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ORIGINAL ARTICLE

Factors affecting inadequate response to HBV vaccine in hemodialysis patients: northeast anatolia survey with six hemodialysis centers

Halil İbrahim Erdoğdu[1] · Eray Atalay[1] · Gül Gürsoy[2] · Başol Canbakan[3] · Serkan Aktürk[4] · Canan Yazıcı[5] · Orhan Yücel[4] · Sinan Mersin[6] · Sengül Üçer[7] · Özgür Merhametsiz[8] · Can Öner[9] · Merve Erat[1]

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Abstract

Background In hemodialysis patients Hepatitis B virus (HBV) infection is one of the problems. Because of HBV vaccine response is lower than in the general population, in this study it is aimed to determine the factors that may cause inadequate HBV vaccine response in hemodialysis patients.

Methods In study, HBsAg, anti-HBs, anti-HBc IgG data belonging to 278 patients were obtained from file and computer records. It was seen that seronegative cases had been given recombinant HBV vaccine. Anti-HBs titers were monitored 1 month after vaccination was completed. According to this, the patients are divided into two groups. Those with anti-HBs < 10 IU/mL were identified as non-responders and with anti-HBs ≥ 10 IU/mL as responders. Factors such as age, serum albumin and urea reduction rate which may affect inadequate response to HBV vaccine were evaluated. As statistical examination, Chi-square test was used for the analysis of the data determined by counting, and logistic regression was used for statistically significant independent variables in chi-square test. p value of < 0.05 was considered statistically significant (Confidence interval: 95%).

Results Out of 278 patients, according to exclusion criteria 81 patients were excluded. 13.2%(26/197) of HBV vaccinated patients had insufficient response. The inadequate response rate to HBV vaccination was found to be higher in patients with age ≥ 65 ($p = 0.039$), serum albumin < 3.5 g/dL ($p = 0.024$) and urea reduction rate ≤ 65 ($p = 0.028$). No statistically significant relationship was found between inadequate response to HBV vaccine and anti-HCV positivity, presence of diabetes mellitus, anemia status, vitamin D therapy and vascular access pathway variability.

Conclusion We conclude that relatively high patient age, low albumin level and insufficient urea reduction rate may cause inadequate HBV vaccine response. Taking these factors into consideration may provide a useful insight for an adequate response to vaccination.

Keywords Hepatitis B vaccines · Hemodialysis · Humoral immune response · Hemodialysis adequacy

✉ Halil İbrahim Erdoğdu
halil-dr@hotmail.com

[1] Department of Internal Medicine, Health Research Center, Kafkas University, Kars, Turkey

[2] Department of Internal Medicine and Endocrinology, Kafkas University, Kars, Turkey

[3] Department of Internal Medicine and Neprology, Kafkas University, Kars, Turkey

[4] Department of Hemodialysis and Nephrology, Kars Harakani State Hospital, Kars, Turkey

[5] Departement of Internal Medicine, Ardahan State Hospital, Ardahan, Turkey

[6] Department of Internal Medicine, Kartal Lütfi Kırdar Education and Research Hospital, Istanbul, Turkey

[7] Department of Clinical Microbiology and Infectious diseases, Kafkas University, Kars, Turkey

[8] Department of Hemodialysis and Nephrology, Iğdır State Hospital, Iğdır, Turkey

[9] Department of Family Medicine, Kartal Lütfi Kırdar Education and Research Hospital, Istanbul, Turkey

Introduction

It is estimated that 257 million people worldwide are positive for hepatitis B surface antigen (HBsAg). In 2015, 887,000 deaths were noted due to HBV infection, mainly caused by cirrhosis and hepatocellular carcinoma.

Hepatitis B virus (HBV), which can survive at least 7 days in the room temperature, can infect by contaminated surfaces, body fluids, medical devices, blood and its products [1]. Seroprevalence of HBsAg is 3.61% in general, 0.5–0.7% in Europe and 4–4.5% in Turkey [2–4]. It is anticipated that the World Health Organization (WHO) will reduce new HBV infections to 90% by 2030 [1].

The rate of HBV exposure is higher in patients undergoing hemodialysis (HD) therapy than in the general population [5]. It is, therefore, important that these patients have to be vaccinated against HBV. In end-stage renal disease (ESRD), antibody response to hepatitis B vaccine is low and titration levels decrease with time [6]. Since 1982, the Center for Disease Control and Prevention (CDC) has recommended hepatitis B vaccination in HD patients. In addition to nonimmune susceptible HD patients, four doses of recombinant hepatitis B vaccine 40 µgr intramuscularly (0, 1, 2 and 6 months) are recommended for patients not responding to previous vaccination [5].

