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Predictors of immune response to hepatitis B vaccine and clinical outcomes in dialysis patients

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ABSTRACT:

— ***Objective:*** The aim of our study was to examine factors associated with response to the hepatitis B virus (HBV) vaccine in incident dialysis patients and verify whether a lack of HBV immune response is associated with adverse clinical outcomes.

— ***Patients and Methods:*** This was a retrospective cohort study of 133 patients initiated on dialysis at an outpatient dialysis facility who received the HBV vaccine series. Vaccine responsiveness was defined as a hepatitis B surface antibody titer equal to or greater than 10 IU/L.

— ***Results:*** Sixty-nine (52.3%) patients were non-responders to the HBV vaccine. Compared to vaccine responders, vaccine non-responders were significantly older (66.5 ± 14.4 *vs.* 71.3 ± 12.7 years old; $p = 0.04$) and had a lower serum creatinine (7.9 ± 29 *vs.* 6.4 ± 2.3; $p = 0.002$). All-cause and infection-related hospitalization, as well as 1-year mortality rate, was not significantly different between HBV vaccine responders and non-responders.

— ***Conclusions:*** Studies with larger sample sizes are required to address the association between non-response to the HBV vaccine and clinical outcomes in dialysis patients.

— ***Keywords:*** *Hepatitis, Dialysis, Infection, Vaccine.*

— ***Abbreviations:*** *HBV - Hepatitis B Virus, ESKD - End Stage Kidney Disease.*

INTRODUCTION

Hepatitis B virus (HBV) infection is the second leading cause of death in patients with end-stage kidney disease (ESKD)[1]. Since patients on maintenance hemodialysis are at an increased risk for exposure to the HBV, vaccination against HBV is a mandated clinical practice. Unfortunately, approximately 50% of dialysis patients do not mount an immune response to the HBV vaccine compared to only 10% among healthy individuals[1]. In one study[2] of hemodialysis patients, 41% did not mount an immune response to the 4-dose vaccine regimen over one year. Poor immune response to the HBV vaccine in dialysis patients may be due in part to advanced age and the presence of diabetes mellitus, which contribute to immune senescence, as well as uremia-related immune dysregulation and persistent chronic inflammation.

The purpose of this study was to examine factors associated with HBV vaccine responsiveness in incident dialysis patients, and verify whether lack of HBV immune response is associated with adverse clinical outcomes.

PATIENTS AND METHODS

This was a single-center retrospective cohort study of incident adult (age ≥ 18 years old) patients with ESKD initiating dialysis at a hospital-based dialysis facility

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between 2012 and 2018, and who received the HBV vaccine series at the facility. The study was approved by the institutional review board, and the requirement for informed consent was waived (Institutional Review Board IRB# HW194).

Data Source and Study Population

The data sources were the electronic health records of the dialysis facility (Clarity, Visonex®, LLC, Green Bay, WI, USA) and the hospital (MEDITECH®, Inc., Westwood, MA, USA). Incident dialysis patients were included if they had received a full series of an approved HBV vaccine. Patients were excluded if the information on the vaccination series was incomplete or if they had received the HBV vaccine at a different facility.

Data Collection and Definition of Variables

Clinical data of interest included sex, age, body mass index (BMI), and selected comorbidities, including hypertension, diabetes mellitus, coronary artery disease, heart failure, and peripheral vascular disease. Selected laboratory data included creatinine, albumin, and hemoglobin levels. Dialysis-related variables included dialysis modality, duration (in days), and access type. The HBV vaccine series type was recorded, as well as the immune response. An adequate HBV vaccine immune response was defined as a post-vaccination hepatitis B surface antibody titer equal to or greater than 10 IU/L, while vaccine non-response was defined as a titer of less than 10 IU/L.

Patients were followed for up to one year after the administration of the vaccine to ascertain clinical outcomes of interest, including all-cause hospitalizations, infection-related hospitalizations, and mortality. An additional outcome of interest was the composite of all-cause hospitalization or mortality, to account for survival bias in the cohort.

Statistical Analysis

Continuous variables are summarized as mean (standard deviation) or median (25^{th}, 75^{th} percentile), and categorical variables as frequency counts (percentages). We compared continuous variables between HBV vaccine immune responders and non-responders using the independent-sample *t*-test, and χ^2 test for categorical variables. Univariate and multivariable logistic regression analyses were performed to examine factors associated with HBV vaccine immune nonresponse. The results of the logistic regression analyses are displayed as odds ratios (OR) with a 95% confidence interval (CI). All analyses were performed using the SPSS statistical package version 22 (IBM Corp., Armonk, NY, USA). Differences were considered statistically significant at a *p*-value lower than 0.05.

