Original Article

COVID-19 vaccine in hemodialysis patients

Time for a boost

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ABSTRACT

الأهداف: لتقييم مستويات الأجسام المضادة للجلوبيولين المناعي IgG المضاد للارتفاع لمرضى غسيل الكلى وربطها بالبيانات الديموغرافية للمرضى وتقييم حاجة هؤلاء المرضى إلى لقاح معزز لمرض فيروس كورونا (COVID-19).

المنهجية: أجريت دراسة مقطعية متعددة المراكز في مركز الملك عبد العزيز للكلى، ومركز حسن طاهر للغسيل الكلوي، ووقف جمعية حياة لغسيل الكلى في المدينة المنورة، المملكة العربية السعودية. اشتملت على المرضى (العدد=167) الذين تلقوا جرعة واحدة كحد أدنى من لقاح COVID-19، وأُجري جمع العينات خلال الفترة مارس 2022م ويناير 2023م. أجرينا كذلك قياس لمستويات الأجسام المضادة IgG المضادة للارتفاع باستخدام مقايسات الممتز المناعي المرتبط بالإنزيم.

النتائج: نسبة أعلى بكثير من المرضى الذين تلقوا 3 جرعات من لقاح COVID-19 كانت لديهم المصل إيجابي مقارنة بالمرضى الذين تلقوا جرعة واحدة أو جرعتين (3 جرعات: 87.2%، جرعة واحدة: 0.0%، جرعتان: 77.3%؛ p=0.000). مقارنة بالمرضى الذين تلقوا جرعة واحدة، اكتشفنا مستويات أعلى بشكل ملحوظ من الأجسام المضادة IgG في المرضى الذين تلقوا جرعتين (p=0.013) و3 جرعات (n=35; p=0.025). في المقابل، لم يكن هناك فرق كبير في مستويات الأجسام المضادة IgG بين المرضى الذين تلقوا جرعتين أو 3 جرعات (p=0.45). تم الكشف عن مستويات كبيرة من الأجسام المضادة IgG في المرضى الذين تلقوا جرعتين و 3 جرعات (p=0.0125) مقارنة مع أولئك الذين تلقوا جرعة لقاح واحدة (p=0.0004). علاوة على ذلك، كان لدى المرضى الذين تلقوا 3 جرعات مستويات أعلى بشكل ملحوظ من الأجسام المضادة IgG من المرضى الذين تلقوا جرعتين (p=0.000).

الخلاصة: تظهر النتائج ارتباطًا يعتمد على الجرعة بين مستويات الأجسام المضادة IgG وعدد لقاحات COVID-19 التي تم تلقيها. تسلط الدراسة الضوء على الحاجة إلى التطعيم المعزز لـCOVID-19 للمرضى الذين يخضعون لغسيل الكلى.

Objectives: To evaluate anti-spike immunoglobulin G (IgG) antibody levels of hemodialysis patients and correlate them with the patients' demographic data and to evaluate these patients' need for a coronavirus disease-19 (COVID-19) vaccine booster.

Methods: A cross-sectional multi-center study carried out at King Abdulaziz Kidney Center, Hasan Tahir Hemodialysis Center, and Hayat Organization Hemodialysis Center in Al-Madinah Al-Munawarah, Saudi Arabia. Patients (n=167) who received a minimum single dose of COVID-19 vaccine were recruited. The samples were collected between March 2022 and January 2023. Anti-spike IgG antibody levels were measured using enzyme-linked immunosorbent assays.

Results: A significantly higher proportion of patients who received 3 doses of COVID-19 vaccine had positive serostatus compared with patients who received one or 2 doses (3 doses: 87.2%, one dose: 0.0%, 2 doses: 77.3%; p=0.000). Compared with patients who received one dose, significantly higher IgG antibody levels were detected in patients who received 2 (p=0.013) and 3 doses (p=0.025; n=35). In contrast, there was no significant difference in IgG antibody levels between patients who received 2 or 3 doses (p=0.45). Significant IgG antibody levels were detected in patients who received 2 and 3 doses (p=0.0125) compared with those received one vaccine dose (p=0.0004). Furthermore, patients who received 3 doses had significantly higher IgG antibody levels than patients who received 2 doses (p=0.000).

