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Original Article

Trend patterns of HBsAg kinetics in chronic hepatitis B patients during nucleos(t)ide analogue therapy based on ARMA models

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KEYWORDS
ARMA model;
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Time series analysis

Abstract *Background:* Trend pattern analysis are lacking for hepatitis B surface antigen (HBsAg) kinetics in chronic hepatitis B (CHB) patients during nucleos(t)ide analogue (Nuc) therapy. We evaluated the trend patterns of HBsAg kinetics by time series analysis and forecasting times to HBsAg seroclearance accordingly.
Methods: A total of 116 CHB patients with documented three-month HBsAg levels during the previous more than five years of Nuc therapy were included. The piecewise linear trends of the autoregressive-moving average (ARMA) model were used for time series analysis of HBsAg kinetics trends. Best fitted models were created for each patient using HBsAg datasets with backtracking capability. Predicted time to HBsAg seroclearance was calculated accordingly.
Results: Four trend patterns of HBsAg kinetics were found: no trend (n = 22, 19.0%), single trend (n = 16, 13.8%), biphasic trend with rapid-slow decline (n = 56, 48.2%) and biphasic trend with rise-decline (n = 22, 19.0%). Except for no-trend patients, the trend became slow reduction as HBsAg declined. Only 6.1% of patients continued rapid decline when the initial HBsAg of the last trend reached <100 IU/mL. Last trend slopes < −10 and rise-decline patterns indicate greater chances of achieving HBsAg seroclearance within two years.
Conclusion: Best fitted ARMA models of HBsAg kinetics can be created individually for patients during Nuc therapy. About 67.2% patients have biphasic trend patterns, suggesting the dynamic

Abbreviations: ARMA, autoregressive-moving average; HBsAg, hepatitis B surface antigen.

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nature of HBsAg kinetics over time. Trend patterns and last trend slopes predict individual times to HBsAg seroclearance.
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Introduction

The therapeutic goal of antiviral therapy for chronic hepatitis B (CHB) is to achieve hepatitis B surface antigen (HBsAg) seroclearance, which is reported to be low.[1—3] Most current studies on patient-specific slopes use linear regression models to predict time to HBsAg seroclearance in CHB patients undergoing Nuc therapy.[4—8] According to these studies, the predicted times to HBsAg seroclearance were more than 50 years, implying life-long therapy.[5,7] This method is based primarily on the hypothesis of a change in HBsAg is a prerequisite for a constant trend. However, the trend of HBsAg kinetics seems to be dynamic because the variability of hepatitis B virus envelope proteins are linked to recognition and antigenicity of the virus and the fluctuated HBsAg levels during therapy are signs of the host immune response.[9,10] From the literatures, different patterns of HBsAg kinetics in the early stage of treatment and one to two years prior to HBsAg seroclearance have been reported.[11—21] These results indicate that HBsAg kinetics may be a slow linear trend of decline globally but also may vary individually during Nuc therapy.

Variable host and viral factors are associated with HBsAg seroclearance but precise estimates are still hard to provide.[22,23] These studies had often used change in or cut-off values of the HBsAg levels at specific time points as the crucial factors.[11—14,16,17,20,21] This way was prone to some difficulties in clinical use mainly because the values of HBsAg trended to fluctuate. Therefore, a new method for the evaluation of the trend of HBsAg kinetics may be needed to avoid selection bias and to provide precise estimates during the journey of long-term Nuc therapy.

Time series analysis is concerned with techniques to analyze this dependence and to incorporate the trend in any forecast of the series. The autoregressive-moving average (ARMA) models are the most frequently used linear models for time series analysis.[24] It estimates coefficient parameters of models in discrete sequences of time but also analyzes the possible changes in structure (turning points of trend) arising from the linear trend. As such, the ARMA models may be a suitable method for evaluating the trend of HBsAg kinetics, although the utility on it remains unknown.

Consequently, this study aimed to create personal ARMA models for the evaluation of HBsAg kinetics trends in CHB patients during long-term Nuc therapy. The time to HBsAg seroclearance would be forecasted according to the model individually. We would like to analyze the dynamic change of the trend patterns of HBsAg kinetics according to the achievement of HBsAg decline during therapy and their impact on the chance of achieving HBsAg seroclearance.

Materials and methods

The quantitative test for HBsAg (Architect QT immunoassays) has been used since January 2013 in the clinical laboratory of Kaohsiung Veterans General Hospital. In this study, the data of CHB patients who received Nuc therapy in our clinics from January 2013 to July 2021 were reviewed retrospectively. Most patients had been included in our previous cohort studies of CHB patients who received telbivudine-based therapy and tenofovir-based or switching therapy.[25—27] The inclusion criteria were as follows: (1) continuous Nuc therapy for at least 5 years during the study period regardless of the initiation of Nuc therapy prior to January 2013 or not; (2) HBsAg levels were checked continuously every three months for more than 20 datasets and without loss of continuous data >3 sets; and (3) the criteria for Nuc therapy were according to the guidelines.[28—30] HBsAg data that were not measured by the same method were excluded. Patients with insufficient datasets or interruptions in Nuc therapy were also excluded. For patients who achieved HBsAg seroclearance or cessation of therapy according to clinicians' orders, the datasets (if more than 20) were collected prior to these conditions. The patients who with HCC prior to the initiation of Nuc therapy would be not excluded if they received curative therapy (such as resection or radiofrequency ablation) and achieved complete tumor necrosis initially. Antiviral therapy would be initiated since the diagnosis of HCC because the antiviral therapy could achieve long-term survival and decreased tumor recurrence in this kind of patients.

Ethical considerations

This study protocol was approved by the ethics committee of the Institutional Review Board of Kaohsiung Veterans General Hospital (KSVGH20-CT9-10). The informed consents were signed in all enrolled patients.