In this study, bearing in mind the importance of HBV vaccine and, the lack of response to this vaccine in HD patients, we planned to determine the factors that could negatively affect HBV vaccine response in HD patients.

Patients and methods

Our retrospective cross-sectional study consisted of 278 patients in six HD centers of Kars, Ardahan, Iğdır cities and their districts in the province of Kars. Hemodialysis and Nephrology Units from Sarıkamış, Kağızman, and Göle State Hospitals participated in the study. The data of the study had been obtained by analyzing the demographic, clinical, laboratory and serological records of patients who underwent hemodialysis treatment for 4 h three times a week in the centers between 29 September and 14 November 2017. 81 of the 278 patients who participated in the study were removed in accordance with the exclusion criteria.

Exclusion reasons and number of excluded patients were stated:

Patients who have not completed the vaccination protocol ($n=25$), those who have natural immunity (total anti-HBc and anti-HBs positive) ($n=11$), those who are HBsAg positive ($n=9$), demographical, clinical, laboratory-related, serological, echocardiographical and radiological evidence deficiencies in records ($n=25$), those who do not complete the HD session and duration for any reason ($n=5$), guest patients ($n=5$) and immunosuppressive treatment ($n=1$) subjects were excluded from the study. The fact that the number of excluded patients is 81, suggests that some of the patients have several criteria.

The information of HBV vaccine and vaccination protocol:

Four doses of 40 µgr recombinant hepatitis B vaccine (Engerix-B, GlaxoSmithKline Biologicals or Genhevac-B, Sanofi Pasteur SA) were recommended into muscle at 0, 1, 2 and 6 months [5]. Patients were divided into two groups according to anti-HBs titrations. Responders with anti-HBs titers < 10 IU/mL were identified as inadequate response and responders with anti-HBs titers ≥ 10 IU/mL as adequate response [5].

According to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K / DOQI) recommendations, before-HD blood samples were taken prior to saline and heparine administration and after-HD blood samples were taken after the blood pump rate was reduced to 100 ml/min for 15 s [7].

For the Kt/V which was the second-generation formulation of Daugirdas was used [8].

$$\text{Single - pool(sp)}Kt/V = -\text{Ln}(R - 0.008 \times t) + (4 - 3.5 \times R) \times \text{UF}/W,$$

R is the ratio of post-dialysis to pre-dialysis blood urea nitrogen, t is the time on hemodialysis in hours, UF is the amount of ultrafiltration in liters and W is the post-dialysis body weight in kilograms.

For the urea reduction rate (URR): URR = 100 × 1 − postdialysis blood urea nitrogen (BUN)/predialysis BUN was used [9].

URR and Kt/V were used to analyze whether dialysis adequacy had a positive effect on HBV vaccine. To compare HD adequacy and response of HBV vaccine URR 65% and Kt/V 1.4 were taken as NKF-K/DOQI suggested [9].

Commonly, hypoalbuminemi is known as indicator of deterioration of nutritional state. To indicate whether nutritional state affects the HBV vaccine response, we took the minimum 3.5 g/dL as cut-off value since the study which takes place in central laboratories take the albumin level (measured by bromocresol green) interval as 3.5–5.5 g/dL. In addition, in a previous study, a relation was shown between albumin level of < 3.5 g/dL and mortality. Therefore, to compare nutritional state and HBV vaccine response, lower boundary of 3.5 was taken as cut-off value [10].

In addition to that, albumin stratification was performed as follows: < 3.5, 3.5–3.9, 4.0–4.4, ≥ 4.5 g/d L and the HBV vaccine responses were compared. In the study, since the number of patients who have albumin level of < 3.0 g/

dL were only 5, they were not stratified separately for the statistical analysis.

In the study we took 5 years as threshold to indicate whether there is a relation between HBV vaccine response and duration of HD, since previous study T helper/ T suppressor ratio decreased in those whose HD duration was > 5 years and their suppresor T lymphocytes level was higher [11].

To determine the response of the elderly to HBV vaccine, the cut-off value was taken as 65 years old which was the median value of the study.

In addition to that, ages are stratified as it is stated below and each level of ages were taken as independent variable and vaccine response conditions were analyzed.

Age stratification was performed as follows: < 45, 45–54, 55–64, 65–74, and ≥ 75 age.

