HBsAg⁻ patients. Besides, patients in HBsAg⁺ group had a worse clinical outcome and prognosis (20). Furthermore, HBV antigen was discovered in lymphoma tissue (20, 21) and bone marrow cells from DLBCL patients (22). Besides, HBV DNA existed in peripheral blood mononuclear cells (23) and tumor tissue (20, 21, 24) from DLBCL patients. Besides, HBV had the ability to infect B lymphocytes *in vitro* (20) and then the integration of HBV DNA into the host genome was found in lymphoma (24), indicating the potential role of HBV infection in lymphoma development. However, the potential role and underlying mechanism of HBV infection in lymphoma development has never been reported before.

Previous research regarding the association of HBV and NHL mostly focused on HBV antigen and HBV DNA. Although the pathogenesis of lymphoma has been correlated with host immunity status, no literature has been reported regarding the association between HBV antibody and DLBCL. Therefore, we carried out the comprehensive study to evaluate the association between HBV antibody status and the clinical prognosis in DLBCL patients.

Methods

Patient selection and treatment

We retrospectively investigated the clinical data of 190 DLBCL patients who had received histological diagnosis and standard treatment at Shandong Provincial Hospital from May 2013 to May 2018. The pathological diagnosis was based on the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues (2008) and the clinical stage was in accordance with the Ann Arbor staging system. Patients enrolled in the study had adequate available clinical information. Patients were excluded from the study if they exhibited positive with HIV or HCV, histological transformation from low-grade lymphoma, previous or secondary cancer without treatment. All patients received 3–8 cycles of first-line regimen, such as R-CHOP, CHOP and R-CHOP/CHOP-like regimens; patients with progression after first-line treatment received second-line chemotherapy, such as Gemox and DICE regimens. Patients with positive HBsAg received nucleos(t)ide analogue (NUC) prophylaxis, such as lamivudine and entecavir, and further HBV DNA monitoring. There were no patients who developed HBV reactivation after therapy. This study was in accordance with the Declaration of Helsinki and it was approved by the

Medical Ethical Committee of the Shandong Provincial Hospital. All patients were obtained for the collection of Informed consent at their first visit.

Date collection

The clinical information, including demographic information, International Prognostic Index (IPI) score, stage, routine blood tests, image examination, bone marrow tests and immunohistochemistry (IHC) results, was collected in the database of Shandong Provincial Hospital. All patients were detected with HBV surface-antigen, e-antigen and antibodies against HBV surface-antigen, e-antigen, core-antigen before chemotherapy. Patients with positive HBV antigen received further tests until negative conversion. A complete history of the chemotherapy course was noted as well.

Definitions

IPI scores were calculated based on the number of present factors (25). Curative effect was categorized based on international response criteria in non-Hodgkin's lymphomas as follows: complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) (26).

Follow-up

127 DLBCL patients were effectively followed up to September 2018, and follow-up information was obtained from medical records or by telephone. Progression-free survival (PFS) was measured from disease diagnosis to disease progression, death, or last follow-up. Overall survival (OS) was measured from disease diagnosis to death or last follow-up.

Statistical analysis

The groups of patients were compared by the Pearson's chi-square test or the Fisher exact test for categorical parameters. The therapeutic efficacy of different groups was analyzed using Kruskal-Wallis test. Survival curves were calculated using Kaplan-Meier and the log-rank test was used to identify differences. The multivariate analysis of prognosis was performed by Cox regression. The differences were considered significant at $p < 0.05$. All calculations were made in SPSS version 20.0.

Results

Baseline characteristics and HBV marker assays

In this study, a total of 190 newly diagnosed DLBCL patients were included. The median onset age was 59 years (range 11–85) and the majority of patients were males (104/190, 54.7%). Most of patients (110/190, 57.9%) were classified as non-germinal center B-cell-like (non-GCB). 76.8% (146/190) of patients were diagnosed with advanced stage (stage III-IV) and 30.5% (58/190) of patients had B symptoms. Effective follow-up was performed in 127 patients and the mean follow-up time was 24 months (range 1–80).

In the total of 190 patients, there were 18 patients in HBsAg-positive group and 172 patients were negative with HBsAg (Supplementary Fig. 1). The prevalence of HBsAg in DLBCL patients was 9.5% (18/190) in our cohort (Supplementary Table 1), which was higher than that in general Chinese population (7.2%) (27). In addition, the prevalence of HBcAb among our study was 51.6% (Supplementary Table 1), which was also higher than that in general Chinese population (34.1%) (27).

Unique clinical characteristics of HBV antibody-positive patients

To exclude the effect of HBsAg on the prognosis of DLBCL patients, we eliminated HBsAg-positive patients and then classified HBsAg-negative patients into various groups based on HBV antibody status. Interestingly, unique clinical features were found in HBV antibody-positive patients. For example, compared with patients in HBeAb-negative group (Table 1), patients in HBeAb-positive group displayed more advanced disease at diagnosis ($p = 0.031$), higher IPI scores ($p = 0.015$), higher LDH level ($p = 0.004$), higher white blood cell (WBC) level ($p = 0.011$), higher platelet lymphocyte ratio (PLR) level ($p = 0.012$) and lower lymphocyte monocyte ratio (LMR) level ($p = 0.05$). In addition, HBsAb-positive patients displayed younger onset age (55.5 years, range 11–77) in comparison with HBsAb-negative patients (60.5 years, range 22–85), which was not statistically significant ($p = 0.067$) possibly due to small sample size. Besides, from the age distribution in Supplementary Fig. 2, it's evident that the onset age of HBsAb-positive patients was lower than that of HBsAb-negative patients, especially among the peak onset age (50–80 years old).

Table 1
Clinical characteristics based on HBeAb status in DLBCL patients

Characteristics	HBeAb negative n (%)	HBeAb positive n (%)	P value
Total	138(80.2%)	34(19.8%)	
Gender			
Male	80(46.5%)	15(8.7%)	0.146
Female	58(33.7%)	19(11.1%)	
With Rituximab			
No	12(10.0%)	2(1.7%)	0.521
Yes	83(69.2%)	23(19.1%)	
Stage			
I/II	36(26.1%)	3(8.8%)	0.031
III/IV	102(73.9%)	31(91.2%)	
IPI score > 2			
No	28(20.4%)	1(2.9%)	0.015
Yes	109(79.6%)	33(97.1%)	
Elevated LDH			
Yes	53(40.2%)	22(68.7%)	0.004
No	79(59.8%)	10(31.3%)	
Elevated WBC			
Yes	19(13.8%)	11(32.4%)	0.011
No	119(86.2%)	23(67.6%)	
PLR			
> 200	46(33.8%)	19(57.6%)	0.012
< 200	90(66.2%)	14(42.4%)	
LMR			
> 3	67(49.3%)	10(30.3%)	0.05

Abbreviations: IPI, international prognostic index; LDH, lactate dehydrogenase; WBC, white blood cell; PLR, platelet lymphocyte ratio; LMR, lymphocyte monocyte ratio.

Characteristics	HBeAb negative n (%)	HBeAb positive n (%)	P value
< 3	69(50.7%)	23(69.7%)	
Abbreviations: IPI, international prognostic index; LDH, lactate dehydrogenase; WBC, white blood cell; PLR, platelet lymphocyte ratio; LMR, lymphocyte monocyte ratio.			

The association of HBV antibody and clinical outcome and prognosis

As patients presented different clinical characteristics based on HBV antibody status, we next explored the correlation between HBV antibody and clinical prognosis in DLBCL patients. In our study, all patients underwent 3–8 cycles of first-line treatment and 69.8% (120/172) of patients were treated with Rituximab-containing regimen, which was similar in different groups divided by the status of HBV antibody ($p > 0.05$). With similar chemotherapy treatment, patients in HBsAb-positive group ($p = 0.013$) and HBeAb-positive group ($p = 0.013$) had worse therapeutic efficiency than negative group, respectively. Although the difference between HBcAb positive and negative group ($p = 0.159$) didn't reach statistical significance, the combination of HBsAb and HBcAb had a close correlation with the clinical outcome of DLBCL patients ($p = 0.019$, Table 2).

Table 2
Negative effect of hepatitis B virus antibody on clinical outcome in DLBCL patients

Factor	Therapeutic Efficacy				P value
	CR	PR	SD	PD	
HBsAb					
Positive	25	8	4	26	0.013
Negative	27	9	0	9	
HBeAb					
Positive	7	0	1	13	0.013
Negative	45	17	3	22	
HBcAb					
Positive	22	4	2	21	0.159
Negative	30	13	2	14	
HBsAb + and HBcAb+					
Yes	16	4	2	20	0.019
No	36	13	2	14	
Numbers in bold are statistically significant.					
Abbreviations: CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.					