Conclusion: The results show a dose-dependent association between IgG antibody levels and the number COVID-19 vaccines received. The study highlights the need for booster COVID-19 vaccination for patients on hemodialysis.

Keywords: hemodialysis patient, COVID-19 vaccine, anti-spike IgG antibody, booster

Saudi Med J 2023; Vol. 44 (9): 882-888
doi: 10.15537/smj.2023.44.9.20230285

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Received 17th April 2023. Accepted 1st August 2023.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the leading cause of coronavirus disease-19 (COVID-19), is connected with enlarged morbidity and mortality in hemodialysis (HM) patients.[1,2] Patients with chronic kidney disease (CKD) signify a concern for international health experts. Saudi Arabia reported nearly 20,000 patients on hemodialysis.[3] Data on patients on maintenance HM shown that they have declined concentrations of antibodies than healthy people.[4,5]

Patients with CKD are at magnified threat of serious disease and mortality because of COVID-19.[6-8] Hence, vaccination against SARS-CoV-2 is considered vital to minimize the severe disease complications.[9]

Data demonstrate that antibody concentrations are lower in HM patients following COVID-19 vaccination in comparison with healthy subjects.[10,11] In addition, a study confirmed fast declining of antibody quantities resulted from COVID-19 vaccination in those patients.[12] Impaired immunity in CKD patient's consequences in reduced antibody production induced by COVID-19 vaccines. Therefore, COVID-19 vaccine booster doses are vital for this group of patients to guarantee the durability of the immune responses that offer them protection from infection.[13]

The current study predominantly aims to inspect the efficacy as well as differences in COVID-19-vaccine derived immunoglobulin G (IgG) antibody levels in HM patients and the necessity for booster dose.

Methods. A cross-sectional data from renal failure patients on HM was carried out. Multiple hemodialysis centers (King Abdulaziz Kidney Center, Hasan Tahir Hemodialysis Center, and Hayat Organization Hemodialysis Center) in Al-Madinah Al-Munawarah, Saudi Arabia, were recruited. Patients were invited to take part in the study via posts that were distributed throughout the centers. After explaining the study aims and data required from each patient, data were collected from patients who signed the consent form and approved to participate in the study. The study has been carried out according to principles of Helsinki Declaration.

All the participants were provided with information regarding the study before obtaining their informed consent to participate in this study. The samples were collected between March 2022 and January 2023. Review Board at King Salman Medical City Institutional, Al-Madinah Al-Munawarah, Saudi Arabia, has reviewed and approved this study (H-03-M-11).

Patients on maintenance HM who had only received one dose of COVID-19 vaccine were involved in the study. Patients who had not received COVID-19 vaccine and those who had undergone kidney transplantation were excluded.

Enzyme-linked immunosorbent assays (ELISA) was used to measure anti-SARS-CoV-2 antibody in patients' sera using IgG kits (BGI, Shenzhen, China) according to the manufacturer's instructions. Briefly, serum samples were diluted and 100 µl were added to plates and kept for 30 minutes. The plates were then washed 5 times. Following adding of anti-human IgG conjugate, the plates were incubated for 20 minutes and then followed by washing and then addition of substrates was carried out. The plates were kept in the dark for 10 minutes, and a stop solution was added. Optical densities (ODs) were measured at 450 nm. Finally, the antibody levels were measured using the assay formula.

Statistical analysis. Data presented in this study were analyzed using the the Statistical Package for the Social Sciences, version 25.0 (IBM Corp., Armonk, NY, USA). Data of continues variables are presented as mean ± standard deviation (SD) and median and interquartile range (IQR), whereas data of categorical variables are presented as frequencies (n) and percentages (%). Fisher's exact test was carried out to assess the association between categorical variables, while Mann-Whitney and Kruskal-Wallis tests were used to compare the median across the different groups. Simple linear regression analysis was carried out to explore predictors of antibody levels in units of ODs among patients on maintenance HM. All tests carried out were 2-tailed and the significant levels was at p=0.05.