The response status to HBV vaccine was identified as the dependent variable of the study. Independent variables were determined as the age of the patients ≥ 65 and, stratified by patient's age, their sex, the level of albumin < 3.5 g/dL, the URR ≤ 65, Kt/V < 1.4, hemodialysis duration ≥ 5 years, whether they are HCV positive, diabetes mellitus, active vitamin D and / or anologic therapy, whether they have received erythropoietin therapy, hemoglobin levels < 11 and ≥ 11 g / dL and vascular access routes (arteriovenous fistula, permanent catheter and graft) and we compared them in the two groups.

For statistical evaluation SPSS Statistics of Windows v.21,0 (SPSS; IBM Corporation, New York, USA) was used. We applied the Chi-square and Fisher's exact test in the analysis of the countable data. Results were evaluated according to a p value of < 0.05 and confidence internal of 95%. We examined statistically significant independent variables in Chi-square test by logistic regression analysis (Backward: LR).

Results

One hundred ninety-seven of the 278 patients were included in the study, according to exclusion criteria 81 patients were excluded. The mean age of the patients was 61.5 (standard deviations 1.0) ($p < 0.05$) and the median value was 65 (range: 20–98). The ratio of male and female patients was 117/80. The rate of anti-HCV positive patients all of which were confirmed with HCV-RNA was 3.9% (11/197). When HBV vaccination was administered the response was inadequate in 13.2% of the 197 patients studied. We determined a response in the titrations of unresponsive patients after 40 µg single dose HBV vaccination (8/26-30.7%).

Table 1 presents the effect of independent variables on HBV vaccine response. A statistically significant difference was observed between inadequate vaccination response and age ($p = 0.005$), albumin ($p < 0.001$), URR ($p = 0.008$), Kt/V ($p = 0.042$), duration of dialysis ($p = 0.039$).

On the other hand, there was no statistically significant difference between chronic diseases and inadequate vaccination response (Table 2).

Age, albumin, URR, Kt/V, and duration of dialysis, which were significant in binary analyzes, were included in the regression analysis. According to this, the risk of inadequate response to HBV vaccine in 65 years old and over was 2.9 (CI: 1.1–7.8) times higher than those who were < 65 years old. The inadequate response to HBV vaccine was also 2.9 (CI:1.2–7.4) times higher in patients who had albumin levels below 3.5 g/dL than those had albumin levels of ≥ 3.5 g/dL. We also found that the risk of lack of response was 3.6 (CI:1.1–11.5) times higher in URR at 65 and below than > 65 (Table 3).

In addition, when albumin level is compared with age, there is a statistically significant difference ($p < 0.001$). However, there is not any statistically significant difference when albumin level is compared with URR ($p = 0.214$) (Table 4).

As Table 5 is followed, when people, who are ≥ 65, have albumin level of < 3.5 g/dL, the vaccine response level is less ($p = 0.008$).

Discussion

It was reported that HBV seroprevalence was 3.1% and anti-HCV positivity was 2.7% in HD patients who continued the treatment in Turkey [12]. The average seroprevalence rates of our centers where the study was conducted were 3.5% and 3.9%, respectively. The rate of HBV vaccine response in our study was 86.8%.

Several previous studies have reported different factors that may affect inadequate response to HBV vaccination. In our study, there was a statistically significant difference between age, albumin, URR, Kt/V, duration of dialysis and inadequate response to HBV vaccination. When these variables were taken into logistic regression analysis, the risk was 2.9 times for age ≥ 65, 2.9 for albumin < 3.5 g/dL and 3.6 times for URR ≤ 65.

The effect of age patient on HBV vaccine response has been addressed in previous studies. In our study of the patients who did not respond, 76.9% (20/26) had an age ≥ 65. When patients' ages were stratified, vaccine response rates were lower for the ages 65–74 and ≥ 75 compared to the ages < 65 which were 81% and 77.1%, respectively. Since the insufficient vaccine response was 2.9 times greater for the people who were ≥ 65 and have albumin level of < 3.5 g/dL in the logistic regression, there was a statistically significant difference in the binary comparison which was made to indicate whether