In the study, the median PFS of patients in HBeAb-negative group and positive group was 51.4 months and 22.3 months, respectively ($p = 0.004$, Fig. 1A), and the median OS between the two groups showed considerable difference (61.3 months vs 29.9 months, $p = 0.007$, Fig. 1D). Besides, there was a trend that HBcAb-negative patients performed better PFS and OS than HBcAb-positive patients ($p = 0.038$ and 0.103 respectively, Fig. 1B and 1E). In addition, patients in HBsAb-positive and HBcAb-positive group displayed worse PFS ($p = 0.008$, Fig. 1C) and OS ($p = 0.035$, Fig. 1F) than patients in HBsAb-negative or HBcAb-negative patients.

The synergistic effect of HBsAb and CD21 in prognostic prediction

Pathological diagnosis based on IHC staining is an important approach for disease diagnosis, classification and prognostic prediction of DLBCL. Our study found that there was an association between HBV antibody and IHC results (Supplementary Table 2). There was a strong tendency that

patients in HBsAb-positive group had higher positive rate of CD21 (53.8% vs 32.4%, $p = 0.06$) and CD30 (30.8% vs 10.0%, $p = 0.051$).

Patients with positive expression of CD21 had similar PFS ($p = 0.50$, Fig. 2B) and OS ($p = 0.82$, Fig. 2E) with patients with negative expression while there was no significant difference in OS ($p = 0.519$, Fig. 2D) between HBsAb positive and negative group. Although HBsAb-positive patients had a worse PFS (41.1 months vs 45.9 months) than HBsAb-negative patients, it was not statistically significant ($p = 0.07$, Fig. 2A). However, when we combined HBsAb and CD21 together, it's found that patients in HBsAb-positive and CD21-positive group displayed significantly worse PFS ($p = 0.035$, Fig. 2C) and OS ($p = 0.079$, Fig. 2F) when compared with patients in HBsAb-negative or CD21-negative group.

Different therapeutic responses to Rituximab based on HBV antibody status

As Rituximab was the most common new immunotherapy drug for DLBCL, we further analyzed the association of HBV infection and the therapeutic reactivity to Rituximab. In this study, the application of Rituximab presented positive effect on clinical outcome ($p = 0.05$, Supplementary Table 3), PFS ($p = 0.015$, Supplementary Fig. 3A) and OS ($p = 0.008$, Supplementary Fig. 3B) when compared with patients receiving Rituximab-free regimen. Interestingly, the effect of Rituximab on prognostic improvement was significantly different depending on the status of HBV antibody. The positive effect of Rituximab on PFS ($p = 0.019$, Fig. 3A) and OS ($p = 0.001$, Fig. 4A) in HBsAb-positive patients was statistically significant while no difference was observed in PFS ($p = 0.251$, Fig. 3D) and OS ($p = 0.987$, Fig. 4D) depending on the use of Rituximab in HBsAb-negative patients. In HBcAb-positive group, patients receiving Rituximab-containing therapy had a better PFS ($p = 0.019$, Fig. 3B) and OS ($p = 0.004$, Fig. 4B) than patients receiving Rituximab-free therapy. However, for HBcAb-negative patients, the PFS ($p = 0.596$, Fig. 3E) and OS ($p = 0.80$, Fig. 4E) were similar in Rituximab-containing group and Rituximab-free group. Similarly, the PFS ($p = 0.004$ vs $p = 0.479$, Fig. 3C and 3F) and OS ($p < 0.001$ vs $p = 0.936$, Fig. 4C and F) according to the use of Rituximab displayed significant difference in HBsAb-positive and HBcAb-positive group rather than in HBsAb-negative or HBcAb-negative group. The different effect of Rituximab in prognostic improvement depending on HBV antibody status indicated the association between host immunity against HBV infection and drug sensitivity of Rituximab in DLBCL patients.

Univariate analysis of potential risk factors for the survival of DLBCL patients

Univariate analysis showed that patients in HBsAb-positive and HBcAb-positive group had a better PFS (HR = 2.18; 95%CI: 1.2-4.0; $p = 0.011$) and OS (HR = 2.23; 95%CI: 1.03-4.81; $p = 0.041$) than patients in HBsAb-negative or HBcAb-negative group (Supplementary Tables 4 and 5). Both the PFS (HR = 2.39; 95%CI: 1.29-4.44; $p = 0.006$) and OS (HR = 2.71; 95%CI: 1.26-5.79; $p = 0.01$) were associated with the status of HBeAb in univariate analysis (Supplementary Tables 4 and 5).

Discussion

Recently, there is a growing amount of evidence which indicate the significant association of HBV infection and NHL progression. Consistent with previous studies, we found that HBV makers assay was different between DLBCL patients and general population. To date, previous studies have been focused on the association between HBsAg, HBV DNA and DLBCL development (20, 24, 28) and it's found that patients with positive HBsAg had higher risk of DLBCL. In fact, HBsAg-positive patients only account for less than 10% of total DLBCL patients and the progression of lymphoma has been reported to be correlated with host immune response. Therefore, we performed this retrospective study and analyzed the consecutive cohort of 190 newly diagnosed and untreated DLBCL patients to explore the correlation between HBV antibody status and clinical prognosis in DLBCL patients.

To clarify the correlation between HBV antibody and clinical characteristics, we divided the HBsAg negative patients into groups based on HBV antibody status. For the first time, it's found that patients with positive HBeAb displayed unique clinical characteristics, such as more advanced stage and higher IPI score. In addition, it's showed that patients in HBsAb-positive group displayed earlier median onset age. However, there was no obvious difference of clinical features in other groups divided by HBsAb and HBcAb status, which was similar to another study (28) reported in China and may be due to the small sample size. The evidence strongly supported that HBV antibody status was associated with DLBCL disease progression.

Although there was broad agreement that both HBV infection and immune response are involved in DLBCL progression, there is no comprehensive study focused on the correlation between HBV antibody and clinical prognosis in DLBCL patients so far. The evidence for the effect of immune response to HBV infection in DLBCL is scarce (16, 18). For the first time, our study indicated that HBV antibody was associated with the clinical outcome and prognosis in DLBCL patients. Patients with positive HBV antibody had worse clinical outcome and worse prognosis. The findings indicated the close correlation between HBV antibody and clinical prognosis of DLBCL patients, and the potential role of HBV antibody in the prognostic prediction in DLBCL patients. Moreover, the correlation points to a novel research direction about the role of immune response to HBV in DLBCL progression.

Immunohistochemical study is essential to make an adequate diagnosis, disease classification and prognostic prediction for DLBCL patients (29). Our study firstly indicated the association between HBV antibody status and IHC results. For example, there was an obvious tendency that patients in HBsAb-positive group had a higher positivity rate of CD21 and CD30, which were involved in the immune response to the pathogens stimulation including virus. In addition, it's found that HBsAb and CD21 had a synergistic effect for prognostic predication in DLBCL patients, indicating the role of immune response to HBV infection in DLBCL progression. In previous investigations(30), the gene rearrangement of MYC and BCL2 in HBsAg-positive group was more common than that in the negative group. However, the status of HBV antibody was not found to be associated with gene rearrangements of MYC and BCL2 in our study, which may be due to small number of patients. Furthermore, we identified that the status of HBV antibody was associated with the positivity of BCL2 and MYC in immunohistochemistry, which were important molecular marker for the apoptosis and proliferation of lymphoma cells. Therefore, our study

suggested that the immune response to HBV infection was associated with DLBCL progression and reasons for this association remained to be elucidated.

In our study, the use of Rituximab obviously improved clinical outcome and prognosis of DLBCL patients, which was consistent with previous studies (31). However, Feng Wang et al (32) reported that the positive effect of Rituximab on the prognosis of DLBCL patients disappeared in HBsAg-positive patients and probably because Rituximab increased the risk of HBV reactivation and HBV-related liver failure (33, 34), especially in HBsAg-positive patients. To explore the relationship between Rituximab effect and HBV antibody status in DLBCL patients, we performed the study and firstly found that the effect of Rituximab on prognosis improvement changed with HBV antibody status. The positive effect of Rituximab on PFS and OS only existed in HBV positive group but disappeared in negative group, indicating that patients in positive group had better drug response to Rituximab. It's the first time to report the correlation between HBV antibody status and the therapeutic effect of Rituximab in DLBCL patients and our data supported the hypothesis that the immune response to HBV infection might be involved in the pathogenesis and progression of DLBCL. Importantly, these results provided potential biomarker to predict the effect of Rituximab in DLBCL patients.