Results. A total of 167 renal failure patients on HM were included in this study. Approximately 71% (n=118) of patients were females. Three-quarters of the study sample were >40 years of age (66.4%, n=111), and the mean age of the patients was 50.0±17.7 years. Mean duration since initial diagnosis with renal failure was 5.15±5.03 years, whereas 68.9% (n=115) of patients were diagnosed with renal failure before receiving their first COVID-19 vaccine. Diabetes was the cause of renal failure in 37.1% (n=62) of patients, and 21.0% (n= 35) of patients had previously been diagnosed with COVID-19. One-third (33.5%, n=56) of patients received heterogeneous vaccines, whereas 56.3% (n=94) of patients received 3 doses of the COVID-19 vaccine. Mean duration since last dose was 10.9±1.00 weeks.

Disclosure. Author has no conflict of interests, and the work was not supported or funded by any drug company.

Mean antibody levels were 2.13±1.17, and 79.6% (n=133) of patients were positive for IgG antibodies. Detailed data concerning the characteristics of the HM patients with renal failure included in this study are presented in Table 1.

Data regarding the association between characteristics of renal failure patients on HM and serostatus are presented in Table 2. A significantly higher proportion of patients who received 3 doses of COVID-19 vaccine had positive serostatus compared with patients who received one or 2 doses (3 doses: 87.2%, one dose: 0.0%, and 2 doses: 77.3%; p=0.000). All other characteristics were similar across the different groups; no significant differences were found between groups regarding gender, age group, or cause of renal failure.

Similarly, median antibody levels were significantly higher among patients who received 3 doses compared with patients who received 2 doses or one dose (3 doses: 3.00 [2.37-3.00], 2 doses: 0.03 [0.03-0.03], and one dose: 2.21 [1.20-3.00]; p=0.000; Figure 1). Median antibody levels were similar across the other different groups (Table 3).

To assess the effect of the number of COVID-19 vaccines on antibody levels, the patients were divided into 2 groups: those with history of previous COVID-19 infection and those without previous COVID-19 infection. Compared with patients who received one vaccine dose, significantly higher levels of IgG antibodies were detected in patients who received 2 (p=0.013) or 3 doses (p=0.025, n=35). There were no significant differences in IgG antibody levels between patients who received 2 and 3 doses (p=0.45; Figure 1). Patients with no history of infection were also investigated. Compared with patients who received one vaccine dose, significantly higher IgG antibody levels were detected in patients who received 2 (p=0.0125)

Table 1 - Sample characteristics (N=167).

Variables	n (%)
Gender	
Male	49 (29.3)
Female	118 (70.7)
Age group (years)	
<19	5 (3.0)
20-40	51 (30.5)
41-60	60 (35.9)
>60	51 (30.5)
Time of diagnosis with renal failure	
Before vaccine was started	115 (68.9)
After vaccination was started	52 (31.1)
Cause of renal failure	
Diabetes	62 (37.1)
Hypertension	32 (19.2)
Hereditary/congenital	9 (5.4)
Other disease(s)	18 (10.8)
Unknown	46 (27.5)
Previous COVID-19 infection	
No	132 (79.0)
Yes	35 (21.0)
Type of vaccines received	
Same type/single dose	111 (66.5)
2 different types	56 (33.5)
Number of doses	
One	7 (4.2)
2	66 (39.5)
3	94 (56.3)
Time since last dose	
10 weeks	91 (54.5)
12 weeks	76 (45.5)

Values are presented as nubers and precentages (%).
COVID-19: coronavirus disease-19

Table 2 - Associations between different groups and characteristics of renal failure patients receiving hemodialysis.

Variables	Positive (n=133)	Negative (n=34)	*P*-values
Gender			
Male	40 (81.6)	9 (18.4)	0.833
Female	93 (78.8)	25 (21.2)	
Age group (years)			
<19	4 (80.0)	1 (20.0)	0.842
20-40	39 (76.5)	12 (23.5)	
41-60	50 (83.3)	10 (16.7)	
>60	40 (78.4)	11 (21.6)	
Time of diagnosis with renal failure			
Before vaccine was started	93 (80.9)	22 (19.1)	0.542
After vaccination was started	40 (76.9)	12 (23.1)	
Cause of renal failure			
Diabetes	47 (75.8)	15 (24.2)	0.890
Hypertension	25 (78.1)	7 (21.9)	
Hereditary/congenital	8 (88.9)	1 (11.1)	
Other disease(s)	15 (83.3)	3 (16.7)	
Unknown	38 (82.6)	8 (17.4)	
Previous COVID-19 infection			
No	108 (81.8)	24 (18.2)	0.236
Yes	25 (71.4)	10 (28.6)	
Type of vaccines received			
Homogenous	86 (77.5)	25 (22.5)	0.417
Heterogeneous	47 (83.9)	9 (16.1)	
Number of doses			
One	0 (0.0)	7 (100)	< 0.001*
2	51 (77.3)	15 (22.7)	
3	82 (87.2)	12 (12.8)	
Time since last dose			
10 weeks	77 (84.5)	14 (15.4)	0.087
12 weeks	56 (73.7)	20 (26.3)	