Data collection

Patients' baseline demographic and clinical characteristics included age, gender, comorbidities and cirrhosis or hepatocellular carcinoma (HCC) were reviewed retrospectively. The baseline data would be within one month prior to the antiviral therapy in the present study. Baseline and on-treatment viral and biochemical data, including results of HBV DNA, HBsAg, HBeAg, anti-hepatitis B antibody and liver biochemistry, were also collected. Patients' history of Nuc therapy using lamivudine, adefovir, telbivudine, entecavir, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), as well as the development of genotypic

resistance to these low genetic barrier drugs, was also reviewed.

HBV DNA was determined using the COBAS TaqMan HBV Test (v2.0; Roche Diagnostics, Pleasanton, CA, USA) or Abbott Real Time HBV assays (Abbott Molecular Inc, Des Plaines, IL, USA) with a lower detection limit of 10 IU/mL. The quantitative HBsAg level was measured using Architect QT immunoassays (Abbott Diagnostics, Wiesbaden, Germany). Serum HBeAg and anti-hepatitis B e antibody were measured using radioimmunoassay kits (Ausria II-125; Abbott Laboratories, North Chicago, IL, USA). Genotypic resistance to Nuc was determined using direct DNA sequencing (SeqHepB; Abbott Diagnostics, Lake Forest, IL, USA).

ARMA models for HBsAg kinetics

An ARMA(p,q) model with one turning point of trend for time series observations Yt is represented as:

$$Y_t = \beta_0 + \beta_1 t + \beta_2 x_t + \varnothing_1 Y_{t-1} + \ldots + \varnothing_p Y_{t-p} + \varepsilon_t + \theta_1 \varepsilon_{t-1} + \ldots + \theta_q \varepsilon_{t-q},$$

Where t is a linear time trend, $x_t = \begin{cases} 0, t < \Psi \\ t - \Psi, t \geq \Psi \end{cases}$, ε_t is a white noise process (that is, $E(\varepsilon_t)=0$ and $E(\varepsilon_t \varepsilon_s) = \begin{cases} \sigma^2, for\ t=s \\ 0, for\ t \neq s \end{cases}$) and $(\beta_0, \beta_1, \beta_2, \varnothing_1, \ldots, \varnothing_p, \theta_1, \ldots, \theta_q, \Psi, \sigma^2)$ are unknown parameters coefficients. All roots of $(1 - \varnothing_1 Z - \varnothing_2 Z^2 - \ldots - \varnothing_p Z^p) = 0$& $(1 + \theta_1 Z + \theta_2 Z^2 + \ldots + \theta_q Z^q) = 0$ lying outside the unit circle are assumed to ensure the model's stationarity and invertibility. In this piecewise linear trend ARMA model, there is a linear time trend with slope β_1 before the trend turning point Ψ; after time Ψ, the turning point of trend, the slope of trend changes to $\beta_1 + \beta_2$. The estimating strategy of the piecewise linear trends developed by Muggeo et al. was used for estimating the unknown turning points Ψ to detect trend changes (structure breaks).[31–33] The Programming R (version: 4.0.4) was the major research tool. The packages included both "segmented" and "forecast".[31–35] The references are shown in Fig. S1.

A formal stationary, linear ARMA (p,q) process is assumed. The experimental design consists of nine combinations in the ARMA model (from 0,0 to 2,2) with three possible combinations, including no trend, a single trend and biphasic trend with one structural change. Therefore, 27 models were made for each patient initially. Then, the model with the minimum corrected Akaike information criteria was selected as the best fitted model.[36] Finally, the possible time to HBsAg seroclearance was calculated by using the trend slope and the interception of the HBsAg level of the last trend in the best fitted model for each patient.

The trend slopes of the models were divided into types A, B and C. Type A was defined as no trend (slope was defined as 0) or slope > -1. Types B and C were defined as slope in -1 to -10 and slope < -10. The predicted time to HBsAg seroclearance were divided into four groups: $\leq$ 24 months, 25–60 months, 61–120 months, and >120 months, respectively.

The intrinsic forecast test for comparing forecast accuracy in the best fitted model and the control model was also checked. The "ARMA model (0,0) with a constant trend" was the control model, which was similar to the linear regression model commonly used previously. Using the same method, both models were created using the series datasets before the last 5th dataset (as the training sets). The last four datasets were then used as test sets for a one-year forecast comparison. The best accuracy is defined as the minimum mean absolute scale error.[31,32,34–37]

Statistical analysis

All statistical analyses were performed using SPSS statistical software, version 20 (SPSS 20.0 for Windows; SPSS. Inc., Chicago, IL, USA). Categorical variables were compared using the Pearson chi-square test or Fisher's exact test. Continuous variables were analyzed by the student's t test. Logistic regression analysis was performed to identify factors associated with the predicted time to HBsAg seroclearance within 24 months. The piecewise linear trends in the ARMA model were done using statistical software R (the Programming R, version: 4.0.4). A two-tailed p-value of <0.05 was considered statistically significant for all analysis.

Results

Patients and Nuc therapy

The data of 225 CHB patients receiving Nuc therapy during the study period were reviewed. Eighty-one patients with data sets less than 20 were excluded. Twenty-six patients with insufficient datasets were excluded due to poor drug compliance and irregular follow-up for HBsAg testing. Two patients achieved HBsAg seroclearance during the study period were also excluded because the datasets prior to HBsAg seroclearance were less than 20 datasets. Finally, 116 patients were enrolled as the analytic sample.

Baseline demographic and clinical characteristics of these patients are shown in Table 1. Thirty-seven (31.9%) patients were HBeAg-positive, 59 (50.9%) patients had cirrhosis and 12 (10.3%) patients had hepatocellular carcinoma (HCC) (all received curative therapy) prior to the initiation of Nuc therapy. Seventy-three (63%) patients received Nuc therapy prior to January 2013. The treatment duration before January 2013 was about 30.8 $\pm$ 17.3 months. Twenty-three (19.8%) Nuc-experienced patients received TDF as the initial therapy for retreatment. The remaining treatment-naive patients received telbivudine-based therapy initially (all were treated before 2013). In this patient group, adding on adefovir or sequential switching to TDF were the choices for rescue therapy if genotypic resistance to telbivudine developed. Also, all 116 patients switched to TAF therapy sequentially after 2018.