Our study still had numerous limitations. Firstly, this study was restricted by its retrospective nature and the small sample size. It was limited to analyzing patients from a single institution in China and it should be verified in other ethnic groups and other region. Further prospective research with larger sample sizes are needed to clarify the relationship between HBV antibody status and clinical prognosis in DLBCL patients. Secondly, in order to eliminate the effect of HBsAg in clinical prognosis and focus on the role of HBV antibody in DLBCL patients, patients with positive HBsAg was not taken into account in our study. Further study covering the status of HBV antibody and HBV antigen could promote the comprehensive understand of the association between HBV infection and DLBCL development. In the future, further investigations on the biological mechanisms underlying the association of HBV antibody status in clinical prognosis and Rituximab sensitivity within DLBCL patients are needed.

Conclusions

Collectively, our study demonstrated that patients with positive HBV antibody presented unique clinical features, worse clinical outcome and worse prognosis. Interestingly, the effect of Rituximab in prognostic improvement was more significant in HBV antibody-positive group than the negative group. Our results provide the evidence to support that there is novel association between HBV infection and DLBCL progression, and HBV antibody could act as potential biomarker to predict prognosis and the effect of Rituximab in DLBCL patients. The prognostic effects of HBV antibody open up a new research direction about the role of immune response to HBV infection in DLBCL progression.

Abbreviations

CI: confidence interval; CR: complete remission; DLBCL: Diffuse large B-cell lymphoma; GCB: germinal center B-cell; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: human immunodeficiency virus; HR: hazard ratio; IHC: immunohistochemistry; IPI: International Prognostic Index; LDH: lactate dehydrogenase; LMR: lymphocyte monocyte ratio; NHL: non-Hodgkin lymphoma; NUC: nucleos(t)ide analogue; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PLR: platelet lymphocyte ratio; PR: partial remission; RR: risk ratio; SD: stable disease; WBC: white blood cell; WHO: World Health Organization.

Declarations

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Ethics approval and consent to participate

This study was approved by the Ethical Committee of the Shandong Provincial Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The data that support the findings of this study are available from corresponding author upon reasonable request.

Authors' contributions

Designed the experiments: HSF, ZXX and WX; Acquisition of data: HSF, CN, LK and ZCQ; Analysis and interpretation of data: HSF, FXS and SXH; Draft of the manuscript: HSF and ZXX; Critical revision of the manuscript for intellectual content: LY, ZXX and WX; Funding Acquisition: ZXX and WX. All authors read and approved the final manuscript.

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Figures

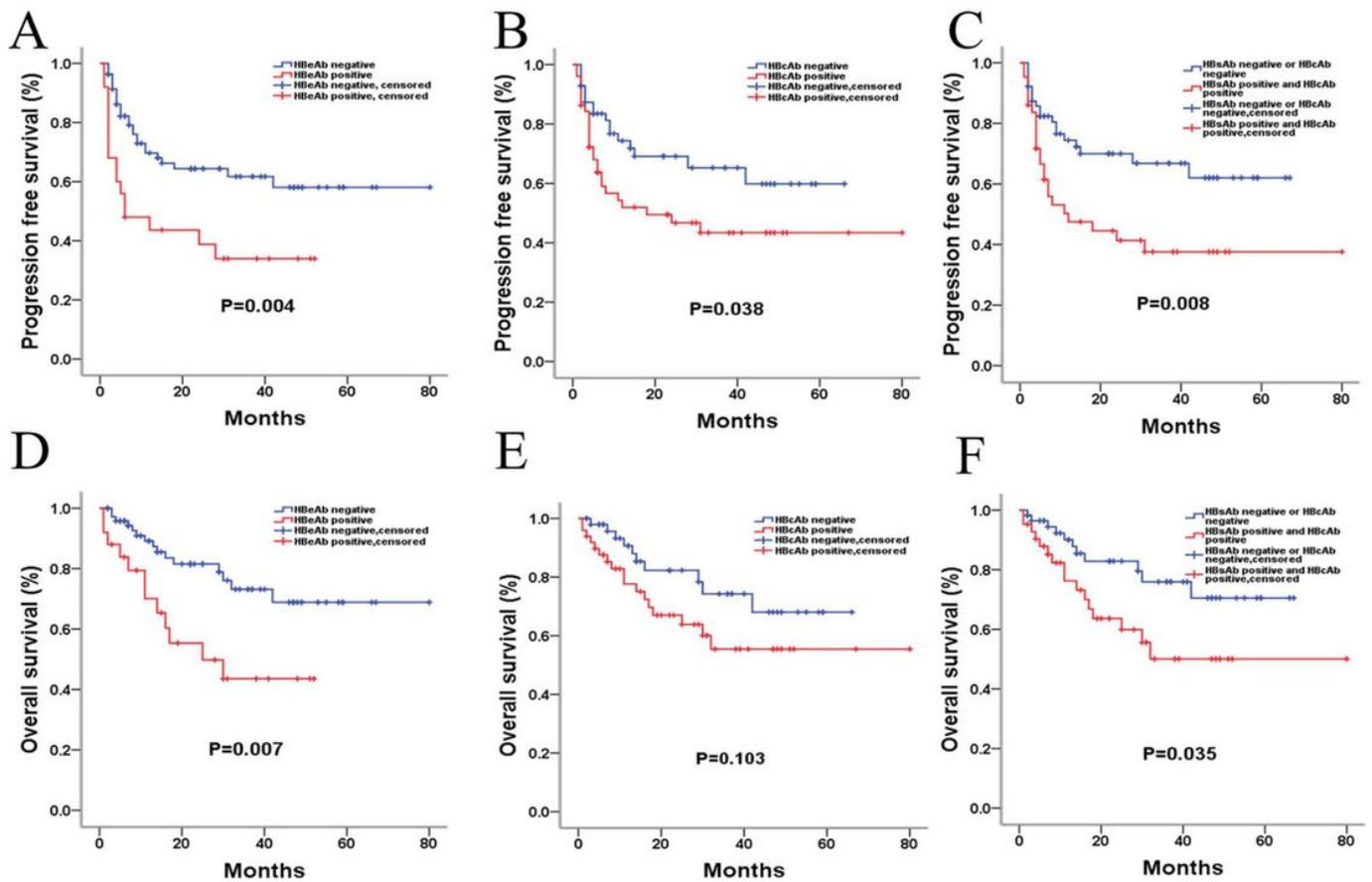


Figure 1

Survival analysis according to HBV antibody status in DLBCL patients (A) Progression-free survival based on HBeAb status. (B) Progression-free survival based on HBcAb status. (C) Progression-free survival based on HBsAb and HBcAb status. (D) Overall survival based on HBeAb status. (E) Overall survival based on HBcAb status. (F) Overall survival based on HBsAb and HBcAb status.