Values are presented as numbers and precentages (%). *Significant at 95% confidence level. Data presented are obtained from Fisher's exact test.
COVID-19: coronavirus disease-19

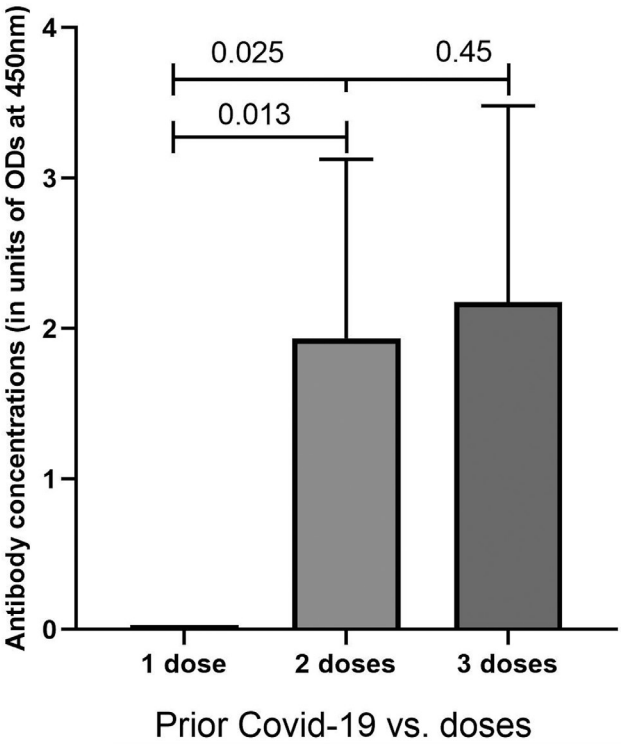

Figure 1 - Immunoglobulin G antibody levels according to the number of coronavirus disease-19 (COVID-19) vaccine doses in patients with prior COVID-19 infection (n=35). Bars show mean ± standard error of the mean (SEM). OD: optical density, vs: versus

or 3 doses (p=0.0004). Furthermore, patients who received 3 doses had significantly increased IgG antibody levels compared with those who received 2 doses (p=0.000; Figure 2). The results indicate a dose-dependent association between IgG antibody levels and the number COVID-19 vaccines.

Data resulting from simple linear regression analysis of predictors of antibody levels among renal failure patients on HM are presented in Table 4. Only the number of doses predicted the antibody level (beta=0.84 [95% CI: [0.56-1.13], p=0.000). The number of doses explained 17% of the change in antibody levels.

Discussion. Generating immunity against SARS-CoV-2 is the ultimate objective of COVID-19 vaccination. Vaccine-mediated immunity to the novel virus aims to prevent the interaction between the viral receptor and SARS-CoV-2, thereby protecting the patient from becoming infected and developing the disease.[14]

The efficacy of COVID-19 vaccines remains a major concern from healthcare authorities around the world. Therefore, investigating the efficacy and persistence of

Table 3 - Association between antibody levels and characteristics of renal failure patients on hemodialysis.

