RESEARCH ARTICLE

REVISED Vaccination against hepatitis B virus in hemodialysis patients: trends in dialysis centers of Northern Pakistan

[version 2; peer review: 1 approved, 1 not approved]

Muhammad Nadeem ¹, Syed Asim Ali Shah ², Naveed Arshad³, Faiza Riaz², Rizwan Saeed Kiani⁴, Muhammad Abdul Quddus⁴

¹Department of Medicine, Poonch Medical College, Rawalakot, Azad Kashmir, Pakistan

²Department of Medicine, Wah Medical College, Wah Cantt, Punjab, Pakistan

³Department of Rehabilitation Medicine, Islamabad Medical and Dental College, Islamabad, Pakistan

⁴Department of Gastroenterology, Poonch Medical College, Rawalakot, Azad Kashmir, Pakistan

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Abstract

Background: Chronic kidney disease (CKD) patients, especially those on hemodialysis, are at increased risk of developing hepatitis B virus (HBV) infection. Guidelines suggest that all patients with CKD should be vaccinated against HBV, but these guidelines are usually not followed. We conducted this study to know the status of vaccination against HBV in CKD patients on regular hemodialysis.

Methods: This observational descriptive study was conducted at the Department of Medicine, Sheikh Khalifa Bin Zayed Teaching Hospital, Poonch Medical College Rawalakot, and POF Teaching Hospital, Wah Medical College Wah Cantt, from March to July 2019. Patients reporting to the dialysis center of both hospitals on regular dialysis were included in the study. Patient information (HBV vaccination status, age, gender, education, socioeconomic status, duration of CKD and duration of dialysis) were collected on a specially designed questionnaire. The statistical analysis of data was done in SPSS for Windows, version 20.

Results: A total 149 patients were included in the study, 63.1% were male and 36.9% were female. Out of these 24.2% were uneducated, 33.6% had 1-10 years school education, 38.2% had 10-14 years education, and 4% had more than 14 years education. About 35% patients were from low socioeconomic class, 54% from middle and 11% from higher class. Only 45.6% (n=68) of patients were vaccinated and 54.4% (n=81) were not vaccinated against HBV. Vaccination status was significantly associated with education (p=0.004) and socioeconomic status (p=0.008).

Conclusion: The HBV status of patients on regular hemodialysis is not satisfactory at the two centers observed. It is associated with education and socioeconomic status of the patient.

Open Peer Review

Approval Status

	1	2
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29 Apr 2021	view	view
version 1		
29 Jan 2021	view	

1. **Chenhua Liu** , National Taiwan University Hospital, Taipei, Taiwan
2. **Lionel Rostaing**, Université Grenoble Alpes, Grenoble, France

Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Dialysis, Education, Hepatitis B, Socioeconomic class, Vaccination

Corresponding author: Muhammad Nadeem (docnadeem78@gmail.com)

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Competing interests: No competing interests were disclosed.

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REVISED Amendments from Version 1

After the comments from reviewer we have made few changes in the methodology section. After interviewing the patients regarding vaccination status it was counter checked from dialysis center record as no formal certificates are issued after hepatitis B vaccination in our setup, this was not mentioned in data collection procedure in version 1 which raised the concern of memory bias in data collection. Details regarding sample size calculation are also omitted on suggestion of reviewer.

Any further responses from the reviewers can be found at the end of the article

Introduction

Chronic kidney disease (CKD) is a global health problem; estimated global prevalence is 11–13% with majority of the patients having stage 3 disease¹. It is an immunosuppressive state, so CKD patients are at increased risk of developing many infections; some of these infections are vaccine preventable². Hepatitis B virus (HBV) infection is among one of those infections. Like other high risk groups including IV drug abusers, homosexual men, having history of piercing and blood transfusions, it is more prevalent in CKD patients as compared to the general population^{3–5}. High risk of HBV among hemodialysis patients is due to increased exposure to blood products, frequent cannulation and shared hemodialysis equipment⁶.