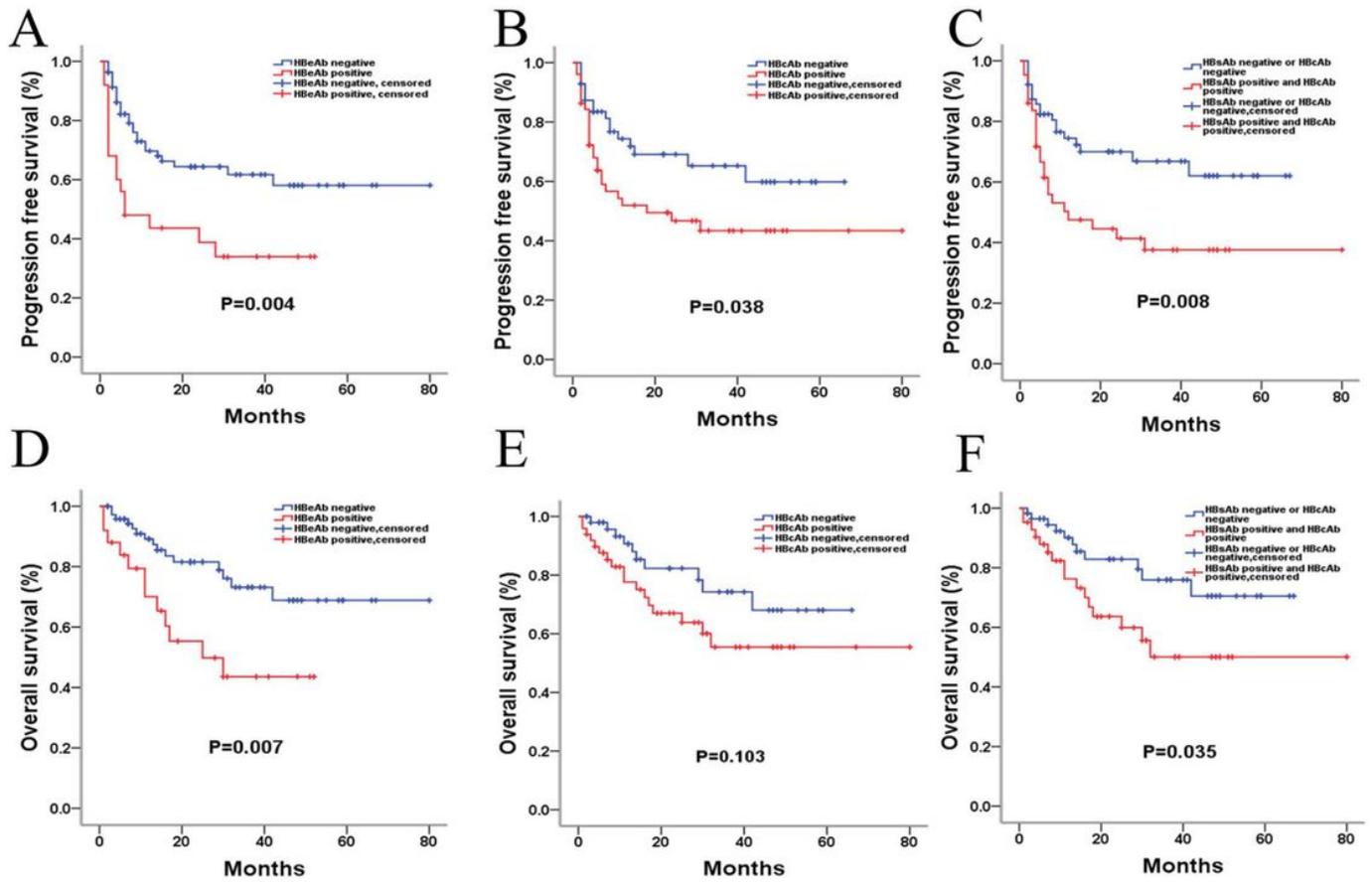


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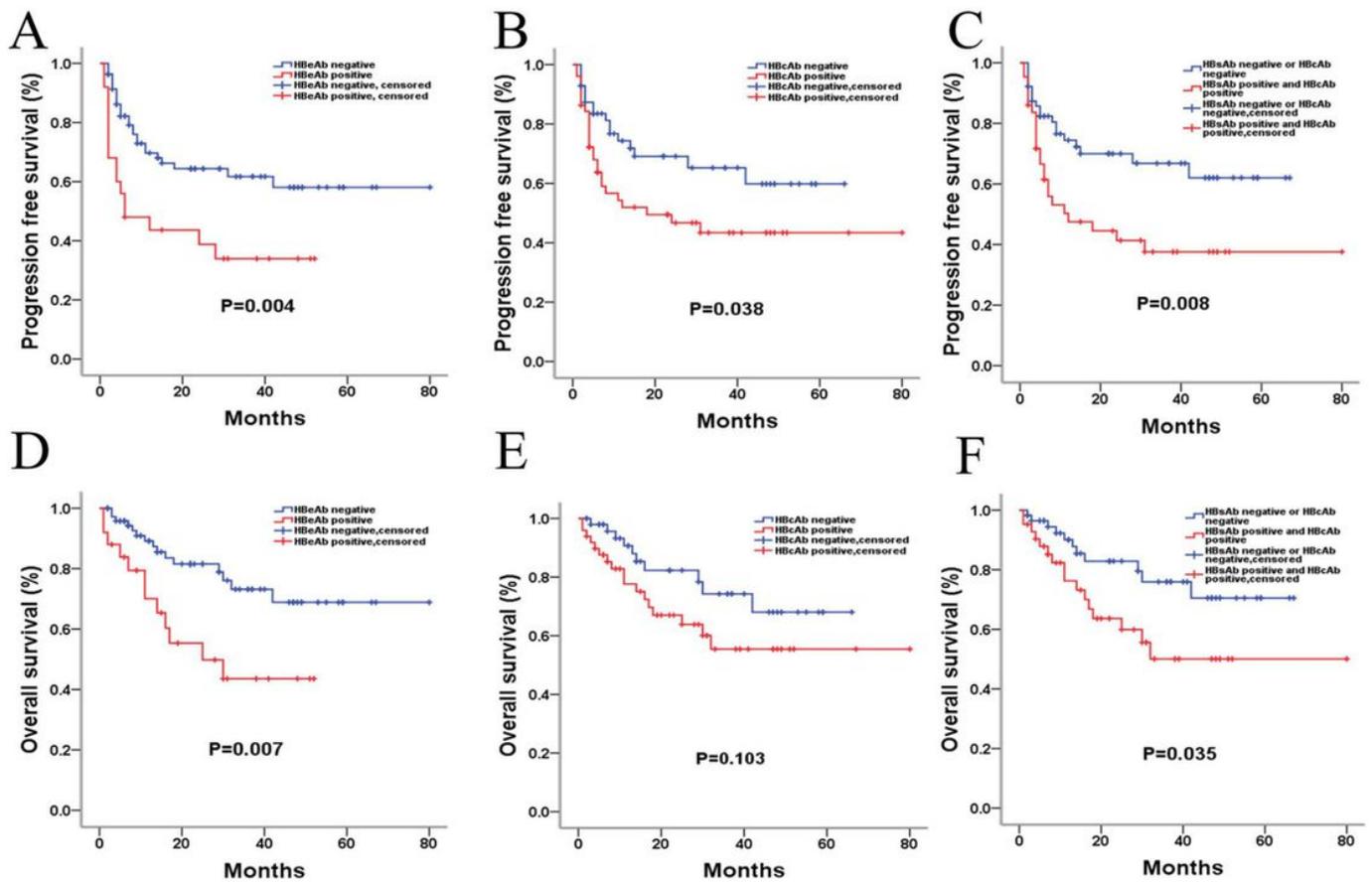


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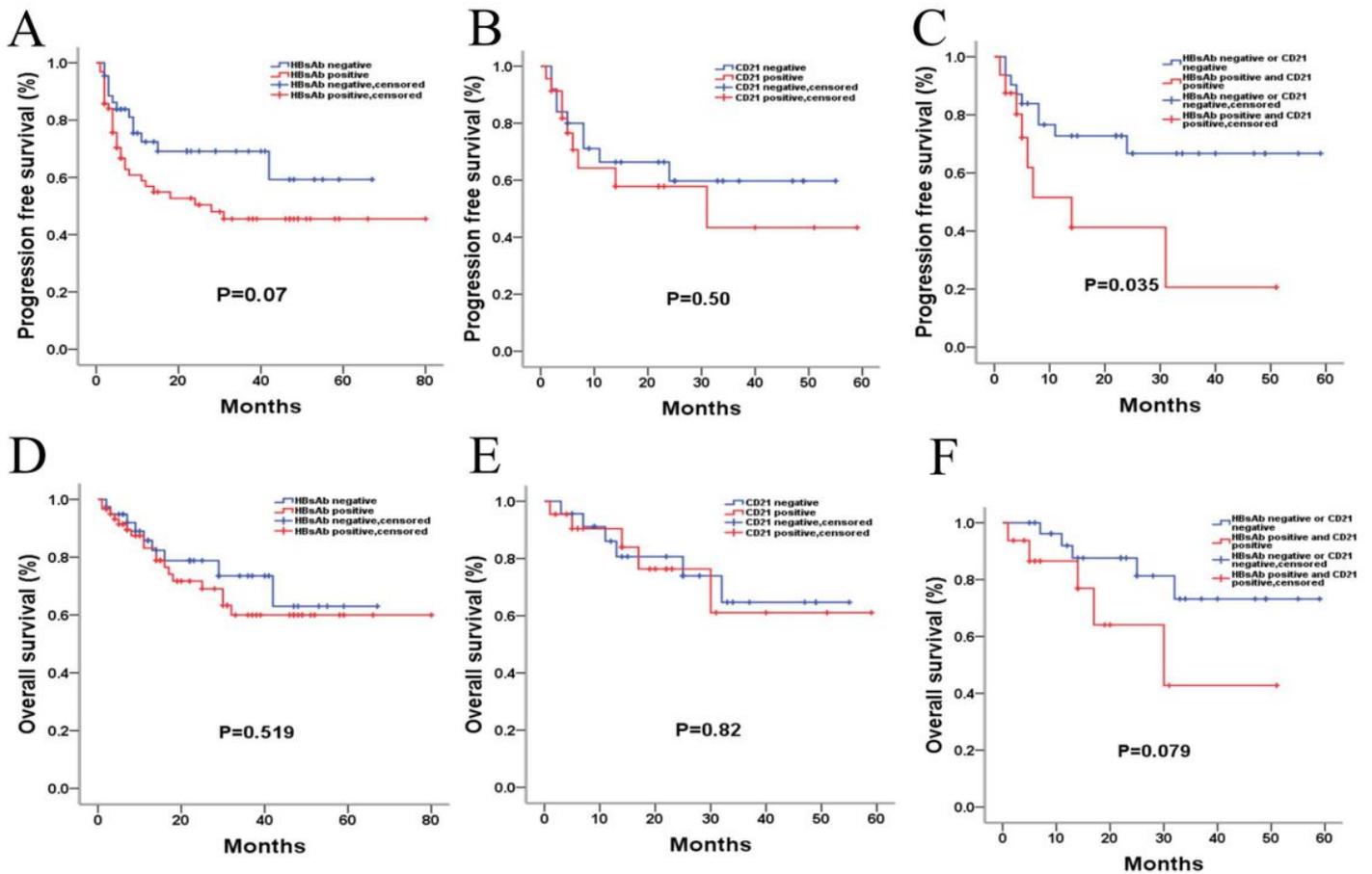