Variables	Mean±SD	Median (IQR)	*P*-values
Gender			
Male	2.26±1.15	3.00 (1.75-3.00)	0.119
Female	2.08±1.18	2.86 (1.35-3.00)	
Age group (years)			
<19	2.12±1.32	3.00 (0.81-3.00)	
20-40	2.08±1.24	3.00 (1.24-3.00)	0.990
41-60	2.21±1.09	3.00 (1.69-3.00)	
>60	2.09±1.21	3.00 (1.28-3.00)	
Time of diagnosis with renal failure			
Before vaccine was started	2.18±1.15	3.00 (1.52-3.00)	0.772
After vaccination was started	2.04±1.21	3.00 (1.30-3.00)	
Cause of renal failure			
Diabetes	2.04±1.24	3.00 (0.84-3.00)	
Hypertension	2.01±1.18	2.56 (1.27-3.00)	
Hereditary/congenital	2.14±1.09	3.00 (1.29-3.00)	0.623
Other disease(s)	2.37±1.11	3.00 (2.25-3.00)	
Unknown	2.26±1.13	3.00 (1.88-3.00)	
Previous COVID-19 infection			
No	2.21±1.13	3.00 (1.54-3.00)	0.182
Yes	1.86±1.30	2.58 (0.04-3.00)	
Type of vaccines received			
Homogenous	2.05±1.20	2.94 (1.27-3.00)	0.178
Heterogeneous	2.31±1.10	3.00 (2.02-3.00)	
Number of doses			
One	0.04±0.02	0.03 (0.03-0.03)	
2	1.87±1.16	2.21 (1.20-3.00)	<0.001*
3	2.48±1.01	3.00 (2.37-3.00)	
Time since last dose			
10 weeks	2.27±1.10	3.00 (1.59-3.00)	0.063
12 weeks	2.00±1.24	2.58 (0.09-3.00)	

Values are presented as mean ± standard deviation (SD) and median and interquartile range (IQR). *Significant at 95% confidence level. Data presented are obtained from Mann-Whitney and Kruskal-Wallis tests. COVID-19: coronavirus disease-19

immune responses following COVID-19 vaccination in CKD patients is of great value. Serosurveys are one of the more effective tools used to detect the prevalence of infectious pathogens, such as SARS-CoV-2.[15,16] Data collected from these surveys will accumulatively produce a wider picture regarding diseases that spread both nationally and globally.

Waning of COVID-19 vaccine-induced immunity in HM patients is common; therefore, full vaccination and boosters are believed to help and support the immune response. This method is well known in vaccination practices against this disease and other infectious diseases.[17]

In the current study, patients with prior COVID-19 infection who received 3 vaccine doses did not have significantly different antibody levels compared with patients who received 2 doses. This finding is consistent

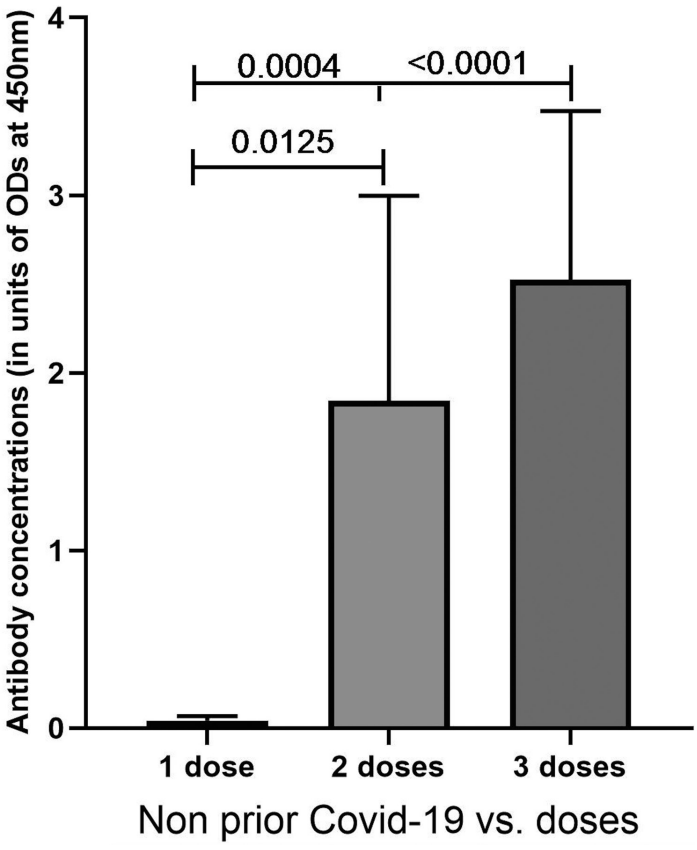

Figure 2 - Immunoglobulin G antibody levels according to the number of coronavirus disease-19 (COVID-19) vaccine doses in patients without prior COVID-19 infection (n=132). Bars show mean ± standard error of the mean (SEM). OD: optical density, vs: versus

Table 4 - Simple linear regression analysis of predictors of antibody levels among renal failure patients on hemodialysis.