RESULTS

Characteristics of the Study Cohort According to HBV Vaccine Immune Response

A total of 132 incident dialysis patients with a verifiable schedule of HBV vaccination were included in the analysis. 128 patients were initiated on hemodialysis and 4 on peritoneal dialysis. Table 1 displays the characteristics of the cohort according to the HBV vaccine immune response. In brief, the mean age was 69.0 ± 13.7 years old, 58.3% were men, 82.6% had hypertension, 64.4% had diabetes mellitus, 40.9% had coronary artery disease, 37.1% had heart failure, and 40.2% had peripheral vascular disease. The mean BMI was 27.9 ± 8.9 kg/m^2. Mean serum creatinine was 7.1 ± 2.7 mg/dL, serum albumin was 3.5 ± 0.5 g/dL, and hemoglobin was 10.7 ± 1.1 g/dL. For patients on hemodialysis, 105 (79.9%) had an arteriovenous fistula, 2 (1.5%) had an arteriovenous graft, and 21 (15.9%) had a central venous catheter. At the time of vaccine administration, the median duration of dialysis was 37 (19-115) days.

Eighty-seven (48.6%) patients received the Engerix-B® 40-mcg 4-dose (at 0, 1, 2, and 6 months) regimen, and 2 (1.1%) patients received the Recombivax-HB® 40-mcg 3-dose (at 0, 2, and 6 months) regimen. The HBV vaccine type was unspecified in the remaining 43 (24.0%) patients. The median time between the last dose of the HBV vaccine and verification of the immune response was 31 (9-86) days. Sixty-nine (52.3%) patients were deemed non-responders to the HBV vaccine, as defined by a hepatitis B surface antibody titer of less than 10 IU/L. Compared to the HBV vaccine responders, non-responders were significantly older (66.5 ± 14.4 *vs.* 71.3 ± 12.7 years old; p = 0.04) and had a lower serum creatinine (7.9 ± 2.9 *vs.* 6.4 ± 2.3 mg/dL; p = 0.002). The other clinical and laboratory variables were not significantly different between the two groups. However, compared to HBV vaccine responders, there was a nonsignificant trend toward a lower prevalence of coronary artery disease (49.2% *vs.* 33.3%; p = 0.06) and a higher prevalence of central venous catheters (7.9% *vs.* 23.2%; p = 0.09), as well as a lower serum albumin (3.6 ± 0.4 *vs.* 3.4 ± 0.5 gm/dL; p = 0.06) in non-responders.

On univariate analysis, older age (OR 1.027; 95% CI 1.001, 1.054; p = 0.04), as well as lower serum creatinine (OR 0.803; 95% CI 0.696, 0.928; p = 0.003), was significantly associated with HBV vaccine non-responsiveness, and there was a non-significant trend observed with lower serum albumin (OR 0.482; 95% CI 0.225, 1.032; p = 0.06). On multivariable analyses, only serum creatinine remained independently associated with HBV vaccine non-responsiveness (OR 0.841; 95% CI 0.723, 0.978; p = 0.02).

Association between HBV Vaccine Immune Response and Clinical Outcomes

With respect to clinical outcomes, compared to HBV vaccine responders, non-responders did not experience an increase in all-cause hospitalizations (54.0% *vs.* 60.9%; p = 0.42) and infection-related hospitalizations (31.7% *vs.* 30.4%; p = 0.87). The 1-year mortality

Table 1. Characteristics of the dialysis cohort according to hepatitis B virus (HBV) vaccine immune response.

	HBV vaccine responders (n = 63)	HBV vaccine non-responders (n = 69)	*p*-value
Age, years	66.5 (14.4)	71.3 (12.7)	0.04
Men	40 (63.5%)	37 (53.6%)	0.25
Body mass index, kg/m^2	28.4 (7.4)	27.6 (10.1)	0.62
Comorbid conditions			
Diabetes mellitus	43 (68.3%)	42 (60.9%)	0.38
Hypertension	55 (87.3%)	54 (78.3%)	0.17
Coronary artery disease	31 (49.2%)	23 (33.3%)	0.06
Heart failure	23 (36.5%)	26 (37.7%)	0.89
Peripheral vascular disease	28 (44.4%)	25 (36.2%)	0.34
Laboratory data			
Creatinine, mg/dL	7.9 (2.9)	6.4 (2.3)	0.002
Albumin, gm/dL	3.6 (0.4)	3.4 (0.5)	0.06
Hemoglobin, gm/dL	10.7 (1.2)	10.7 (1.1)	0.97
Dialysis access type			0.09
Arteriovenous fistula	54 (85.7%)	51 (73.9%)	
Arteriovenous graft	1 (1.6%)	1 (1.4%)	
Central venous catheter	5 (7.9%)	16 (23.2%)	
Peritoneal dialysis catheter	3 (4.8%)	1 (1.4%)	
Duration of dialysis, days	265 (629)	116 (318)	0.11
HBV vaccine type			0.02
Engerix-B®	35 (55.6%)	52 (75.4%)	
Recombivax®/unspecified	28 (44.4%)	17 (24.6%)	