Figure 2

Survival analysis according to HBsAb and CD21 status in DLBCL patients (A) Progression-free survival based on HBsAb status. (B) Progression-free survival based on CD21 status. (C) Progression-free survival based on HBsAb and CD21 status. (D) Overall survival based on HBsAb status. (E) Overall survival based on CD21 status. (F) Overall survival based on HBsAb and CD21 status.

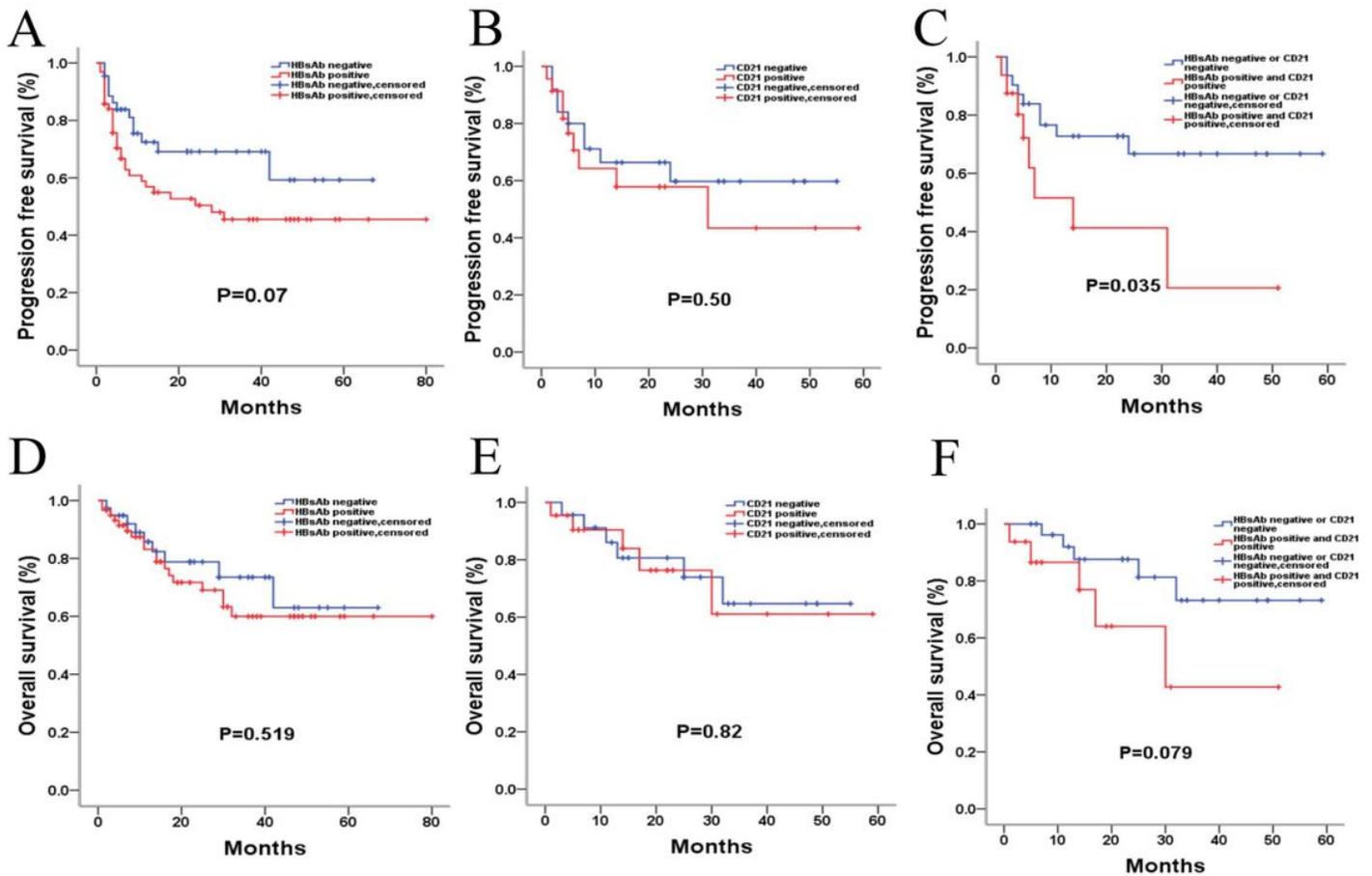


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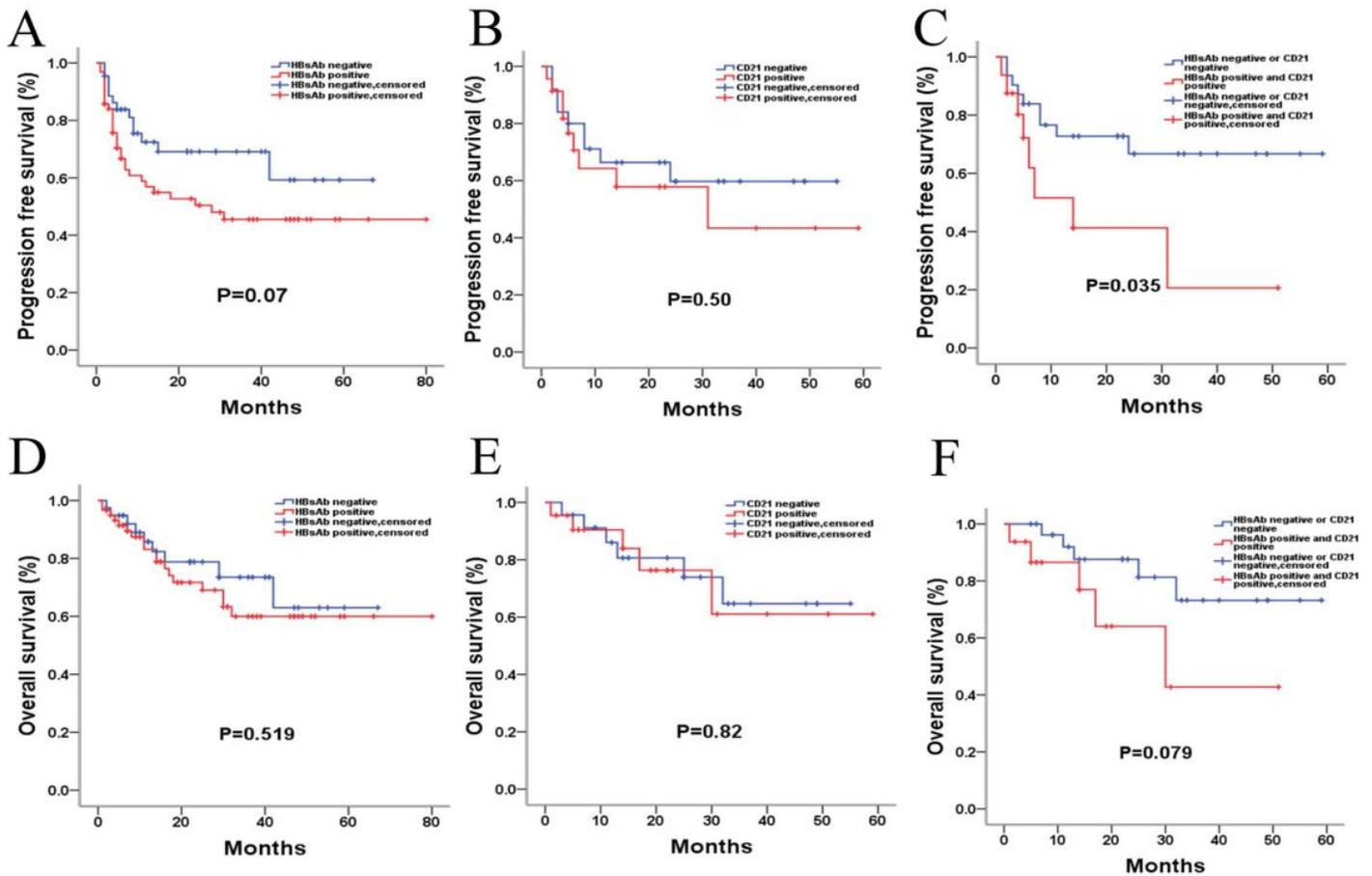