HBV infection in CKD patients varies globally and correlates with the prevalence in the general population. Decreasing trends have been seen in developed countries; in the US it decreased from 7.8% in 1976 to 1% in 2002³. The exact prevalence among CKD and dialysis patients in the developing world, including Pakistan, is not well known. There are scattered reports, mostly single-centre surveys; according to these surveys hepatitis B surface antigen (HBsAg) carrier rate ranges between 2% to 20%⁶. In Pakistan, the prevalence rate is about 4% in the general population⁷, indicating that it will be more than 4% in CKD patients.

Prevention is the best option in the general population, as well as in high risk groups to reduce the prevalence of hepatitis B infection because treatment is lengthy, costly and not 100% effective. As HBV can be transmitted easily from the medical equipment used during dialysis, as it remains viable and stable in the environment for weeks at room temperature⁸, vaccination against HBV is most effective way to prevent it in CKD patients on hemodialysis. Complete vaccination was found to be protective in ≥90% in the general population, even 30 years after vaccination⁹. Although response is not good in chronic renal failure patients, up to 40% were found to be non-responders in some studies^{3,10}. Still routine vaccinations of patients and healthcare workers has dramatically reduced the prevalence of HBV infection in hemodialysis patients¹¹. It was found 70% lower among vaccinated patients as compared to non-vaccinated hemodialysis patients¹².

Guidelines from nephrology societies and Centers for Disease Control and Prevention suggest that all patients with CKD should be vaccinated against HBV². Special formulation of

recombinant vaccine is advised, either higher dosage or increased number of doses (4 doses) should be administered for good results². Although guidelines strongly recommend vaccination of CKD patients against vaccine preventable diseases, it has been shown that they are not in fact routinely vaccinated against HBV. A study published in the UK showed that only 46% dialysis units were routinely immunizing patients according to the Renal Association's recommendations¹³, while only 20% of patients were found to be vaccinated in a study conducted in Pakistan¹⁴.

Vaccination against HBV decreases the overall mortality in CKD patients, but, to the best of our knowledge, no recent data is available regarding the status of vaccination against HBV in CKD patients internationally. In developing countries, including Pakistan where hepatitis B is still a common problem, there is limited data available on this topic. The aim of this study was to observe the immunization status of CKD patients on regular hemodialysis against hepatitis B in Pakistan. The data can help in future for necessary measures to improve the vaccination against hepatitis B in CKD patients.

Methods

Study design and sampling

This was an observational descriptive study conducted at the Department of Medicine, Sheikh Khalifa Bin Zayed Hospital, Rawalakot and POF Hospital, Wah Cantt, from March 2019 to July 2019. Calculated sample size was 139 by using the formula for cross sectional studies¹⁵. Patients reporting to the dialysis centre of both hospitals with a diagnosis of CKD on regular dialysis of any age were included in the study by consecutive sampling. CKD was defined as individuals with markers of kidney damage or those with eGFR<60 mL/min per 1.73 m² regardless of the cause¹⁶. Hepatitis B surface antigen positive, newly diagnosed CKD patients not on dialysis and patients not sure about their vaccination status were excluded from the study.

Data collection

Data was collected using a structured questionnaire (*Extended data*¹⁷). The questionnaire included items intended to assess socio-demographic variables and hepatitis B vaccination status of the patients. The questionnaire was filled by the authors of the study after interviewing the participants. Every participant was interviewed before their dialysis session when they reported to the dialysis center for the scheduled dialysis. Record of dialysis centers was checked regarding vaccination status of patients to validate the patients statement, if any contradiction was found, such patient was excluded from the study.

Socio-demographic factors

Age was entered in years, gender was entered as male or female, education level was considered as uneducated (those not able to read and write), up to secondary level education (1 to 10 years education), secondary level to graduation (10–14 years education) and post-graduation (more than 14 years education). Socioeconomic status was defined as lower class (monthly income ≤ 20000 Pakistani Rupees), middle class (monthly income 21000 to 99000 Pakistani Rupees) and upper class (monthly

income $\geq$ 100000 Pakistani Rupees) based on gross monthly income and access to educational and healthcare facilities. Duration of CKD was considered in months.

Vaccination status

Patients were interviewed in detail about their vaccination status against hepatitis B. Only those were considered as vaccinated who completed the course of vaccination of 4 doses or 3 doses at an interval specified for hepatitis B vaccination. Those who did not receive vaccine at all and those who had an incomplete course were considered as unvaccinated.