Trend patterns and slope types in ARMA models of HBsAg kinetics

Four patterns of HBsAg kinetics were found, including no trend (n = 22, 19.0%), single trend (n = 16, 13.8%),

Table 1 Baseline characteristics of 116 enrolled patients.

Age, years, mean ± S.D.	49.7 ± 12.6
≤50/> 50 years	62/54
Gender, male/female	87/29
Cirrhosis, Yes/No	59/57
HCC, Yes/No	12/104
DM, Yes/No	15/101
HBeAg, positive/negative	37/79
HBV DNA, log IU/mL, mean ± S.D.	6.16 ± 1.64
≤5 log/> 5 log IU/mL	37/79
ALT ≤ 200/> 200 U/L	83/33
Nuc experienced, Yes/No	23/93
Resistance to LdT, Yes/No	35/81
Nuc regimens[a]	
TDF-TAF	23
LdT ± ADV-TDF-TAF	93
Treatment months, mean ± S.D.	109.5 ± 26.1
After January 2013	87.3 ± 16.4
Before January 2013 (n = 73)	30.8 ± 17.3
HBsAg, IU/mL[b]	
≥1000/101–999/ ≤ 100	39/54/23

ADV, adefovir; ALT, alanine transaminase, DM, diabetes mellitus; HCC, hepatocellular carcinoma; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; LAM, lamivudine; LdT: telbivudine; NA, not analysis; Nuc, neucleos(t)ide analogue; S.D.: standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a] Sequential switching regimens.

[b] Since January 2013.

biphasic trend with rapid-slow decline (n = 56, 48.2%) and biphasic trend with rise-decline (n = 22, 19.0%) (Fig. 1 and Table 2). There were 9 and 13 patients with no trend, 9 and 7 patients with single trend, 28 and 28 patients with rapid-slow decline pattern and 13 and 9 patients with rise-decline pattern in patients with (n = 59) and without (n = 57) cirrhosis. The trend pattern of HBsAg kinetics were similar in both patient groups (p = 0.643). For patients with biphasic trends, the period of the initial trend and the last trend were 35.1 ± 11.2 and 55.0 ± 15.1 months in the rapid-slow decline pattern as well as 16.9 ± 12.4 and 70.4 ± 22.3 months in the rise-decline pattern. Combining both results, the period of the last trend in patients with biphasic trends was about 59.2 ± 18.5 months.

The rates of type A, B and C of the last trend slopes were 39.6% (n = 46), 27.6% (n = 32) and 32.8% (n = 38) in all patients, respectively. The trend patterns and slope types were similar in patients with HBeAg-positive with or without seroconversion and HBeAg-negative (Table 2). However, except for patients with no trend, the slope types correlated with the initial HBsAg levels of the last trend (LT-HBsAg) (Table 3 and Fig. 2). In patients with single trend (Fig. 2A, **B and 2C**), rapid-slow decline patterns (Fig. 2D, E, 2F) and rise-decline patterns (Fig. 2G, H, 2I), the rates of type C slope were 100%, 50% and 87.5%, 44.4%, 42.9% and 66.7% as well as 0%, 6.9% and 0% in patients with LT-HBsAg >1000 IU/mL, 100–1000 IU/mL and <100 IU/mL, respectively. In summary, the rates of type C slope were 78.9%, 50% and 6.1% in patients with LT-HBsAg >1000 IU/mL, 100–1000 IU/mL and <100 IU/mL, respectively. Hence, the trend became slow reduction as the HBsAg levels declined, especially when achieving LT-HBsAg <100 IU/mL (p < 0.001) (Table 3).

Intrinsic forecast tests for forecast accuracy

Only 6 (5.2%) patients showed that the best fitted model was also the control model. Twenty-five (21.6%) patients showed significant differences (>5 years) in the predicted time to HBsAg seroclearance between the best fitted model and control model (Fig. 3). All of these patients had biphasic trends (20 rapid-slow decline pattern and 5 rise-decline pattern). Besides, from the intrinsic forecast tests, changes in the trend patterns were noted in only 14 (12.1%) patients after deleting data of one year (4 datasets).

Predicted time to HBsAg seroclearance in ARMA models

The predicted times to HBsAg seroclearance within ≤ 24 months, 25–60 months, 61–120 months and >120 months were found in 31.0% (n = 36), 15.5% (n = 18), 9.5% (n = 11) and 44.0% (n = 51) of patients, respectively. Multivariate analysis showed that the last trend slope for type C (hazard ratio = 2.839, 95% confidence interval = 1.106–6.953, p = 0.022) and rise-decline pattern (hazard ratio = 3.972, 95% confidence interval = 1.390–11.353, p = 0.010) were both associated with the predicted time to HBsAg seroclearance ≤ 24 months (Table 4).

Four patients achieved HBsAg seroclearance during the study period (Fig. S2). We performed ARMA model analysis by using the last data sets before HBsAg loss as validation. Two patients had the rapid-slow decline pattern with slope types C/C and C/B and low LT-HBsAg (139.97 IU/mL and 30.50 IU/mL) (case a and case b). The periods from the beginning of the last trend to HBsAg seroclearance were 48 months and 30 months, respectively. The other two patients had the rise-decline pattern with slope types A/B and A/B and low LT-HBsAg (123.11 IU/mL and 79.85 IU/mL) (case c and case d). The periods from the beginning of the last trend to HBsAg seroclearance were 90 months and 72 months, respectively. Therefore, the trend slope of type C and the rise-decline pattern may play an important role toward achieving subsequent HBsAg seroclearance.