Table 1 Effect of independent variables on response to HBV vaccination

Independent variables		Dependent variable		Total[a]	*p*
		Anti Bs ≥ 10 IU/mL	Anti Bs < 10 IU/mL		
		number(%)	number(%)	number(%)	
Age (years)	≥ 65	81 (80.2)	20 (19.8)	101(51.2)	0.005
	< 65	90 (93.8)	6 (6.3)	96(48.8)	
Age at every 10 years	< 45	27 (87.1)	4 (12.9)	31 (15.7)	0.048
	45–54	23 (95.8)	1 (4.2)	24 (12.2)	
	55–64	40 (97.6)	1 (2.4)	41 (20.8)	
	65–74	54 (81.8)	12 (18.2)	66 (33.5)	
	≥ 75	27 (77.1)	8 (22.9)	35 (17.8)	
Serum albumin (g/dL)	≥ 3.5	143 (91.1)	14 (8.9)	157(79.7)	< 0.001
	< 3.5	28 (70.0)	12 (30.0)	40 (20.3)	
Stratified analysis of serum albumin (g/dL)	< 3.5	28 (70.0)	12 (30.0)	40 (20.3)	0.004
	3.5–3.9	71 (89.9)	8 (10.1)	79 (40.1)	
	4.0-4.4	59 (92.2)	5 (7.8)	64 (32.5)	
	≥ 4.5	13 (92.9)	1 (7.1)	14 (7.1)	
URR (%)	≤ 65	12 (66.7)	6 (33.3)	18 (9.1)	0.008[d]
	> 65	159 (88.8)	20 (11.2)	179 (90.9)	
Kt/V	< 1.4	35 (77.8)	10 (22.2)	45 (22.8)	0.042
	≥ 1.4	136(89.5)	16 (10.5)	152 (77.2)	
Gender	Female	72 (90.0)	8 (10.0)	80 (40.6)	0.273
	Male	99 (84.6)	18 (15.4)	117 (59.4)	
Duration on HD (years)	< 5	95 (82.6)	20 (17.4)	115 (58.4)	0.039
	≥ 5	76 (92.7)	6 (7.3)	82 (41.6)	
Anti-HCV	Positive	11 (100)	0 (0.0)	11 (5.6)	0.183
	Negative	160 (86.0)	26 (14.0)	186 (94.4)	
Diabetes Mellitus	Yes	52 (86.7)	8 (13.3)	60 (30.5)	0.970
	No	119 (86.9)	4 (14.9)	137 (69.5)	
Vitamin D treatments[b]	Yes	91 (88.3)	12 (11.7)	103 (52.3)	0.502
	No	80 (85.1)	4 (14.9)	94 (47.7)	
Erithropoetin treatments	Yes	138 (86.8)	21 (13.2)	159 (30.5)	0.994
	No	33 (86.8)	5 (13.2)	38 (69.5)	
Hemoglobin (g/dL)	< 11	90 (84.1)	17 (15.9)	107 (54.3)	0.224
	≥ 11	81 (90.0)	9 (10.0)	90 (45.7)	
Vasculer Access	AVF	129 (89.0)	16 (11.0)	145 (73.6)	0.299
	CVC (cuffed)	36 (80.0)	9 (20.0)	45 (22.8)	
	Greft	6 (85.7)	1 (14.3)	7 (3.6)	
Total [c]		**171 (86.8)**	**26 (13.2)**	**197 (100.0)**	

URR Urea reduction rate, *HD* Hemodialysis, *AVF* Arteriovenous fistulae, *CVC* Central Venous Catheter
[a]Percent of column, [b]Active Vitamin D or analog or calcimimetic, [c]Percent of line, [d]with Fisher's exact test

there is an interaction between age and the albumin level (Table 4, $p < 0.001$). It was seen that the people who were ≥ 65 had the least vaccine response rate when their albumin cut-off value < 3.5 g/dL was compared to the HBV vaccine response which was 64.5% (Table 5, $p < 0.008$). This finding is matching with the results of logistic regression analysis in the study.In the literature an increase in the incidence of inadequate response has been reported as the age increases from 40 to 60 [13]. In most of the studies, when the age cut-off value was taken 65, the risk of inadequate response increased [14–16]. However, there were studies where no age effect on response to vaccination was determined like the study of Novarro et al. [17].