Statistical analysis

The statistical analysis of data was done in SPSS for Windows, version 20. Means and standard deviations were calculated for quantitative variables like age and duration of CKD. Frequencies were calculated for gender, education, socioeconomic status and vaccination status of hepatitis B. Chi square test was applied to see the relation between different factors and status of vaccination. $P \leq 0.05$ was considered as significant.

Ethics statement

Ethical approval was obtained from Hospital Research Ethics Committee of POF Teaching Hospital, Wah Cantt (letter no. POFH/ERC/99053/05) and Hospital Research Ethics Committee of Sheikh Khalifa Bin Zayed Teaching Hospital (letter no. SKBZ/REC/019/08). Informed verbal consent to participate was obtained from the patients or their close relatives (when patients were unable to comprehend the researchers due to old age or uremic encephalopathy) where relevant. Verbal consent over written consent was taken because many patients were uneducated and unable to read a consent forms or were reluctant to sign a document. The ethics committee gave permission for this route of consent to be obtained. Consent for minors was taken from one of their parents.

Results

A total of 200 patients were asked to take part in the study, but only 149 responded. A total of 63.1% ($n=94$) were male and 36.9% ($n=55$) were female. Mean age was 50.5 ± 16.7 years, with minimum age of 7 years and maximum 83 years. Mean duration of CKD was 38.9 ± 47.2 months. Out of these 149 patients, 24.2% ($n=36$) were uneducated, 33.6% ($n=50$) had 1–10 years school education (up to secondary level), whereas 38.2% ($n=57$) had 10–14 years education (secondary level to graduation) and 4% ($n=6$) had more than 14 years education (post-graduation). About 35.6% ($n=53$) patients were from low socioeconomic class, 53.6% ($n=80$) from middle, and 10.8% ($n=16$) from higher class. Only 45.6% ($n=68$) patients were vaccinated and 54.4% ($n=81$) were not vaccinated against HBV (Table 1).

A significant association was found between vaccination status and education of the patient; better educated patients were more likely to be vaccinated (Table 2). A significant association was also found between vaccination and socioeconomic status of the patients; patients from middle and upper classes were more likely to be vaccinated as compared to lower class. (Table 3). Vaccination status of the patients was not significantly associated

Table 1. Descriptive statistics of vaccination status in patients (n=149).

		N	%
Vaccination status	Yes	68	45.6
	No	81	54.4
	Total	149	100.0

Table 2. Association between education of patients and vaccination status.

	Hepatitis B vaccination status, n (%)		Total (n= 149)	p-value
	Yes (n = 68)	No n = 81		
Uneducated	14 (39)	22 (61)	36	0.004
Up to secondary level	20 (40)	30 (60)	50	
Secondary level to graduation	34 (59.6)	23 (40.4)	57	
Post-graduation	5 (83.3)	1 (16.7)	6	

Table 3. Association between socioeconomic class of patients and vaccination status.

	Hepatitis B vaccination status, n (%)		Total (n= 149)	p-value
	Yes (n = 68)	No (n = 81)		
Lower	15 (30)	37 (70)	53	0.008
Middle	42 (52.5)	38 (47.5)	80	
Upper	11 (68.7)	5 (31.3)	16	

with age ($p= 0.540$), gender ($p= 0.517$), and duration of CKD ($p= 0.719$).

Discussion

In our study, we found that 45.6% patients of CKD on regular dialysis were found to be vaccinated against HBV. We concluded that education and socioeconomic status are two important factors associated with status of vaccination, and was not associated with age, gender, and duration of CKD.

Results showed that 63% patients were male, and the mean age of patients was 50 years. This suggests that more male patients are on hemodialysis and CKD is also more common

in the older age group. This is the same as the United States Renal Data System 2011 Annual Data Report that showed that the initiation of dialysis was much higher in males as compared to females¹⁸. However, a meta-analysis reported that in some studies CKD was more common in females, while in other studies it was more common in males¹. Many studies showed that CKD is more common in an older age group¹, comparable with our findings. For example, in a study conducted in India¹⁹, the mean age was 51 years in CKD patients, while in a Chinese study it was found to 63.6 years²⁰, almost the same as in our study. We did not find any association between status of vaccination and age or gender; this was also concluded by Amjad *et al.* in a study conducted in Pakistan¹⁴.