Discussion

In the present study, by using datasets of HBsAg levels from previous series, we created the best fitted ARMA models of HBsAg kinetics for CHB patients during Nuc therapy. To the best of our knowledge, the present study is the first to evaluate the trend of HBsAg kinetics instead of the changes in or cut-off values of the HBsAg levels, which avoids selection bias in these fluctuating datasets. Furthermore, the purpose of this study would like to proof the hypothesis of non-constant trend pattern of HBsAg kinetics "during" Nuc therapy. Therefore, we enrolled the patients with continuous Nuc therapy for at least 5 years during the study period irrespective of the time of the initiation of Nuc therapy. Results showed four trend patterns of HBsAg kinetics in these patients after more than 5 years of Nuc therapy. Notably, the trends of HBsAg kinetics during Nuc

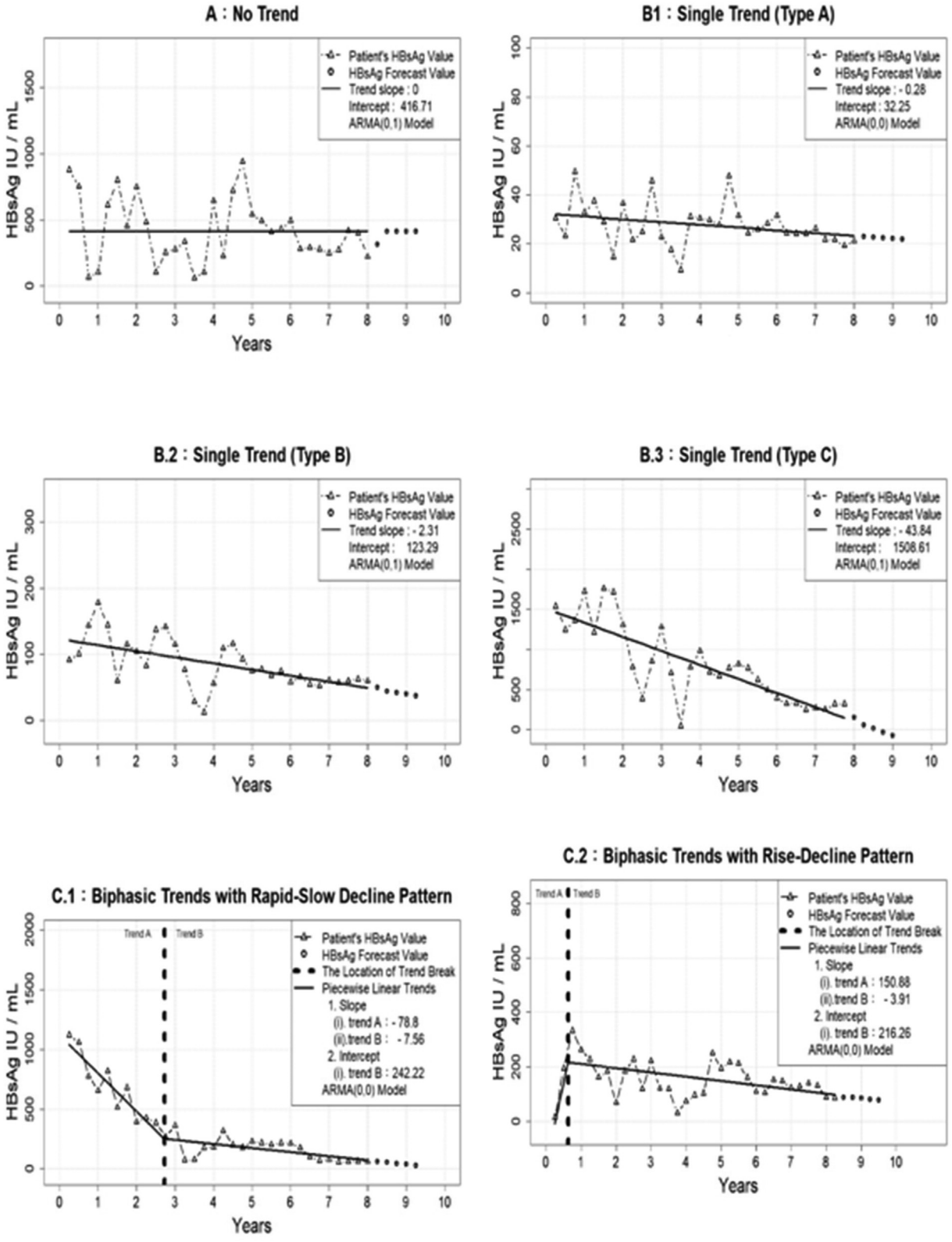

Figure. 1 Illustration of the personal ARMA models of HBsAg kinetics according to trend patterns and slope types. A: no trend (the trend line was located on the level of the mean of HBsAg; the slope was equal to zero). B: single trend with different slope types (type A in B1, type B in B2 and type C in B3).C: Biphasic trends of rapid-slow decline pattern (C1) and rise-decline pattern (C2). The slope types were defined as follows: type A = no trend or slope > -1; type B = slope between −1 and −10; type C = slope <-10.

Table 2 Trend patterns and slope types of HBsAg kinetics in ARMA models and predicted time to HBsAg seroclearance by HBeAg status.

	Overall (n = 116)	HBeAg (+) & seroconversion(−) (n = 17)	HBeAg (+) & seroconversion(+) (n = 20)	HBeAg (−) (n = 79)	p value
Trend patterns					
No trend	22	5	3	14	0.719
Single trend	16	3	3	10	
Biphasic trend	78	9	14	55	
Rapid-slow decline	56	7	11	38	0.713
Rise-decline	22	2	3	17	
Slope types[a]					
Single trend					
Type A/B/C	2/5/9	0/1/2	0/2/1	2/2/6	0.529
Rapid-slow decline pattern					
Type C–C	14	2	0	12	0.137
Type C–B/B–B	21/1	1/0	5/1	15/0	
Type C-A/B-A	16/4	4/0	4/1	8/3	
Rise-decline pattern					
Type A-C/B–C	12/3	1/0	2/1	9/2	0.332
Type A-B	5	0	0	5	
Type A–A	2	1	0	1	
Time to HBsAg seroclearance					
≤ 24 months	36	2	7	27	0.485
25–60 months	18	3	3	12	
61–120 months	11	1	1	9	
>120 months	51	11	9	31	

ARMA models: autoregressive-moving average models; HBsAg, hepatitis B surface antigen.
[a] Slope types: Type A: no trend or slope ≥ −1; Type B: slope between −1 and −10; Type C: slope < −10.