Aging affects bone marrow, and thymus. Disruption of function of CD4 + cells, decreased CD4 +/ D8+ rate, decreased number of T-cell receptors, having less naive B and T cells by the elderly individuals could lead to failure

Table 2 Binary comparison of HBV vaccine responses with Chi-square test for etiology of end-stage renal disease

Etiology	Dependent variable		Total: *n*(%)	*p*
	Anti-HBs ≥ 10 IU / mL *n* (%)	Anti-HBs < 10 IU / mL *n* (%)		
Hypertension	61/72 (84.7)	11/72 (15.3)	72/197 (36.5)	0.513
Diabetes mellitus	52/60 (86.7)	8/60 (13.3)	60/197 (30.5)	0.970
Polycystic renal disease	10/12 (83.3)	2/12 (16.7)	12/197 (6.1)	0.488
Other*	10/11 (90.9)	1/11 (9.1)	11/197 (5.6)	0.679
Unknown	38/42 (90.5)	4/42 (9.5)	42/197 (21.3)	0.428
Total: n(%)	171 (86.8)	26 (13.2)	197/197 (100.0)	

*Chronic glomerulonephritis (4), Urogenital diseases (2), Alport disease (2), Nephrotic syndrome (1), Familial Mediterranean Fever (1), Systemic Lupus Erythematosus (1)

Table 3 Results of logistic regression analysis which independent variables affecting response to HBV vaccine

Independent variables*		Dependent variable: Response to HBV vaccine					
		B	S.E.	Wald	Odds ratio	% 95 confidence interval (CI)	*p*
Age (years)	≥ 65	1.056	0.512	4.257	2.9	1.1–7.8	**0.039**
	< 65				Reference		
Serum albumin (g/dL)	< 3.5	1.075	0.474	5.131	2.9	1.2–7.4	**0.024**
	≥ 3.5				Reference		
URR (%)	≤ 65	1.292	0.587	4.842	3.6	1.1–11.5	**0.028**
	> 65				Reference		
Kt/V	< 1.4	0.092	0.615	0.022	1.0	0.3–3.6	0.881
	≥ 1.4				Reference		
Duration on HD	≥ 5	-0.769	0.513	2.251	0.4	0.1–1.2	0.134
	< 5				Reference		

URR urea reduction rate, *HD* hemodialysis

*When five variables with p < 0.05 in Table 1 were taken into logistic regression analysis (Backward: LR), we found three independent variables with p < 0.05 in the final step

Table 4 Comparison of the albumin level with the age and URR using Chi-square test

Parameters		URR (%)			p	Serum albümin (g/dL)			p
		≤ 65 n (%)	> 65 n (%)	Total n (%)		< 3.5 n (%)	≥ 3.5 n (%)	Total n (%)	
Age (years)	< 65	7 (7.3)	89 (92.7)	96 (48.7)	0.381	9 (9.4)	87 (90.6)	96 (48.7)	< 0.001
	≥ 65	11 (10.9)	90 (89.1)	101 (51.3)		31 (30.7)	70 (69.3)	101 (51.3)	
Serum albümin (g/dL)	< 3.5	6 (15.0)	34 (85.0)	40 (20.3)	0.214*	–	–	–	–
	≥ 3.5	12 (7.6)	145 (92.4)	157 (79.7)		–-	–	–	–

URR urea reduction rate, *n* number

There is a statistically significant difference between age and the albumin ($p < 0.001$). However, there is not any statistically difference between URR and albumin ($p = 0.214$). *With fisher's exact test.

in response to HBV vaccination as a result of impaired humoral and cellular response, possibly referred to as "immunosenescence" [18, 19]. Therefore, in the light of studies, it seems that HBV vaccination at early ages may be beneficial to obtain adequate immunization in ESRD [14]. Since the albumin level is lower for old people compared to the people who are below 65 in our study, it can also be said that if the patient starts HD treatment at a later age, at least maintaining nutritional status and other factors such as dialysis adequacy may be beneficial for the vaccine response.

Table 5 Comparing HBV vaccine response situations with Chi-square test for people who are ≥65 years old by their albumin levels 3.5 g/dL

Albumin level (g/dL)	Dependent variable		Total: *n* (%)	*p*
	Anti-HBs ≥ 10 IU/mL *n* (%)	Anti-HBs < 10 IU/mL *n* (%)		
< 3.5	20 (64.5)	11 (35.5)	31 (100.0)	**0.008**
≥ 3.5	61 (87.1)	9 (12.9)	70 (100.0)	
Total: *n* (%)	81 (80.2)	20 (19.8)	101 (100.0)	

When the data were compared in our study, it was seen that one of the factors influencing the vaccination response was low albumin level. It is well known that low levels of albumin show poor prognosis whatever the cause of ESRD [10]. Although there is no correlation between albumin levels and HBV vaccine response in some studies, it has been shown that low albumin adversely affects the vaccine response in many studies [13]. In our study, there was a statistically significant relationship between inadequate vaccine response and low albumin level. The incidence of inadequate response was 2.9 times higher when the albumin was < 3.5 g/dL. When albumin levels were stratified every 0.5 g/dL in the study, HBV vaccine response rate was 70% below 3.5 g/dL. When albumin level was between 3.5 and 3.9, vaccine response rate was 89%. When albumin level was between 4.0 and 4.4, vaccine response rate was 92.2% and albumin level ≥ 4.5 g/dL, vaccine response rate was 92.9%. We think that low albumin levels causes mortality, malnutrition and adversely affects immunity [10, 14, 17, 20].