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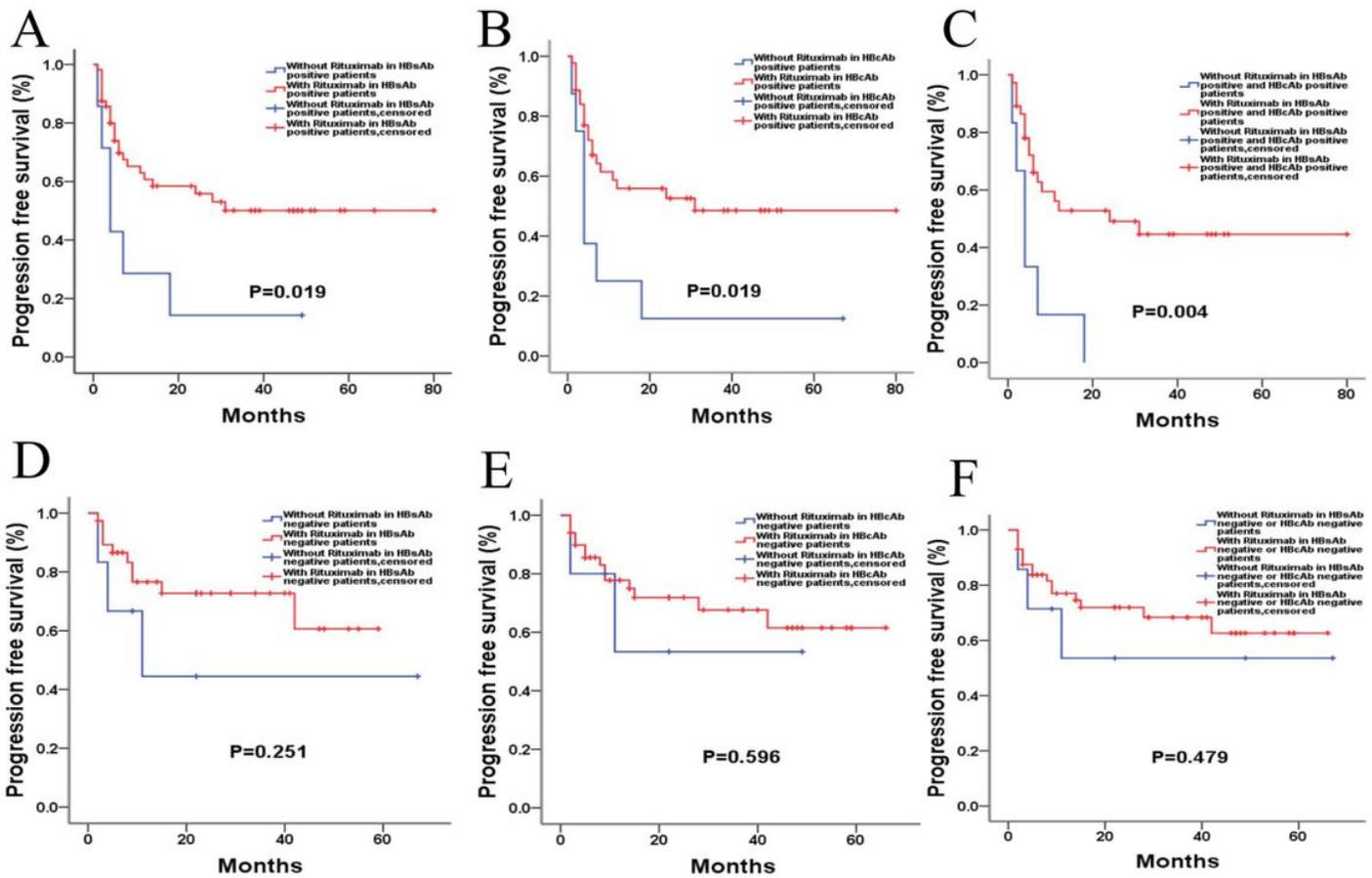


Figure 3

Progression-free survival analysis according to therapy regimen and HBV antibody in DLBCL patients between Rituximab-containing group and Rituximab-free group (A) in HBsAb positive patients. (B) in HBcAb positive patients. (C) in HBsAb positive and HBcAb positive patients. (D) in HBsAb negative patients. (E) in HBcAb negative patients. (F) in HBsAb negative or HBcAb negative patients.