Table 3 Last slope types and the initial HBsAg levels of the last trend (LT-HBsAg) (exclusion for the patients with no trend).

LT-HBsAg, IU/mL	Last slope types**			p value
	Type A	Type B	Type C	
Single trend				<0.001*
>1000 (n = 5)	0	0	5 (100%)	
100–1000 (n = 9)	0	5 (55.6%)	4 (44.4%)	
<100 (n = 2)	2 (100%)		0	
Rapid-slow decline pattern				0.026*
>1000 (n = 6)	2 (33.3%)	1 (16.7%)	3 (50%)	
100–1000 (n = 21)	5 (23.8%)	7 (33.3%)	9 (42.9%)	
<100 (n = 29)	13 (44.8%)	14 (48.3%)	2 (6.9%)	
Rise-decline pattern				0.045*
>1000 (n = 8)	1 (12.5%)	0	7 (87.5%)	
100–1000 (n = 12)	0	4 (33.3%)	8 (66.7%)	
<100 (n = 2)	1 (50%)	1 (50%)	0	
Overall				<0.001*
>1000 (n = 19)	3 (15.8%)	1 (5.3%)	15 (78.9%)	
100–1000 (n = 42)	5 (11.9%)	16 (38.1%)	21 (50.0%)	
<100 (n = 33)	16 (48.5%)	15 (45.4%)	2 (6.1%)	
Overall	Type non-C	Type C	<0.001*	
≥100 (n = 61)	25 (41.0%)	36 (59.0%)		
<100 (n = 33)	31 (93.9%)	2 (6.1%)		

HBsAg, hepatitis B surface antigen.
*p < 0.05; **Slope types: Type A: no trend or slope ≥ −1; Type B: slope between −1 and −10; Type C: slope < −10.

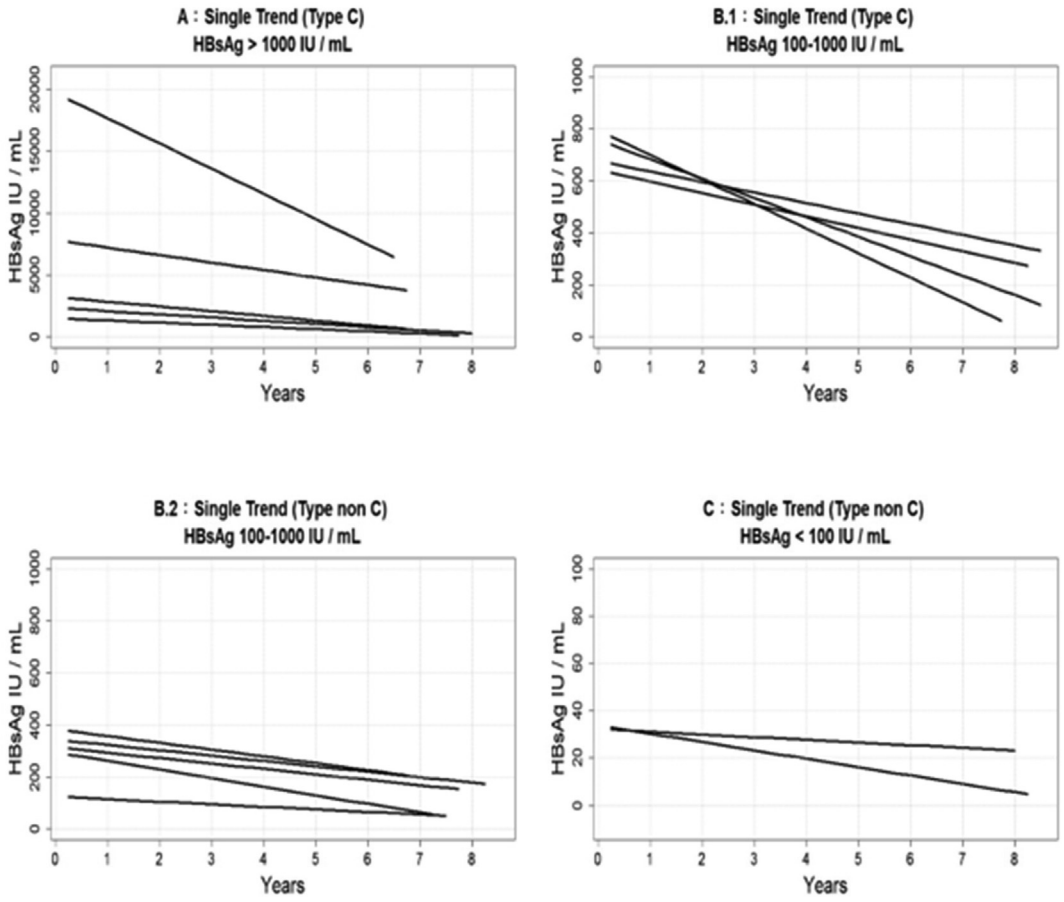

Figure. 2 Summary of the trend lines of personal ARMA models stratified by trend patterns, slope types and initial HBsAg levels of the last trend (LT-HBsAg) (excluding patients with no trend). Slopes of the last trend were stratified as type C and type non-C. A to C: single trend. D to F: fast-slow decline pattern. G to I: rise-decline pattern. The LT-HBsAg levels (IU/mL) were stratified as >1000, 100−1000 and < 100. No cases were found in 3 conditions: (1) single trend plus LT-HBsAg >1000 with slope type non-C; (2) single trend plus LT-HBsAg <100 with slope type C; (3) rise-decline pattern plus LT-HBsAg <100 with slope type C.