Nephrology societies and Centre for Disease Control and Prevention recommends that all CKD patients should be vaccinated against HBV². These guidelines are not followed even in the developed world; 73.1% patients of CKD were found vaccinated in US²¹, and only 31% patients were vaccinated in a study conducted in Belgium²². Our results are also not encouraging, only 45.6% were found vaccinated, while in another study from Pakistan only 20% patients were vaccinated, consistent with our results¹⁴. A study conducted in Brazil showed better vaccination rates compared to our results, almost 60% patients were completely vaccinated, and another 15% were partially vaccinated²². The low vaccination rate in Pakistan indicates that dialysis centers and nephrologists are not following the guidelines of nephrology societies regarding vaccination against hepatitis B.

Our study reported that vaccination status in dialysis patients was significantly associated with socioeconomic class and education of the patients. A vaccinated status was found to be higher in CKD patients with better socioeconomic status in another study conducted in Pakistan¹⁴. Another study conducted by Ertekin *et al.* showed that better socioeconomic status was associated with higher rates of vaccination in the general population²³. These results are same as we found in our study. Low vaccination rates among lower socioeconomic groups may be due to non-affordability. As far as education is concerned, no association was found between vaccination against HBV of

CKD patients and education in a study conducted by Amjad *et al.*¹⁴, which differs from our results. Studies from the general population and healthcare workers showed that education was significantly associated with vaccination status against HBV, comparable to our results^{24–26}. Individuals who have more education may be better aware of the preventive role of vaccination, which may be the cause of better vaccination status in higher educated people.

Our study is subject to some limitations. First, we only included those patients who were on regular dialysis. Second, only two dialysis centers were included in the study and few factors were studied related to vaccination status. We recommend future studies to include all patients of CKD from many centers.

Conclusion

Currently dialysis centers are not following guidelines regarding vaccination against HBV in hemodialysis patients. Vaccination status of patients on hemodialysis is not satisfactory in dialysis centers we sampled in Northern Pakistan. We found that vaccination status is significantly associated with education and socioeconomic status of the patients.

Data availability

Underlying data

Figshare: Vaccination against hepatitis B virus in hemodialysis patients: trends in dialysis centers of Northern Pakistan, <https://doi.org/10.6084/m9.figshare.13359713.v1>¹⁷.

Extended data

Figshare: Vaccination against hepatitis B virus in hemodialysis patients: trends in dialysis centers of Northern Pakistan, <https://doi.org/10.6084/m9.figshare.13359713.v1>¹⁷.

This project contains the following extended data:

- Copy of the questionnaire used in the study.

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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Open Peer Review

Current Peer Review Status:

Version 2

Reviewer Report 08 November 2022

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Lionel Rostaing

Service de Néphrologie, Hémodialyse, Aphérèses et Transplantation Rénale, Centre Hospitalier Universitaire Grenoble Alpes (CHU), Université Grenoble Alpes, Grenoble, France

This is an observational descriptive study that was conducted in 2 departments of hemodialysis in Azad-Kashmir (Pakistan). The study took place between March and July 2019. HBV infection still remains a public health problem in many Asian countries. In addition, its prevalence amongst hemodialysis patients is increased (i.e., because of nosocomial transmission). It is therefore of utmost importance to limit the spread of HBV infection in hemodialysis patients: this can only be achieved with universal HBV vaccination. However, many people are reluctant to HBV vaccination.

In this original work, Nadeem M. *et al.* looked at the factors associated with HBV vaccination in a cohort of 149 hemodialysis patients; of these 63.1% were male. Overall, 24.2% were uneducated, 33.6% had 1-10 years school education, 38.2% had 10-14 years education, and 4% had more than 14 years education. In addition, about 35% patients were from low socioeconomic class, 54% from middle and 11% from higher class. At the end of the day, only 45.6% (n=68) of patients were vaccinated. In addition, vaccination status was significantly associated with education (p=0.004) and socioeconomic status (p=0.008).

In the discussion's section the authors should emphasize the fact that educational programs should be implemented in chronic kidney disease patients as well as in hemodialysis ones in order that they are aware of the importance of « fighting » HBV infection. Indeed, HBV vaccination should be done for free as well as the boosters (is it the case in Pakistan?).