Variables	Beta	Standard error	95% confidence interval	*P*-values	R-square
Gender	-0.18	0.20	-0.57 - 0.22	0.372	0.01
Age (years)	0.00	0.01	-0.01 - 0.01	0.948	0.00
Time of diagnosis with renal failure	-0.13	0.20	-0.52 - 0.25	0.499	0.00
Cause of renal failure	0.07	0.05	-0.04 - 0.18	0.205	0.10
Previous COVID-19 infection	-0.35	0.22	-0.78 - 0.09	0.120	0.02
Type of vaccines received	0.26	0.19	-0.12 - 0.64	0.174	0.01
Number of doses	0.84	0.14	0.56 - 1.13	<0.001*	0.17
Time since last dose (weeks)	-0.16	0.09	-0.33 - 0.02	0.089	0.02

*Significant at 95% confidence level. COVID-19: coronavirus disease-19

with published data.[18-20] Administering a single vaccine dose to patients receiving HM triggers a considerable increase in SARS-CoV-2-specific antibody levels and has become routine clinical practice for protection against the virus.[21] Moreover, booster immunization elicits greater humoral immunity in responder patients compared with a 2 dose vaccination.[22] It has been suggested that patients on maintenance HM might require multiple or higher doses of COVID-19 vaccines to achieve a sufficient immune response, as vaccine responses are expected to be reduced in these patients compared with the general population. Furthermore, only highly effective vaccines should be used in these patients.[23,24]

A study revealed that COVID-19-naive patients require the usual vaccination doses; however, patients with a history of COVID-19 infection only require a single vaccine dose to produce similar potency or a more extensive immune response compared with COVID-19-naive dialysis patients who received a double vaccine dose.[25]

In the current study, patients who received 2 doses were 77.3% seropositive, whereas patients who received 3 doses were 87.2% seropositive. This finding emphasizes the need for HM patients to receive booster COVID-19 vaccinations to strengthen their immune response and maintain high antibody levels. The current finding is in line with a study that reported a seroconversion rate of 88.7% in chronic HM patients who received 3 vaccine doses.[26] Therefore, the third challenge involves consolidating the humoral response against SARS-CoV-2. The immunity that develops in individuals with prior COVID-19 infection who received the vaccine named as hybrid immunity, and it has the highest magnitude and persistent protection against hospital admission and severe COVID-19 disease.[27-29] Vaccination is thus a more effective deterrent against severe disease consequences and post-COVID-19 complications.[30] Therefore, individuals with prior COVID-19 infection and full primary scheduled vaccination should postpone the booster dose up to 6 months as they retain a high quality and magnitude of immune response (antibodies and B cells), which contribute to protection against severe disease.[31]

In the current study, there was no statistically significant difference between antibody levels after 10 weeks and 12 weeks; however, the decline in antibody levels is concerning. Therefore, monitoring the immune responses of HM patients is necessary during follow-up to evaluate antibody levels and advise for booster vaccination.

Study limitations. First, a longitudinal series of samples were not obtained at different time points to determine when the decrease in antibody levels occurred, namely at which time point. Second, functional assays, such as a neutralizing antibody assay, were not conducted to evaluate the tendency of the induced antibodies to neutralize the virus and thereby combat the infection.

Multiple nationwide studies are required to reach a conclusion and build solid evidence to help the decision-maker in implementing legislation that would help the Ministry of Health in Saudi Arabia to encourage patients on HM to be fully vaccinated and receive booster doses.

In conclusion, the key finding from this study is that a significant proportion of the HM patients were able to produce an immune response to COVID-19 vaccines, with decreasing superiority from 3, 2, to one dose. This finding highlights the need for booster COVID-19 vaccination in patients on HM to produce an effective immune response.

Acknowledgment. *The author gratefully acknowledge Cambridge Proofreading LLC (https://proofreading.org/) for their English language editing.*

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