therapy seemed to be dynamic since about 67.2% of patients had biphasic trends and only 13.8% of patients had consistent trends. In addition, the trend became slow reduction as the HBsAg levels declined, especially when achieving HBsAg <100 IU/mL. This phenomenon was abridged shown before,[19] where the slow reduction of HBsAg decline was noted in patients with baseline HBsAg <1000 IU/mL. The HBsAg decline usually slow down as the transient restoration of T-cell function in the early stage of Nuc therapy passes over later.[9,14] Therefore, as shown in patients with the rapid-slow decline pattern, the initial trends of HBsAg decline were rapid because of the high HBsAg levels in this stage, followed by the last trends of slow decline or even steady state, which occurs because of HBsAg achieving low levels.

Our results also showed that trend patterns and the last trend slopes may predict the time to HBsAg seroclearance. In previous studies, great reduction of HBsAg levels and achieving low HBsAg levels in the early stage of Nuc therapy predicts the possibility of subsequent HBsAg seroclearance.[11,12,16,17,20,21] Three patterns of HBsAg decline (rapid, slow and steady patterns) were also found in HBeAg-positive patients receiving telbivudine therapy for three years.[21] In that study, the rapid decline pattern was also associated with enhanced antiviral T-cell immunity. In the present study, the last trend slope of type C and the rise-decline pattern, comparable to the more rapid HBsAg reduction, were both factors associated with the shorter time to HBsAg seroclearance. The phenomenon of the rise-decline pattern implies transient immune tolerance when faced with rapid viral suppression in the early stage of Nuc therapy, followed by a rebound of immune activation when HBsAg increases to high levels.

In addition, about 21.6% of patients also showed significant differences between the best fitted model and control model on the predicted time to HBsAg seroclearance. Our approach differed significantly from the approach of Chevaliez et al. by use of the linear regression model for forecasting.[5] This is primarily because our model determined the possible trend changes and the existence of the trend patterns by the model itself rather than subjectively identified as a constant trend. Therefore, we believe that the method of the ARMA model provide a more objective and reasonable way for personal forecasting.

Results of the present study have provided a reasonable model for patients undergoing Nuc therapy to predict the

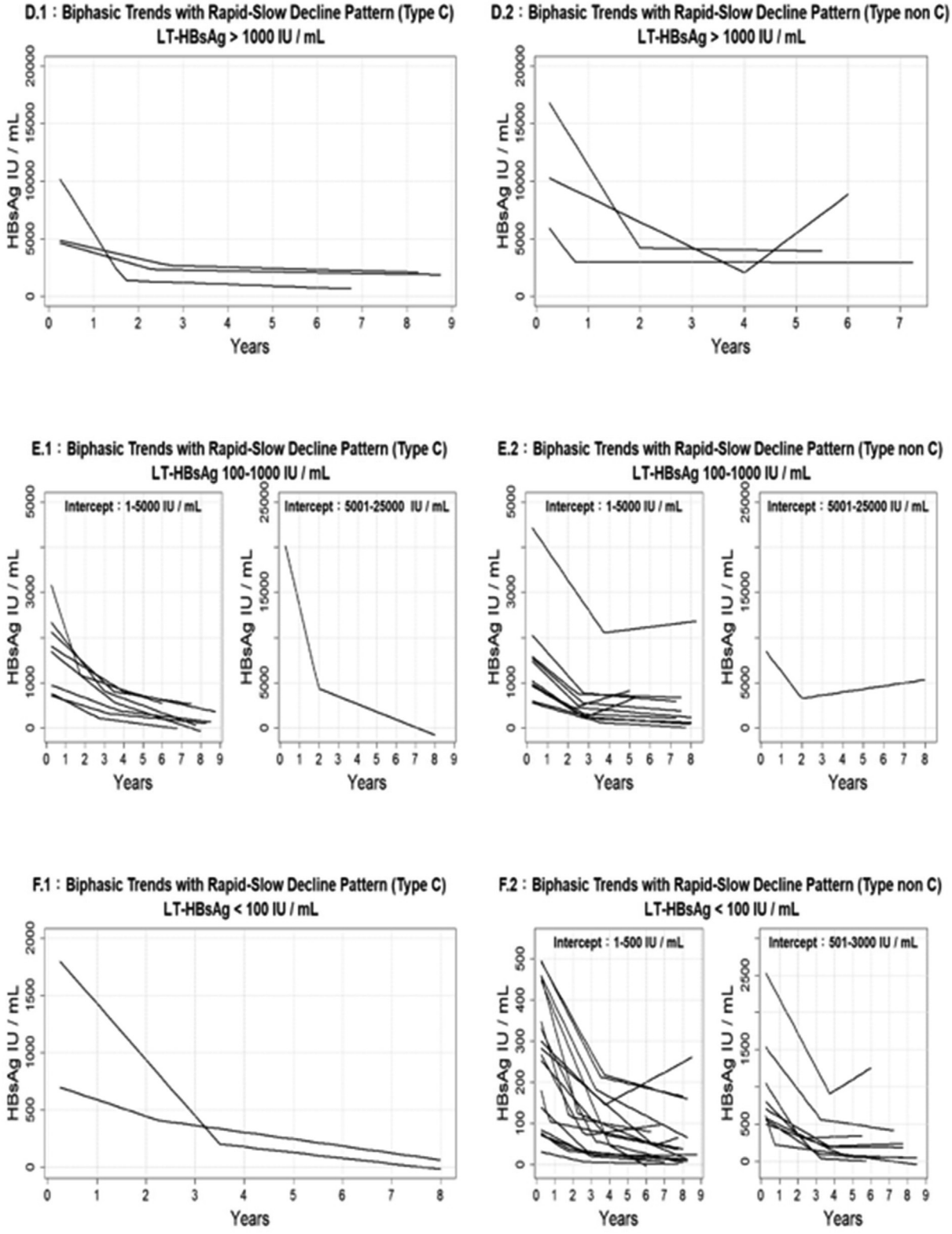

Figure. 2 (*continued*).

approximate time when they may achieve their treatment goals. However, the predicted time to HBsAg seroclearance within two years was demonstrated in 31% of patients in the present study. This seemed higher than previous real-world clinical experience. However, further prospective, continuous follow-up is needed. We also suggest to re-evaluating the ARMA models by adding on new datasets every one or 2 years as needed since the trend of HBsAg kinetics may be dynamic during Nuc therapy. Indeed, the forecast accuracy of the ARMA model decreases over time.