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Nephrology, Dialysis, Kidney transplantation, Transplant Immunology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 10 Nov 2022

Muhammad Nadeem, Poonch Medical College, Rawalakot, Pakistan

We would like to thank the reviewer for his valuable time and comments on our article; this will be very helpful for us in future research as well.

Competing Interests: No competing interests were disclosed.

Reviewer Report 29 April 2021

<https://doi.org/10.5256/f1000research.56293.r84207>

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Chenhua Liu

Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

1. The authors claimed that all CKD patients should be vaccinated for HBV by guidelines. However, the authors should be more cautious about the claims, all the guidelines did not recommend vaccination for all CKD patients for HBV. eg. the MMWR report (cited by the author in the revision) clearly indicated that "Vaccination of individuals who possess antibodies against HBV from a previous infection is not necessary" and "Pre-vaccination serologic screening for susceptibility". Furthermore, the CDC guideline did not mention universal HBV vaccination.

2. The author focused on hemodialysis patients. Although eGFR < 60 was defined as CKD, I wondered if patients with eGFR ranging from 15-60 need hemodialysis. The illustration of CKD as a cutoff value of 60 is meaningless.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Hepatitis B, hepatitis C, chronic kidney disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 06 Jun 2021

Muhammad Nadeem, Poonch Medical College, Rawalakot, Pakistan

1. The authors claimed that all CKD patients should be vaccinated for HBV by guidelines. However, the authors should be more cautious about the claims, all the guidelines did not recommend vaccination for all CKD patients for HBV. eg. the MMWR report (cited by the author in the revision) clearly indicated that "Vaccination of individuals who possess antibodies against HBV from a previous infection is not necessary" and "Pre-vaccination serologic screening for susceptibility". Furthermore, the CDC guideline did not mention universal HBV vaccination.

Response: Reviewer pointed out that "Vaccination of individuals who possess antibodies against HBV from a previous infection is not necessary" and rejected the article on the basis of this statement. No doubt that these individuals do not need the vaccination but routine pre vaccine serology to rule out immune individual is not recommended in any guideline. MMWR report which summarizes recommendations from the Advisory Committee on

Immunization Practices (ACIP) and CDC clearly mentions "ACIP recommends vaccination of adults at risk for HBV infection, including universal vaccination of adults in settings in which a high proportion have risk factors for HBV infection"¹ supporting our claims of vaccination of all individuals on hemodialysis. ACIP also mentions "Serologic testing should not be a barrier to vaccination of susceptible persons"¹ and "Vaccination of persons immune to HBV because of current or previous infection or HepB vaccination does not increase the risk for adverse events"¹. It clearly indicates that pre vaccination serology is not necessary. CDC also adopted these guidelines. (<https://www.cdc.gov/hepatitis/hbv/vaccadults.htm>) Further reviewer stated "Pre-vaccination serologic screening for susceptibility" but the Advisory Committee on Immunization Practices states "Testing is not a requirement for vaccination, and in settings where testing is not feasible, vaccination of recommended persons should continue"¹. Routine pre vaccination serology is also not recommended by WHO especially when it is not cost effective². As routine pre vaccination serology except HBsAg is not done in our setup, so we included all patients except HBsAg positive patient. This is in accordance with Advisory Committee on Immunization Practices, CDC and WHO guidelines in view of above mentioned statements contrary to the perception of reviewer.

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2. World Health Organization. (Hepatitis B vaccines: WHO position paper, July 2017 – Recommendations [published online July 22, 2017]. Vaccine. doi: 10.1016/j.vaccine.2017.07.

2. The author focused on hemodialysis patients. Although eGFR < 60 was defined as CKD, I wondered if patients with eGFR ranging from 15-60 need hemodialysis. The illustration of CKD as a cutoff value of 60 is meaningless.

Response: Reviewer either did not read the methodology section in detail or he was unable to comprehend the need of this definition. We want to explain this; usually there are two types of patient on hemodialysis. 1. Patients of CKD 2. Patients with AKI, as our study was limited to CKD patients there was need to define CKD. We included the internationally accepted definition of CKD with reference, we also requested the reviewer in our previous response to provide any alternate definition of CKD with reference, if this definition is not appropriate for this article.