In binary analysis comparison, there was a significant correlation, between the vaccination response and the dialysis efficacy parameters URR ≤ 65 and Kt/V < 1.4. However, in the regression analysis performed, only in patients with URR ≤ 65, a statistically significant difference was found in terms of inadequate response to HBV vaccination. In a small number of studies it was found that the adequacy of dialysis was correlated with these parameters and better HBV vaccine response (anti-HBS ≥ 100) [21]. It was determined that in uremia expression of B7-2 (CD86) monocytes is deteriorated by antigen presentation to T cells and T cell activation is impaired [22]. The improvement of these functions with adequate dialysis probably affects the vaccination response positively. According to NKF-K/DOQI recommendation, the minimum value for the Kt/V is 1.2 and the target value is 1.4 [9]. In our study only four of the patients in the study (4/197) had Kt/V lower than 1.2. Because of this great difference no statistical comparison was made with the 1.2 value in terms of response to vaccination.

Occurrence of the antibody response is associated with induction of B lymphocytes through T cells and MHC class II antigens. The immun reaction caused by MHC I and MHC II mediated T lymphocyte activation in the presence of HCV can lead to liver damage. In the study, the response to HBV vaccination of HCV seropositive patients was sufficient. Liver enzymes were at normal levels and responses were sufficient in all 11 patients confirmed with HCV-RNA. Although in many studies HCV seropositivity did not affect the HBV vaccine response, in some studies it was found that HCV seropositive patients responded adequately to HBV vaccine but titration levels were lower than seronegative patients [13, 17, 23, 24]. There are also studies showing increased risk of inadequate response to HBV vaccination in HCV seropositive patients compared to HCV seronegative ones [16].

It was found that in a multicentre study, HD patients had increased risk of inadequate response to vaccination in > 5 years [16]. This can be interpreted as a sign of insufficiency in the immune response when the HD duration is prolonged [11]. In our study when the duration of dialysis and the vaccination response were compared, the response level was lower in patients with HD duration less than 5 years. However, when the data were taken into the regression analysis, we saw that HD duration did not affect the vaccination response similar to previous studies.

In the study we presented although the response rate for women is higher than for men, there was no statistically significant difference in the response rate between women and men. Similarly, in most studies, there was no significant difference between sex and vaccination response [13, 16, 20, 24, 25].

There was no relationship between the presence of diabetes mellitus and the response to HBV vaccination in the study. In some studies where binary comparisons were made, there was a higher incidence of inadequate response in patients with diabetes [16, 20, 25]. Since there are different conclusions in the literature, further larger studies are needed to clarify the effect of diabetes on vaccination.

In our study, the rate of response to vaccination in those who had and did not have the treatment with erythropoietin was found to be equal similar to previous studies, but when older literature was searched, it was seen that there was a relation between erythropoietin treatment and higher anti-HBs titrations [13, 26].

The generally accepted hemoglobin target value in HD patients is 11–12 g/dL [27]. When the basal value of 11 g/dL was taken as the lower value of this range, inadequate response rate under 11 g/dL was higher, but we found that the presence of anemia in the binary comparison did not affect the HBV vaccination response like a previous prospective study [13]. In our study, there was no statistically significant difference between the vaccine response and treatment of active Vitamin D, analogue or calcimimetic, vascular access route and causes of ESRD.

The strength of our work is being multi-centered. However, our study had a limitation. As analysis of the data were obtained from the research records and residual renal functions, protein catabolism rate (PCR) levels, hormonal parameters like vitamin D levels of patients were not satisfactory.

In conclusion, we found that age 65 and above, low albumin levels of 3.5 g/dL, 65% and lower URR levels were factors that negatively affected the HBV vaccine response in HD patients. These findings must be considered before planning vaccination to achieve a positive response. Future studies should consider other independent parameters that may be associated with these factors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol was approved by the Ethics Committee for Clinical Research, Faculty of Medicine, Kafkas University, Kars, Turkey. Our study was conducted according to the declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

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