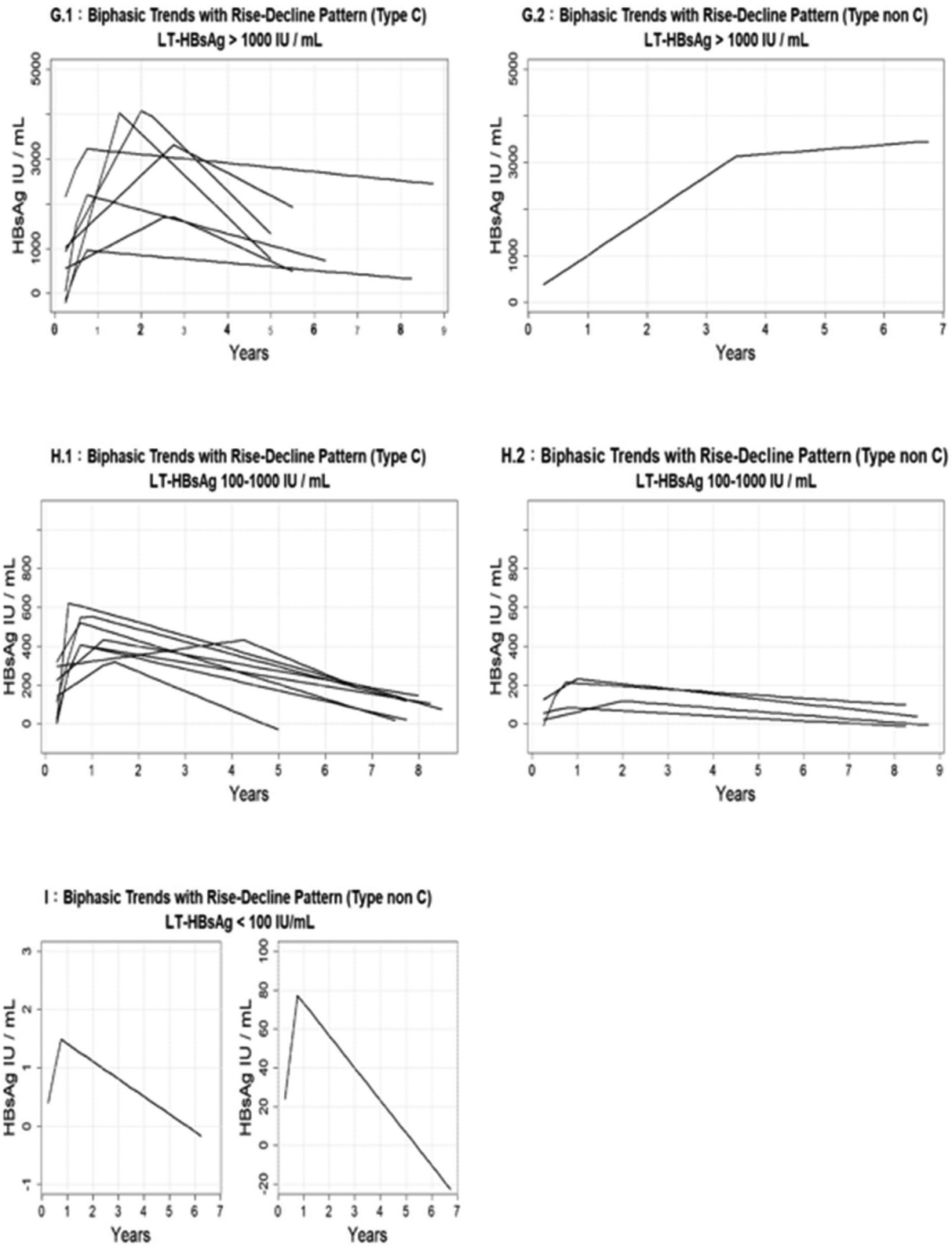

Figure. 2 (*continued*).

We must emphasize that the clinical utility of the ARMA model should be to realize the last trend of the HBsAg kinetics of each patient and to give them the treatment goal in the future.

The present study has some limitations. First, this was a retrospective study, which does not support inferences of causality. It was also based in only one hospital, which limits generalization of results to other patient populations and