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 15 April 2021

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Chenhua Liu

Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

Nadeem *et al.* conducted an observational study about the vaccination status in Pakistan and to correlated the socioeconomic status with HBV vaccination.

Major concerns:

1. The authors interviewed the vaccination status in all patients. However, the patients had prone to have a high probability of recall bias, making sampling interviewing not reliable. Furthermore, patients who had HBsAg (-)/anti-HBs (+)/anti-HBc (-) or HBsAg (-)/anti-HBs (+)/anti-HBc (+) did not need vaccination. Furthermore, patients with isolated anti-HBc (+) may not need vaccination. The lack of HBV status in all patients is not scientific and should be comprehensively assessed.
2. Why did the author define CKD as eGFR < 60 on dialysis? Lots of patients with eGFR > 30 need not receive hemodialysis. The authors poorly defined the patient in this study.
3. Since this was an observational study without any pre-specified hypothesis, a sample size calculation was not needed. The author erroneously cited and used the sample size calculation in the study.

Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

No source data required

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Hepatitis B, hepatitis C, chronic kidney disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 18 Apr 2021

Muhammad Nadeem, Poonch Medical College, Rawalakot, Pakistan

I would like to thank the reviewer for reviewing the article and giving his precious time and valuable comments. Reviewer had few concerns regarding the study, as a corresponding author I want to respond on this report.

1. Main concern of the reviewer was about data collection. According to reviewer interviewing the patient regarding vaccination is not a reliable method, it is a genuine concern but due to unavailability of formal certification of hepatitis B vaccination in our setup we were left only with this method. Although we counter checked the information provided by the patient from record of dialysis centers which we did not mention in methodology. I would like to add this in data collection procedure.
2. According to reviewer "patients who had HBsAg (-)/anti-HBs (+)/anti-HBc (-) or HBsAg (-)/anti-HBs (+)/anti-HBc (+) did not need vaccination. Furthermore, patients with isolated anti-HBc (+) may not need vaccination." This statement does not match the recommendations of CDC, WHO and Nephrology societies, as they recommend the vaccination of all CKD patients [1,2,3,4]. Routine pre vaccination serology is also not recommended by WHO especially when it is not cost effective [5]. The only logical cost effective serological test is HBsAg as there is no benefit of vaccination in HBsAg positive patients not the HBsAg negative as mentioned by reviewer, we did this and excluded the HBsAg positive patients mentioned in data collection procedure. If reviewer can provide the reference regarding the recommendation of all these serological tests before vaccination in CKD and exclusion of patients with serological results mentioned in his statement it will help us and other researchers in future.
3. Another observation was regarding definition of CKD. Definition provided is internationally accepted definition established by The Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) and Kidney Disease Improving Global Outcomes (KDIGO) [4]. This definition cannot be changed; if reviewer can provide some other definition with reference we can include that definition. As for as selection of patients for this study is concerned it is clearly mentioned that only those patients of CKD were included who were on regular hemodialysis, so the observation of reviewer "Lots of patients with eGFR > 30 need not receive hemodialysis. The authors poorly defined the patient in this study" is not justified.
4. As for as details of sample size calculation are concerned, these were not included in initial manuscript. These details were provided on the demand of journal.

References:

1. Recommendation of the Immunization Practices Advisory Committee (ACIP). Inactivated

hepatitis B virus vaccine. *MMWR Morb Mortal Wkly Rep.* 1982;31(24):317–22. , 27-8.

2. Recommendations of the Advisory Committee on Immunization Practices (ACIP): Use of vaccines and immune globulins for persons with altered immunocompetence. *MMWR Recomm Rep.* 1993;42:1–18.

3. Guidelines for vaccination in patients with chronic kidney disease. *Indian J Nephrol.* 2016; 26(Suppl 1): S15–S18.

4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013; 3: 1-150; <http://dx.doi.org/10.1038/kisup.2012.73>

5. World Health Organization. Hepatitis B vaccines: WHO position paper, July 2017 – Recommendations [published online July 22, 2017]. Vaccine. doi: 10.1016/j.vaccine.2017.07.046)

Competing Interests: I am corresponding author for this article

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