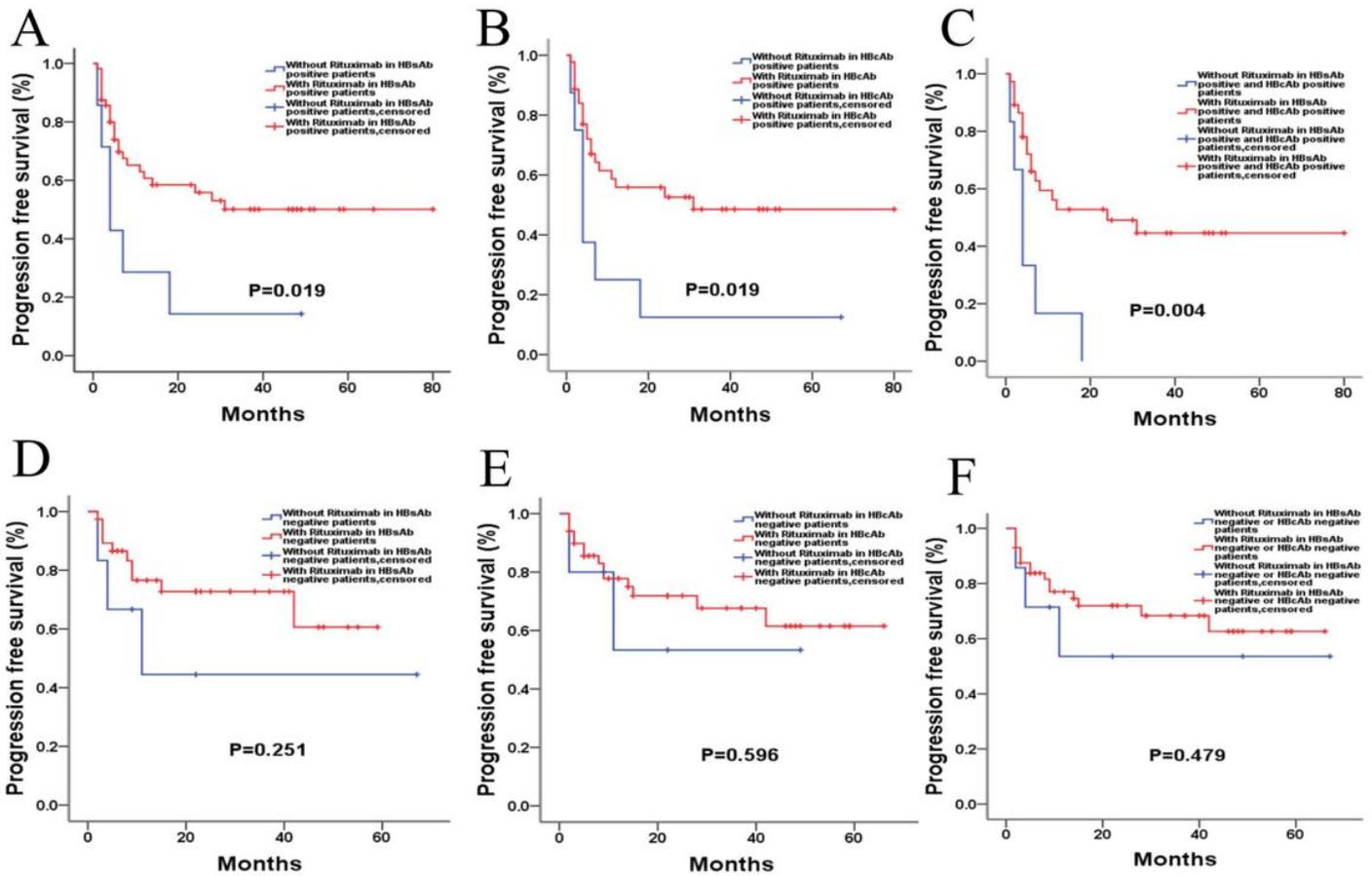


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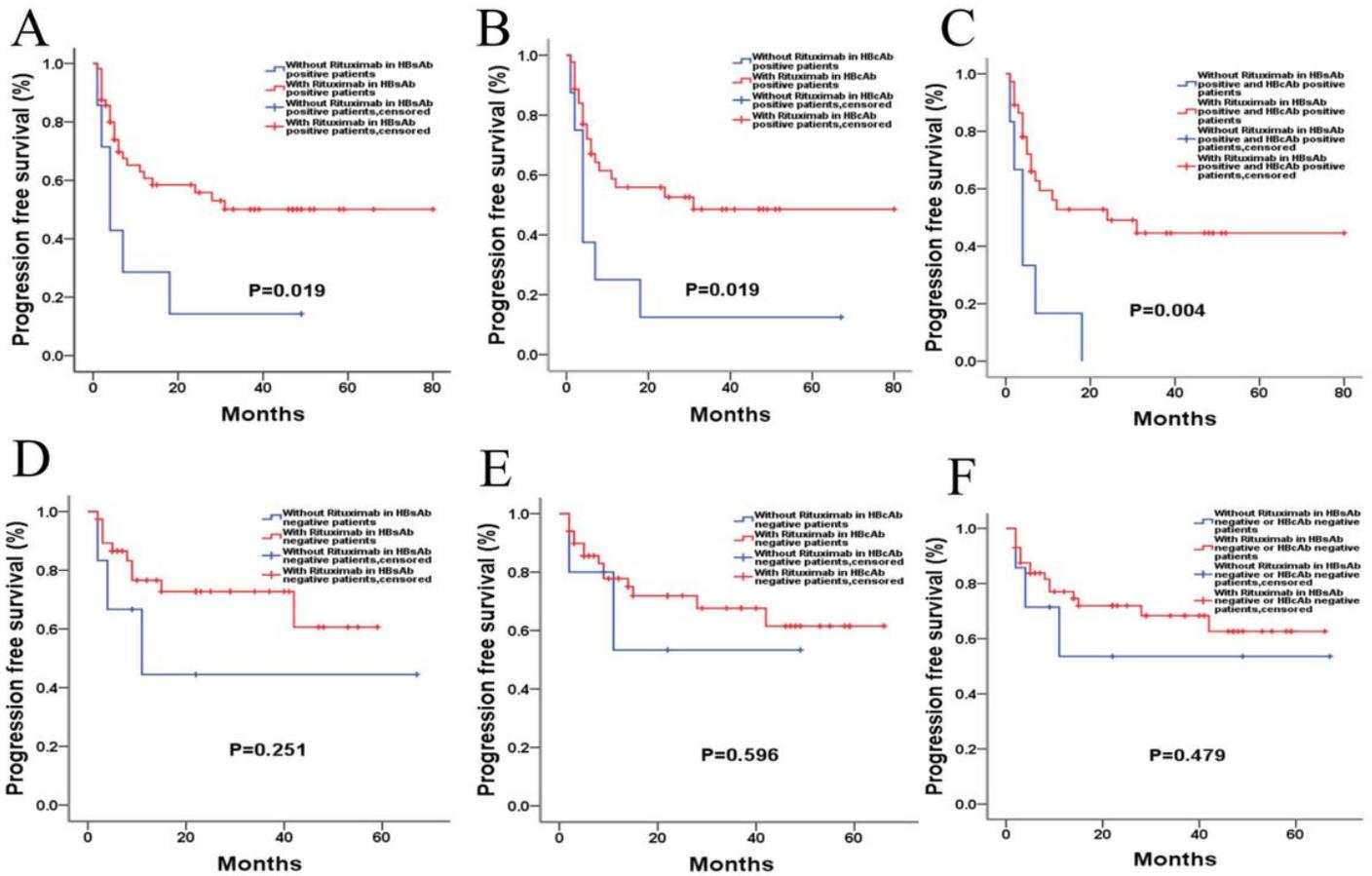


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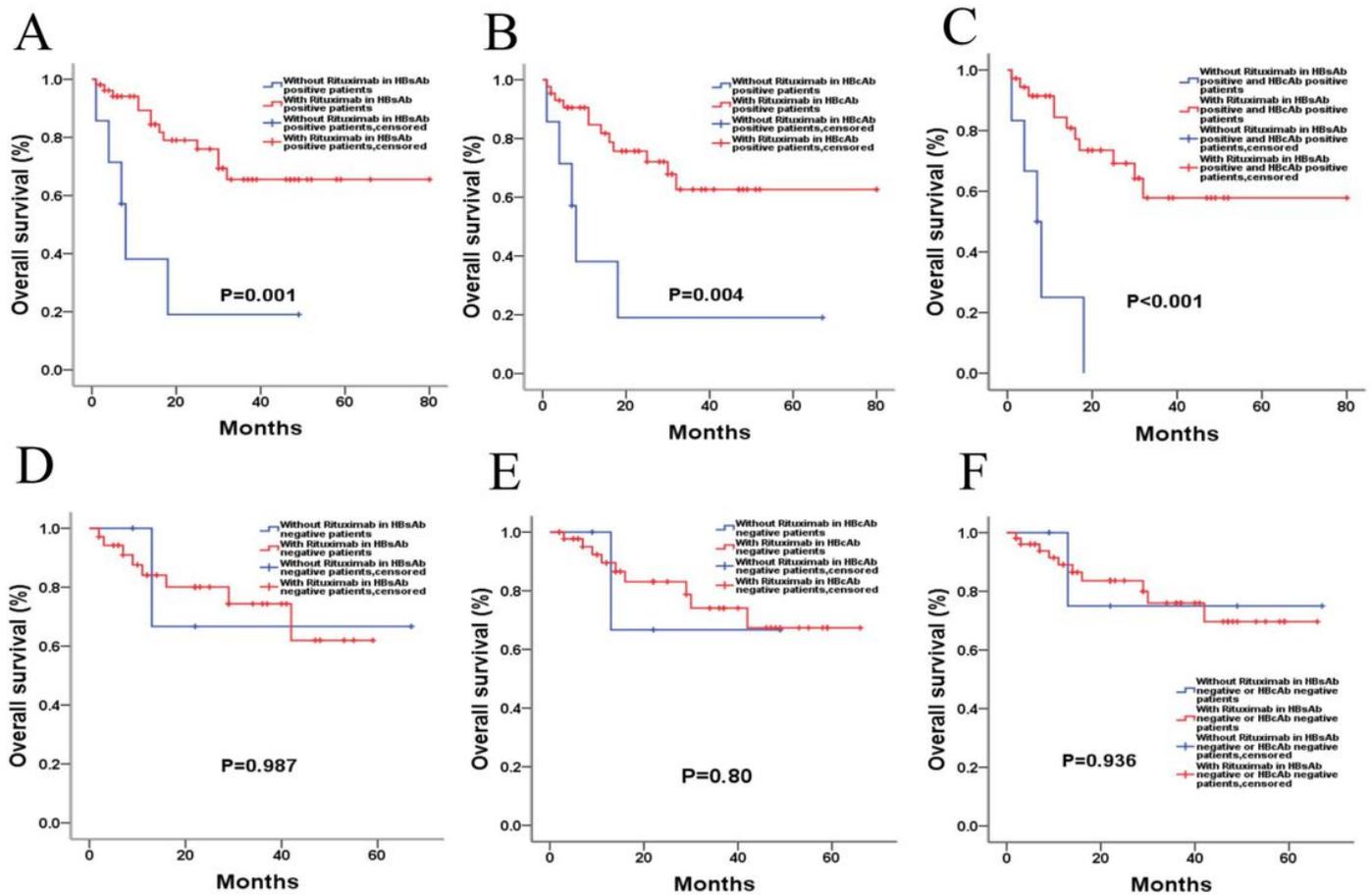


Figure 4

Overall survival analysis according to therapy regimen and HBV antibody in DLBCL patients between Rituximab-containing group and Rituximab-free group (A) in HBsAb positive patients. (B) in HBCAb positive patients. (C) in HBsAb positive and HBCAb positive patients. (D) in HBsAb negative patients. (E) in HBCAb negative patients. (F) in HBsAb negative and HBCAb negative patients.