Continuous variables are displayed as mean (standard deviation) and categorical variables as frequency counts (percentages).

rate was not significantly different between vaccine responders and non-responders (11.1% *vs.* 17.4%; $p = 0.31$). The composite outcome of all-cause hospitalization or mortality was also not significantly different between vaccine responders and non-responders (54.0% *vs.* 66.7%; $p = 0.16$).

DISCUSSION

In this retrospective cohort study, we examined patient-related factors that are associated with HBV vaccine immune response in adults with ESKD initiating dialysis and explored whether HBV vaccine immune non-responders are at an increased risk for adverse clinical outcomes. In brief, 52.3% of our dialysis patients did not respond to the HBV vaccine, which is slightly higher than previously reported in literature for this patient population. This likely reflects the higher burden of comorbidities that was observed in our patients. Older age and lower serum creatinine, likely reflecting age-related immune senescence and poor nutritional status, were associated with non-response to the HBV vaccine. In multivariable analyses, only lower serum creatinine remained independently associated with HBV vaccine immune non-response. A recent meta-analysis[3] observed an association between lack of HBV vaccine response and older age, presence of diabetes mellitus, poor nutritional status, lower hemoglobin, lower parathyroid hormone levels, HLA-DR3 carrier status, and lower dialysis adequacy. In our cohort, we found no association between the HBV vaccine response and the presence of diabetes, and no significant association between the lack of response to the HBV vaccine and all-cause hospitalization, infection-related hospitalization, mortality, as well as the composite of all-cause hospitalization or mortality within one year. This contrasts with previous studies[1,4] demonstrating a lower all-cause and cardiovascular mortality risk among HBV vaccine responders compared to non-responders.

Erythropoietin hypo-responsiveness in dialysis patients, usually reflecting malnutrition and a persistent inflammatory state, has been associated[5] with non-response to HBV vaccination. Adequate sleep has been associated[3] with better response to the HBV vaccine in the general population, but not in dialysis patients. There have been numerous efforts[6-12] to develop adjuvanted HBV vaccines to improve immunogenicity, including use of the calcineurin B subunit to trigger innate immunity[6], interleukin-18 to enhance interferon-gamma production[7], and granulocyte-macrophage colony-stimulating factor[8], recombinant interferon-α2[9], and levamisole[10], to modulate T-lymphocyte and B-lymphocyte function[11]. However, the evidence[12] for these approaches remains experimental and limited.

Further studies with larger sample sizes are required to address the association between non-response to HBV vaccination and clinical outcomes in dialysis patients. In addition, the potential role of the newest commercially available 2-dose CpG-adjuvanted recom-

binant HBV vaccine (Heplisav-B®), which has enhanced immunogenicity in the general population[13], needs to be formally assessed in the dialysis population. In a recent open-label, single-arm small study evaluating the immunogenicity and safety of the Heplisav-B® vaccine in adults receiving hemodialysis, after 4 doses administered at 0, 4, 8, and 16 weeks, there was an impressive seroprotection rate of 89%, and there were no observed safety concerns[14]. This vaccine and other adjuvanted HBV vaccines need formal testing in this vulnerable population.

CONCLUSIONS

Based on our study, the lack of responsiveness to the HBV vaccine in dialysis patients was not correlated with negative outcomes, specifically infection-related hospitalizations, all-cause hospitalizations and 1-year mortality. Larger studies with increased power must be conducted to assess the possibility of an association between responsiveness to the hepatitis B vaccine and improved clinical outcomes.

Conflict of Interest:
The authors declare that they have no relevant financial interests pertaining to this study.

Ethics Approval:
The study was approved by the Institutional Review Board (IRB# HW194).

Informed Consent:
The requirement for informed consent was waived due to the retrospective nature of the study.

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Authors' Contributions:
Research project idea and study design: VSB; data acquisition JC, NI. KD, AD; data analysis/interpretation JC, NI, BLJ, VSB; statistical analysis: BLJ; drafting the manuscript: JC, NI, BLJ, VSB; supervision and mentorship: BLJ, VSB. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. VSB takes full responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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