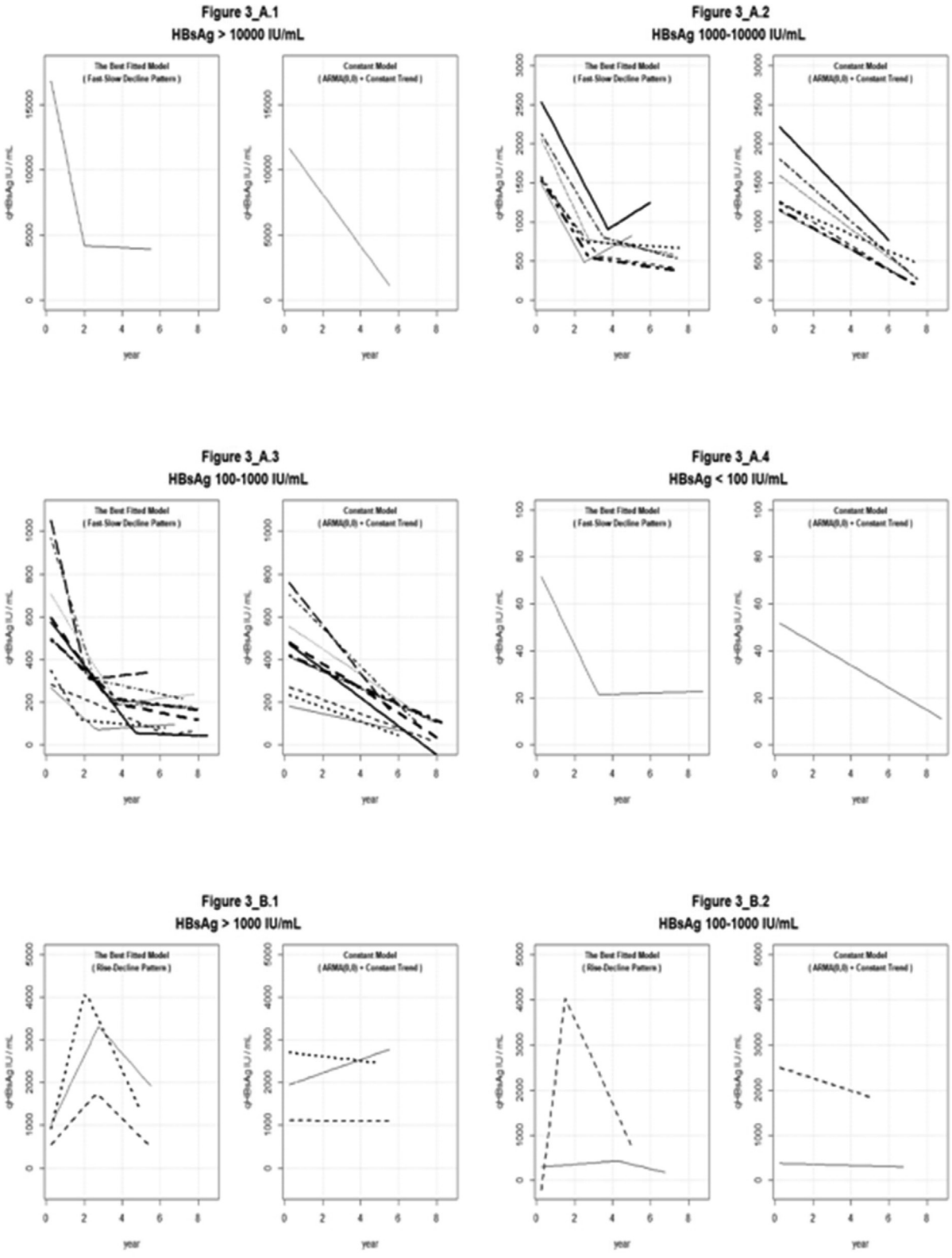

Figure. 3 The dissociation of the best fitted models and control models in 25 patients with biphasic trends. The predicted times to HBsAg seroclearance were different in more than 5 years between two models. A: Fast-slow decline pattern versus control pattern. B: Rise-decline pattern versus control pattern. HBsAg levels (IU/mL) were stratified as >1000, 100—1000 and < 100. Slope types were stratified as type C and non-C. Each single line indicates one case. In both models, each case has corresponding lines within the same drawing.

Table 4 Factors linked to predicted time to HBsAg seroclearance within 24 months.

Risk factor	Univariate HR(95% CI)	p value	Multivariate HR(95%CI)	p value
Age: ≥50 years	1.860(0.828−4.177)	0.133		
Sex: male	1.571(0.602−4.105)	0.356		
HBeAg: positive	0.619(0.256−1.497)	0.287		
HBe-seroconversion	4.038(0.710−22.966)	0.115		
Cirrhosis	1.314(0.596−2.896)	0.498		
Hepatocellular carcinoma	1.682(0.496−5.710)	0.404		
TDF-based therapy	1.238(0.471−3.252)	0.665		
DNA ≤ 5 log IU/mL	0.502(0.203−1.246)	0.138		
ALT ≤ 200	0.802(0.364−2.042)	0.736		
LT-HBsAg <100 IU/mL	1.243(0.543−2.847)	0.606		
Last slope, type C**	4.013(1.741−9.250)	0.001*	2.839(1.160−6.953)	0.022*
Single trend pattern	1.904(0.648−5.596)	0.242		
Rapid-slow decline pattern	0.679(0.307−1.504)	0.340		
Rise-decline pattern	5.727(2.126−15.432)	0.001*	3.972(1.390−11.353)	0.010*

*p < 0.05; ** type C: slope < −10.
ALT: alanine transaminase; CI: confidence interval; HBeAg: hepatitis B e-antigen; HR: hazard ratio; LT- HBsAg: initial hepatitis B surface antigen levels of the last trend; TDF: tenofovir disoproxil fumarate.

hospital centers. Secondly, only 37% of patients had complete HBsAg datasets from baseline data to follow-up data covering the whole treatment period. The trend pattern may include changes for the remaining patients if missing data could be added in before January 2013. However, the period of the last trend in patients with biphasic trend pattern was about mean five years. It seems to be unimportant to analyze the early datasets before five to seven years because only the last trend seems to be useful. Continuous follow-up and re-evaluation of ARMA models may provide more valuable information in future study. Finally, a limitation of the personal ARMA model was that the datasets should be continuous and regular. The number of datasets should be larger than the variables for forecasting. Skewed data are not suitable for use with this method.

In conclusion, by using previous series of HBsAg datasets, we created the best fitted ARMA model of HBsAg kinetics for each patient during Nuc therapy. Four trend patterns of HBsAg kinetics, including 67.2% of biphasic trends, suggest the dynamic nature of HBsAg kinetics over time. The trends typically become slow reduction as HBsAg levels declines. The trend patterns and the last trend slopes may predict the time to HBsAg seroclearance individually.

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Declarations of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2023.01.004.

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