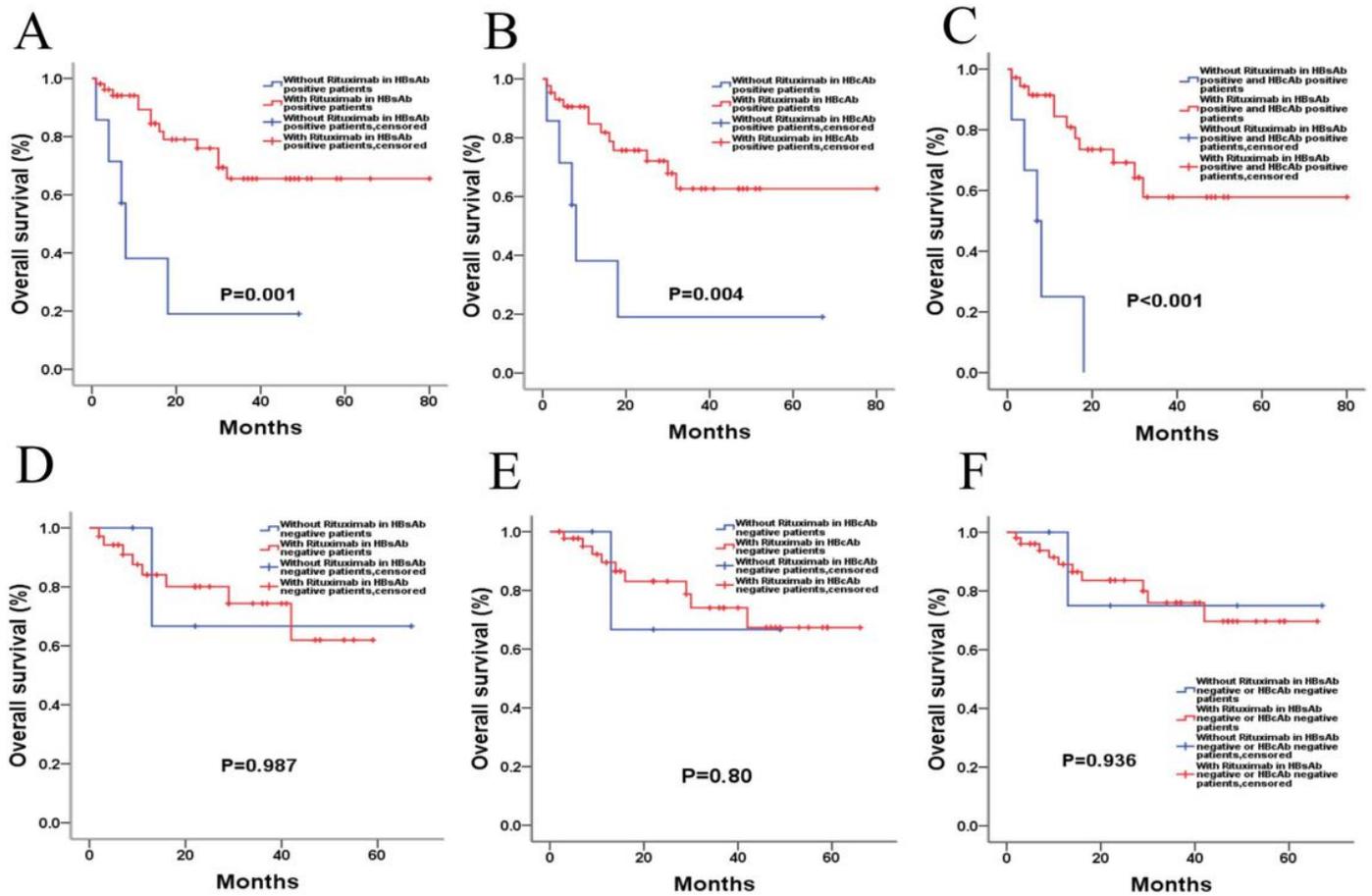


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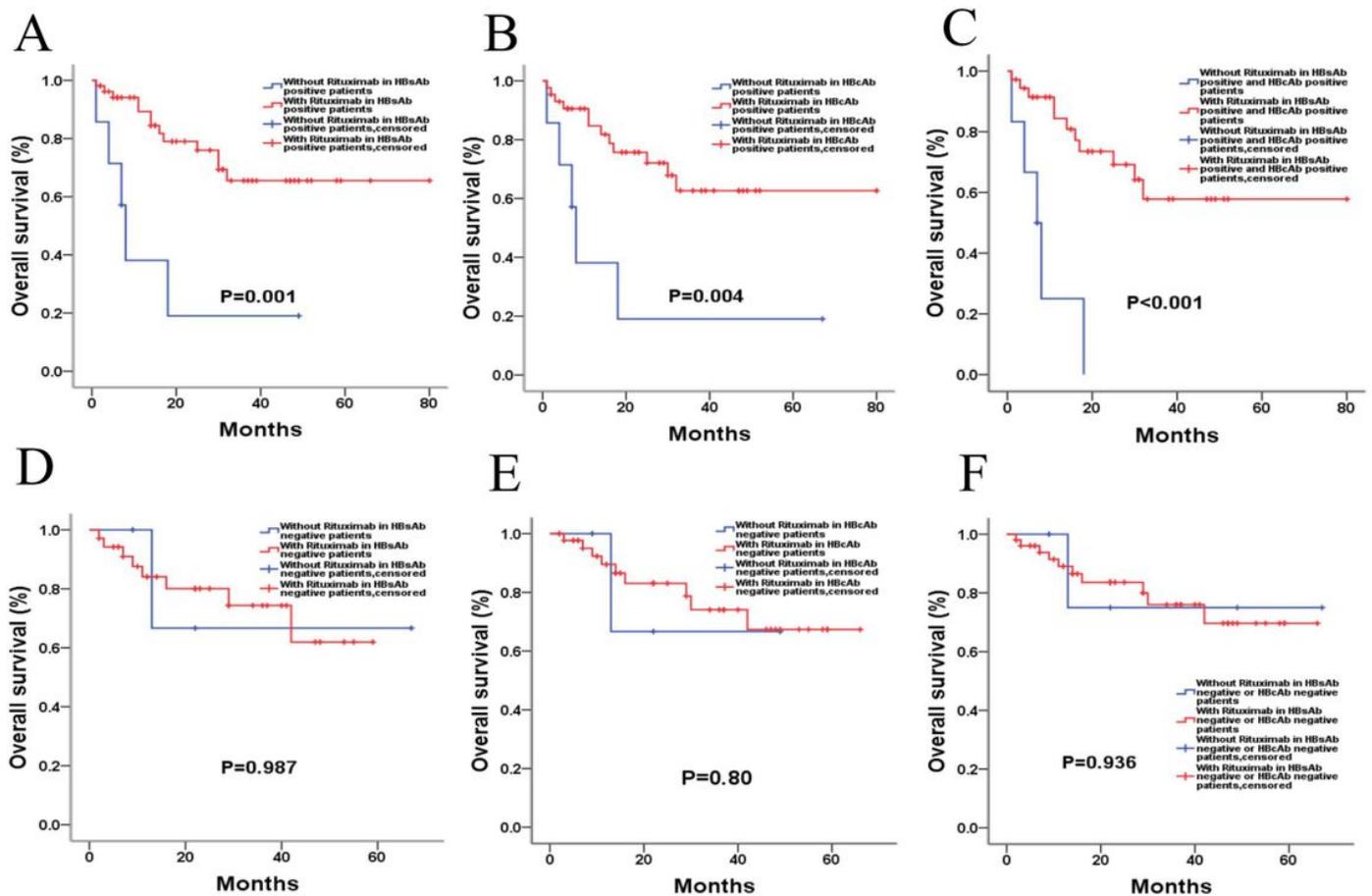


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